**Point of view**

Crystallloids, colloids, or blood?

Protagonists in the ‘crystalloid versus colloid controversy’ commonly argue their cases based on the primary deficit in fluid compartments in shock states, the volume of fluid required for resuscitation, the significance of oedema formation, the fate of albumin once infused, and finally the costs of each fluid infusion (Table 1). Data are available to support each viewpoint in this controversy. In part, this apparent disparity in the data relates to the variations in the species studied, resuscitation protocols, the presence of pre-existing disease as well as the type and stage of disease in the subjects in the many comparative studies performed.

**Table 1. Relative merits of colloids and crystalloids**

<table>
<thead>
<tr>
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<th>Crystallloid</th>
<th>Colloid</th>
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<tr>
<td><strong>Primary defect</strong></td>
<td>Decreased ISFV</td>
<td>Decreased plasma volume, increased ISFV</td>
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<tr>
<td><strong>Volume</strong></td>
<td>2-4 times volume</td>
<td>Less volume, faster administration</td>
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<tr>
<td><strong>Oedema</strong></td>
<td>Cosmetic only</td>
<td>Decreased wound healing &amp; nutrient transport</td>
</tr>
<tr>
<td><strong>π</strong></td>
<td>Not important (πc - πt maintained)</td>
<td>Important (πc-PCWP gradient)</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>Leaks out of pulmonary capillary</td>
<td>Draws water from ISFV</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Inexpensive</td>
<td>Expensive</td>
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ISFV = interstitial fluid volume, πc = plasma oncotic pressure, πt = tissue oncotic pressure, PCWP = pulmonary capillary wedge pressure.

A number of recent publications have attempted to address these limitations by undertaking a systematic review of randomised controlled trials of resuscitation with colloids compared with crystalloids for volume replacement in critically ill patients. The first of these reviews involved analysis of 37 trials (26 unconfounded) in 1622 patients through to June 1997. Due to the heterogeneous populations studied within these trials, the review was stratified according to patient type (trauma, burns, surgery, or sepsis). The main study outcome was all cause mortality at the end of the trial, though this particular endpoint was not necessarily used in the individual studies reviewed. The major finding was that colloids were associated with an increased absolute risk of mortality of 4% (95% confidence intervals 0% to 8%) compared with crystalloids and that there was no evidence of differences in effect according to patient type. The authors acknowledged that their systematic review was limited by variations in the patients studied, interventions, resuscitation regimens, and types of fluid.

Shortly afterwards, the same authors conducted a second systematic review, on this occasion considering randomised controlled trials comparing administration of albumin or plasma protein fraction with either no administration or with administration of crystalloids in critically ill patients with hypovolaemia, burns or hypoaalbuminaemia. Using similar methodology, 30 trials involving 1419 patients up to March 1998 were examined. For each patient category, the risk of death was greater in the albumin treatment group, the pooled relative risk of death with albumin administration was 1.68 (1.26 to 2.23), and the pooled difference in the risk of death with albumin was 6% (95% confidence intervals 3% to 9%). Within the concluding remarks from this study, a number of emotive comments were made which sparked a spirited response within the literature. The authors stated that there was no evidence that albumin administration reduces mortality in critically ill patients with hypovolaemia, burns or hypoaalbuminaemia, and a strong suggestion that it increases mortality. Furthermore, they concluded that for every 17 patients treated with albumin there is one additional death, and finally that the use of albumin be urgently reviewed, and not used outside the context of rigorously conducted, randomised controlled trials.

Interestingly, an accompanying editorial stated that the study findings were credible as appropriate inclusion criteria ensured relevant studies were not missed, the validity of studies were appropriately appraised, and a plausible pathophysiological mechanism was available to explain excess mortality. It concluded by stating “…administration of albumin should be halted until, as the authors suggest, the results of a high quality large clinical trial are available.” The strength of that conviction diminished considerably over the ensuing week, such that in a letter to the BMJ the author of that accompanying editorial wrote “my use of the word ‘halted’….was intended to mean that clinicians should pause and consider the issues of validity, clinical relevance, and applicability…before giving albumin to the next critically ill patient”.

A number of passionate responses followed, highlighting that the papers were written without clinical insight and that the results were used to produce a sweeping generalisation that was scientifically inept. In contrast, the Director of the UK Cochrane Centre threatened legal action should he be prescribed albumin, further stating his refusal to participate in any
randomised trial involving albumin. A spurned reviewer of one of the systematic reviews felt impassioned to write to the editor, highlighting that no account was taken of the purpose, design or specific endpoints of the studies used in the systematic review. Most of the deaths occurred outside the study times, and variables ignored included age, medical conditions, severity of illness, dose of albumin, mode of administration, and attributable mortality of the states of disease that were treated. These would all appear to be valid criticisms of those systematic reviews.

A third systematic review was subsequently published by a separate group of investigators who specifically considered studies in which isotonic crystalloids were compared to colloids. They found no differences in mortality or pulmonary oedema between the treatment groups. However, the power of aggregated data was insufficient to detect small but potentially clinically important differences. A subgroup analysis found a mortality advantage for crystalloids in trauma (relative risk 0.39, 95% confidence intervals 0.17 - 0.89). They concluded that methodology limitations precluded any evidence-based clinical recommendations in the comparison of these types of fluids.

