# Albumin is a blood product too — is it safe for all patients?

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**ABSTRACT**

Albumin has been used for volume resuscitation and supplementation in critically ill patients for over 50 years. While regarded as a "gold standard" colloid solution, albumin is associated with substantial cost, and questions have been raised about its safety and efficacy.

A large-scale randomised controlled trial (the Saline vs. Albumin Fluid Evaluation [SAFE] study) demonstrated that albumin and saline were clinically equivalent treatments for intravascular volume resuscitation in a heterogenous population of critically ill patients. However, in patients with traumatic brain injury, albumin was associated with a significantly higher mortality and cannot be recommended for acute resuscitation of such patients.

A potential beneficial role of albumin in patients with severe sepsis, particularly malaria, requires further study. Extrapolation of the results of the SAFE study to other, synthetic, colloid solutions requires caution, and a randomised controlled trial comparing albumin, starch and crystalloids in patients with severe sepsis is warranted. The safety of synthetic colloids in patients with traumatic brain injury should not be assumed.

Although hypoalbuminaemia is associated with increased mortality, use of albumin for volume resuscitation of critically ill patients with a serum albumin concentration $\leqslant$ 25 g/L is not associated with reductions in mortality, duration of ICU stay or mechanical ventilation, or in use of renal replacement therapy. Similarly, there is no substantive evidence to justify the use of hyperoncotic albumin solutions for resuscitation or supplementation in critically ill patients.

Albumin is a safe and effective resuscitation solution in critically ill patients without traumatic brain injury. However, the acquisition costs of albumin and synthetic colloids are more than those of crystalloids, and, as yet, colloids have not been proven to confer substantive benefits over crystalloids such as saline.

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The administration of human albumin in acute and chronic illness has been practised since fractionation of human blood began during the Second World War. Albumin was initially used as a resuscitation fluid but, after it was recognised that albumin supplementation was inversely related to mortality risk,[1] its indications broadened to include a number of acute and chronic illnesses associated with hypoalbuminaemia.

Proponents of albumin administration base their recommendations on the principles outlined by Starling in 1896,[2] which describe the role of hydrostatic and oncotic forces in the movement of fluid across capillary membranes ($J_v$):

$$J_v = K_f([P_c - P_i] - \sigma[\pi_c - \pi_i])$$

where $P$ is hydrostatic pressure; $\pi$ is the colloid osmotic pressure in the capillary ($c$) and interstitium ($i$), respectively; $\sigma$ is the reflection coefficient; and $K_f$ is a filtration constant.

## Physiological considerations

Because of the molecular weight of albumin (70 kDa), the administration of 4% albumin increases intravascular hydrostatic and colloid oncotic pressure, resulting in increased intravascular volume. When hyperoncotic preparations of albumin (10%–20%) are used, expansion of intravascular volume may exceed the volume of albumin administered and augment movement of fluid from the interstitial space into the intravascular space, potentially reducing pathological interstitial oedema. For these theoretical reasons, colloid-based resuscitation, particularly using albumin, has been advocated for the past 50 years.

Under conditions of hypoalbuminaemia, such as nephrotic syndromes, and liver and autoimmune diseases, the intravenous supplementation of albumin, usually in hyperoncotic preparations, has been advocated to expand intravascular volume and to augment colloid osmotic pressure, thereby potentially reducing interstitial oedema and optimising protein-binding, transport and bioavailability of drugs.

## Pathophysiological considerations

While these theoretical benefits seem attractive, the benefits of albumin for resuscitation and supplementation have not been confirmed in clinical trials.

Under pathological conditions, the Starling relationship between hydrostatic and plasma oncotic pressure may be markedly influenced by changes in capillary permeability. This is represented by the reflection coefficient ($\sigma$) that compensates for the relative ineffectiveness of the oncotic pressure gradient to maintain a driving force to hydrostatic pressure across capillary membranes. Under conditions of diffuse increased capillary permeability, such as sepsis, or regional alterations of permeability, such as occur in the

brain following traumatic brain injury, there is a propensity for net efflux of fluid from the intravascular to interstitial spaces, resulting in increases in hydrostatic pressures, particularly with higher molecular weight compounds, producing interstitial oedema and hypovolaemia.

Albumin is an acute-phase protein that is rapidly sequestrated during acute injury or insult, perhaps representing teleological mechanisms directed at optimising haemorheological properties of the intravascular volume, resulting in hypoalbuminaemia and reductions in colloid osmotic pressures.[3] The combination of altered capillary permeability and hypoalbuminaemia-induced reduction in effective colloid osmotic pressure may negate the potentially beneficial effect of albumin administration in acute illness, so that the directly attributable effects of albumin (or colloid) administration on intravascular volume and interstitial oedema are unpredictable in critically ill patients.[4]

## The albumin debate

Albumin is a pooled solution produced as a by-product of whole blood fractionation for blood components such as immunoglobulins. Accordingly, the potential for allergic reactions and transmission of infection increases exponentially as the number of donors used to produce the albumin increases, but, in Australia, rates of transmission of infection associated with albumin are negligible. Albumin is costly — and the most expensive of the colloid solutions — to produce, thereby limiting its availability in income-poor countries. However, Australia is in a unique situation, with highly purified albumin produced by a single manufacturer and provided without an acquisition cost to public hospitals.