Why might albumin be harmful? Purported mechanisms include interstitial lung oedema following rapid intravascular volume replacement and exacerbation of oedema due to leakage into the interstitial fluid volume in altered capillary permeability states. In addition, impairment of coagulation and inhibition of platelet aggregation due to enhanced inhibition of factor Xa by antithrombin III have been described. Finally, impairment of sodium and water excretion and worsening of renal failure have been reported with albumin use.

One key point of disagreement for the adverse effects of each respective fluid relates to its fate after infusion. Theoretically, each fluid infusion is initially present within the plasma volume, though isotonic crystalloid fluids redistribute within the extracellular fluid volume (ECFV) from the plasma to the interstitial volume. Colloids maintain expansion of the plasma volume for a longer duration compared with isotonic crystalloid fluids. To clarify this issue, we determined the relative distribution of fluid within the ECFV after infusing either 0.9% saline or 5% albumin in 0.9% saline in septic critically ill patients. Plasma volume and ECFV were measured by dilution of $^{131}$I- albumin and $^{35}$S sodium sulphate respectively. Interstitial fluid volume was calculated as ECFV - plasma volume. We found that infusion of 0.9% saline increased the ECFV by approximately the volume infused, and the expansion of the plasma volume to interstitial fluid volume was in a ratio of 1:3. Infusion of 5% albumin in 0.9% saline however increased the ECFV by double the volume infused, both the plasma volume and interstitial fluid volume expanding by approximately equal amounts (Figure 1). The expansion of the ECFV in excess of the volume of 5% albumin in 0.9% saline infused suggests that fluid may move from the intracellular fluid volume to the ECFV in septic patients who receive this fluid. More importantly, a wide variation was found between patients with respect to their changes in PV and interstitial fluid volume following the fluid infusion despite their comparable clinical states. Such variability in the distribution of fluid would suggest that any apparent adverse effects from the fluid resuscitation are unlikely to be explained on the basis of its volume of distribution.
supply dependency of oxygen, that is, if the body is provided with greater \( \text{DO}_2 \) it will be able to increase its oxygen consumption. There is no doubt that this phenomenon occurs at critically low levels of \( \text{DO}_2 \). However, there are no studies in critically ill patients where oxygen consumption and delivery have been measured independently that supports the concept of a pathological supply dependency of oxygen. Increasing \( \text{DO}_2 \) would appear to have its greatest benefit in the post-operative setting but it is unknown which intervention or approach is better with regard to producing this increase (e.g. fluids, inotropes, blood or a combination).\(^{13}\) A counter argument to the rationale of increasing \( \text{DO}_2 \) submits that blood transfusions may increase global \( \text{DO}_2 \) yet will not have beneficial effects on \( \text{DO}_2 \) at the level of the microcirculation, because storage related changes in the red blood cell reduces its deformability and ability to offload \( \text{O}_2 \).

Patients with ischaemic heart disease represent an important subgroup when considering transfusion thresholds. It is known that the mortality rates in anaemic (i.e. haemoglobin < 95 g/L) critically ill patients increase according to the presence of cardiac disease. For example, there is an increased adjusted risk of death from 2.3 to 12.3 as pre-operative haemoglobin (Hb) values decreased from 100 - 109 g/L to 60 - 69 g/L in Jehovah’s Witness patients with cardiac disease undergoing surgical interventions.\(^{14}\) For patients undergoing coronary revascularisation, it was found that the conservative transfusion groups (transfuse if haematocrit < 25% or Hb < 70 g/L) received less post-operative blood transfusions (by design), and that there were no differences in post-operative morbidity, mortality or exercise tolerance.\(^{15,16}\)

A recently published prospective randomised trial addressing transfusion requirements sought to compare thirty day mortality and organ dysfunction in critically ill patients managed using either a restrictive or liberal blood transfusion strategy.\(^{17}\) The study was conducted in 26 top level intensive care units in Canada over a three year period, randomising patients to either a conservative (transfusion trigger of 70 g/L, aiming for a Hb of 70 - 90 g/L) or liberal (transfusion trigger of 100 g/L, aiming for a Hb of 100 - 120 g/L) strategy. The key finding suggested that a threshold transfusion trigger of 70 g/L was as effective and possibly superior to the liberal strategy in normovolaemic critically ill patients. In addition, there was a trend to decreased thirty-day mortality in the restrictive strategy, as well as decreased hospital mortality, cardiac complications and organ dysfunction. Furthermore, the restrictive strategy enabled a 54% reduction in the number of units of blood transfused, and decreased the likelihood of a patient’s exposure to blood transfusion by 33%.

The choice of fluid for resuscitation or the decision to transfuse blood should ultimately be based on the needs of the patient. However, if recent analyses are to be believed, the use of colloids confers no advantage over crystalloids, and potentially may be associated with a less favourable outcome. A balanced view, however, would suggest that at present either fluid may be used for fluid resuscitation providing due care be taken. Similarly it would appear that transfusing normovolaemic anaemic patients without intercurrent cardiac disease to a commonly accepted Hb concentration of 100 g/L might confer no specific benefit compared with a more conservative strategy. The extent to which the findings of these recent publications after clinical practice remains to be seen.

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REFERENCES


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