Although administration of colloids may have some theoretical benefits, and purified albumin may represent the "gold standard" for colloids, its availability and affordability are limited in many countries. This has led to the development of a range of synthetic colloids, including dextrans, gelatins and starch preparations. The adoption and use of these fluids in clinical practice is widespread, with marked variability in the use of colloids for a variety of clinical conditions. The selection of colloids by clinicians largely depends on the availability of solutions, which is substantially influenced by cost and marketing. This was demonstrated in a survey conducted by the CRYCO Study Group in Europe, which found that starch preparations were the most commonly used colloids, and that the use of albumin was declining.[5]

The use of albumin was called into further question by a meta-analysis by the Cochrane Injuries Group Albumin Reviewers, published in 1998.[6] This meta-analysis included 1419 patients from 30 studies, including a range of small studies comparing albumin to crystalloids for hypovolaemia, burns and hypoalbuminaemia. It found an overall increase in mortality of 6% associated with albumin (relative risk [RR], 1.68; 95% CI, 1.25–2.23). This result prompted a strong response in the popular and scientific media, questioning the role of albumin for resuscitation and supplementation in critically ill patients. Consequently, the use of albumin decreased significantly, particularly in the United Kingdom.[7]

To address whether albumin was indeed associated with increased mortality, a large-scale randomised controlled trial was needed. Given the unique availability of albumin to Australian and New Zealand hospitals, the Saline vs. Albumin Fluid Evaluation (SAFE) study was conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group, the George Institute for International Health, and the Australia Red Cross Blood Service, from 2001–2003.[8] The SAFE study was a prospective, double-blind, randomised controlled trial designed to determine whether there was a difference in all-cause 28-day mortality between patients resuscitated in the intensive care unit with either 4% albumin or its carrier solution, 0.9% saline. Powered to detect a 3% absolute reduction in mortality (the lower limit of the 95% CI observed in the Cochrane review), 6997 patients were randomised in 16 ICUs in Australia and New Zealand. The study was stratified by an admission diagnosis of trauma, which specified a definition for patients with an associated traumatic brain injury, and two additional a-priori subgroups were identified: diagnosis of severe sepsis, and the acute respiratory distress syndrome at randomisation.

The SAFE study demonstrated no difference in mortality between patients who received albumin or saline (RR, 0.99; 95% CI, 0.91–1.09). This result refuted the conclusion of the Cochrane review, and the authors concluded that albumin and saline should be considered clinically equivalent treatments for intravascular volume resuscitation in a heterogeneous population of critically ill patients. A revised systematic review of colloids and crystalloids by the Cochrane group, incorporating the SAFE study results,[9] affirmed the conclusion of the SAFE study and concluded that, as colloids were not associated with improved survival, and as they are more expensive than crystalloids, continued use in patients outside the context of randomised controlled trials was difficult to justify.

Apart from being the largest and most definitive fluid resuscitation study conducted to date, the SAFE study also revealed a number of additional insights into fluid resuscitation.

### Albumin for trauma resuscitation

Evidence of heterogeneity between patients with and without an admission diagnosis of trauma was demonstrated ($P = 0.04$ by the test for a common RR).[8] Albumin was

associated with an increased risk of death compared with saline (RR, 1.36; 95% CI 0.99–1.86). These observations were consistent with a previous meta-analysis of 302 trauma patients that concluded that crystalloid resuscitation was associated with a lower mortality than colloid resuscitation.[10] On closer examination of the trauma patients in the SAFE study, the increased number of deaths occurred almost exclusively in patients with associated traumatic brain injury, with a significantly higher 28-day mortality in patients who received albumin (24.5% v 15.1%, $P = 0.009$). For patients with trauma but no brain injury, the mortality was the same: 6.2% for those assigned albumin and also those assigned saline.

Given the potential importance of these results, a detailed post-hoc analysis of patients with traumatic brain injury was conducted (the SAFE-TBI study).[11] The primary objective of this study was to determine mortality and functional neurological outcome at a follow-up time relevant to traumatic brain injury — 2 years post-randomisation. Following confirmation of equivalence in baseline and injury-specific parameters, albumin was associated with a significantly higher 2-year mortality compared with saline (33.2% v 20.4%; RR, 1.63; 95% CI, 1.2–2.38; $P = 0.003$) and a significantly greater proportion of patients with unfavourable neurological outcomes. Importantly, most of the deaths were attributed to the underlying traumatic brain injury and occurred in the ICU, predominantly in patients with severe traumatic brain injury (defined as a last pre-randomisation unsedated score on the Glasgow Coma Scale less than 9). In these patients, the comparative mortality was 41.5% v 22.2% (RR, 1.88; 95% CI, 1.31–2.70; $P < 0.001$).

The biological mechanisms for increased mortality associated with albumin administration in patients with severe traumatic brain injury remain unclear. Potential exacerbation of primary brain injury appears the most likely mechanism, possibly due to intracranial hypertension from increased cerebral oedema associated with extravasation of albumin across regions of increased permeability of the blood–brain barrier. To investigate the potential pathological mechanisms, further analyses of intracranial pressure and associated treatments are being conducted.

The SAFE study therefore provides compelling evidence about the selection of fluids for trauma resuscitation. Albumin confers no benefit compared with saline in trauma patients, and is associated with increased mortality and worse functional outcomes in patients with traumatic brain injury. Albumin is therefore not recommended for resuscitation in these patients.

### Albumin for sepsis

A statistical trend to lower mortality was observed in patients with an admission diagnosis of sepsis who received albumin compared with saline (30.7% v 35.3%; RR, 0.87; 95% CI, 0.74–1.02; $P = 0.09$). Mortality rates in this subgroup were comparable to those in an Australasian epidemiological study conducted over a similar time period to the SAFE study (32.4%).[12] A recent study comparing 10% hydroxyethyl starch (HES 200/0.62) to modified Ringer's lactate in patients with severe sepsis was stopped prematurely because of an increase in rates of acute renal failure and requirements for renal replacement therapy.[13] The safety of alternative colloid solutions, particularly starch preparations, in patients with severe sepsis therefore remains uncertain; given the results observed in the SAFE sepsis subgroup, a definitive study comparing albumin, starch and balanced crystalloid solutions is warranted.

In addition, a potential role for albumin in sepsis is suggested from studies comparing albumin and saline[14] or gelatin[15] in children with severe malaria. These studies, powered to demonstrate a reduction in base deficit and resolution of shock, demonstrated reductions in mortality, and a large-scale phase III trial is underway to confirm or refute these preliminary results.

A potential cost-effective role for albumin in patients with severe sepsis remains possible, and further trials are therefore required.

### Albumin for hypoalbuminaemia

An additional analysis was conducted of patients in the SAFE study who had hypoalbuminaemia (defined as baseline serum albumin concentration $\leqslant 25$ g/L) to determine whether outcomes of resuscitation with albumin or saline depended on baseline serum albumin concentration.[16] This analysis confirmed that the "normal" serum albumin concentration in critically ill patients was 27 g/L, and that hypoalbuminaemia below this threshold was associated with increased mortality. However, mortality rates were not influenced by the administration of either albumin or saline. No difference in length of hospital stay, duration of mechanical ventilation or renal replacement therapy was observed between the two groups. Based on this analysis, the routine use of albumin to increase serum albumin concentration in hypoalbuminaemic critically ill patients is not supported.

The role of albumin supplementation in highly selected groups of hypoalbuminaemic patients, such as those with liver disease, remains uncertain, but there is no definitive evidence supporting the practice.

### Hyperoncotic albumin

Resuscitation of critically ill patients with hyperoncotic albumin offers theoretical advantages, particularly small-volume resuscitation in time-critical conditions, such as traumatic brain injury, burns and severe sepsis.

Although hyperoncotic albumin has been used for acute resuscitation since the 1940s, no large-scale randomised controlled trials have been conducted. A recent systematic review of small-volume resuscitation identified 25 randomised controlled trials with a total of 1485 patients. Overall, the quality of studies analysed was poor, with a median number of patients per trial of 30 (interquartile range, 18–58); a minority (16%) were conducted under blinded conditions; and a range of "control" regimens were used for a wide range of clinical conditions. Overall, no difference in survival was demonstrated between hyperoncotic albumin and "control" groups (RR, 0.95; 95% CI, 0.78–1.17). Furthermore, survival data from the patients with sepsis opposed the trend observed in patients with sepsis in the SAFE study. Given the uncertainty of these results, extrapolation of the results of the SAFE study analyses, and the substantial cost associated with hyperoncotic albumin solutions, the use of these solutions for resuscitation of critically ill patients outside the context of randomised controlled trials is hard to justify.

Albumin continues to be widely used by intensive care physicians for the resuscitation of patients across Australia and the rest of the world. This was confirmed in a cross-sectional study of fluid resuscitation on a single day in 392 ICUs in 24 countries following the publication of the SAFE study (SAFE Translation of Research into Practice study — SAFE TRIPS). Furthermore, albumin and starch are used equivalently for treating patients with severe sepsis, further suggesting that a definitive study of colloids in sepsis is justified (SAFE TRIPS Study Investigators, unpublished data).

## Conclusions

Although the SAFE study confirmed the safety of using albumin compared with saline in a heterogeneous population of critically ill patients, and many ICU clinicians continue to favour colloid resuscitation, there is no definitive evidence that colloid solutions offer benefits over crystalloid solutions such as saline. Crystalloid solutions appear equally effective and are substantially cheaper; use of saline is associated with significantly improved outcomes in patients with traumatic brain injury.

The use of colloids in patients with severe sepsis requires further study to determine firstly whether starch is safe, and secondly whether the use of any colloid improves outcomes compared with crystalloid.

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