

REGULAR REVIEW

Albumin And Its Role In Trauma Resuscitation

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Introduction

The debates over fluid resuscitation in trauma continue: aggressive fluid resuscitation or permissive hypotension? Which fluid is best? This latter debate is expanding with the advent of synthetic fluids. It is far from clear as to which is the best and there is still no definitive answer to the colloid versus crystalloid question. Notwithstanding this, there is also a colloid versus colloid arm to the puzzle: albumin or other synthetic plasma substitutes? This particular debate received a significant shake up following the Cochrane report (1) in 1998, which inferred that albumin could be harmful.

Albumin is a plasma protein with a molecular weight of 96,000, is negatively charged at physiological pH and produces 75 – 80% of the intravascular colloid osmotic pressure (COP). It does not permeate the endothelial barrier in normal conditions and is collected using pooled human plasma from whole blood, is heat-treated and sterilized by ultra-filtration. With the advent of vCJD in the UK, British plasma is not currently being used to produce albumin and we use imported albumin, although there have been no reports to date suggesting transference of vCJD in this manner.

Albumin is supplied in glass vials and bottles in units of 20g as 400ml of 4-5% solution (isotonic) or 100ml of 15-25% solution (concentrated) and should be stored at room temperature (2,3). It contains 130-150mmol/l of sodium as well as other plasma proteins and stabilisers, but there are no clotting factors, blood group antibodies or plasma cholinesterases present in albumin; it may, therefore, be given without regard to the recipient's blood group.

Trauma, hypovolaemia and its consequences – areas for consideration

Excessive blood loss in the trauma patient produces hypovolaemic shock - defined as inadequate tissue perfusion and oxygenation. Blood flow is diverted to vital organs and there is concomitant release of inflammatory mediators. It is the damage caused to the microvasculature by these mediators that is thought to be responsible for organ damage even after an apparently successful primary resuscitation. Recent studies have identified the endothelium as a significant factor in the regulation of the microcirculation by its

production of prostaglandins, nitric oxide, endothelins and angiotensin II, all of which have an effect on vascular tone (4). The effects of specific fluid therapy on endothelial function is not yet known.

In the trauma patient poor perfusion and inflammatory mediator release cause damage to membrane integrity and result in an increase in protein permeability. Under Starlings law this creates an increase in hydrostatic pressure and decrease in intravascular colloid osmotic pressure (COP) as proteins move across the damaged membrane producing interstitial fluid accumulation (e.g. pulmonary oedema). This in turn further compromises the micro-circulation. Hypovolaemia also results in sodium, chloride and water retention due to the stimulation of the renin-angiotensin system and antidiuretic hormone release. This, coupled with the potential for interstitial fluid accumulation and oedema is thought to be involved in the pathway in the development of the systemic inflammatory response syndrome (SIRS) and organ failure. Natural responses to hypovolaemia in conjunction with excessive fluid resuscitation, sodium, chloride and water retention may be detrimental.

Albumin effects – the good and the bad

Colloid Osmotic Pressure Effects

Conventionally albumin has been used in hypovolaemia as a volume expander by maintaining COP, enhancing fluid resorption from the interstitial space and retaining fluid in the vascular space for longer. Haemodynamic improvement has been shown to persist for up to 36 hours (5). It is also noted that four times the volume of a crystalloid is required to obtain an equal volume enhancement. This may seem a logical conclusion given the known characteristics of albumin but recent evidence has shown that, with the exception of the gut and renal circulation, there is no sustained resorption of fluid at the venous end of capillaries. There is, however, a small constant level of filtration from capillaries, restricted by the effect of the plasma proteins. Only in circumstances of significant hypovolaemia do you get resorption of fluid, thought to be about 500ml over 15 minutes (6).

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Conversely, a laboratory study compared early albumin infusion with normal saline in the reperfusion of haemorrhagic shock, particularly the effects on mesenteric microcirculation, abdominal blood flow and central venous pressure (CVP). Albumin improved mesenteric microcirculation and global haemodynamics, with the effects on the microcirculation occurring before a change in either the abdominal blood flow or CVP, suggesting that the benefits of albumin are not solely due to its hyperoncotic properties (7).

Albumin's hyperoncotic effects can also be deleterious. By increasing the COP, when capillary permeability is compromised following trauma and sepsis, albumin administration will allow for further movement across the membrane taking with it more water, increasing interstitial oedema, compromising tissue oxygenation and leading to multi organ failure. It is also known that by various mechanisms, predominantly its effect on the COP, albumin may alter sodium and water excretion and worsen renal failure in critically ill patients.

Transport, Anti-inflammatory and Scavenger Effects

Albumin as a natural protein binds lipids, drugs and toxins and thus exhibits a transport function. In animal models it has been shown to have potential antioxidant effects and is known to reduce leukocyte-endothelium cell-cell interaction, one of the important reactions at the beginning of an inflammatory response syndrome making albumin a potential anti-inflammatory agent in the Adult Respiratory Distress Syndrome (7,8). Albumin also acts as a free radical scavenger, suppressing the release of reactive oxygen species, and has been shown to reduce reoxygenation injury (9,10). A study on rat bone marrow has demonstrated that a small volume of albumin may prevent trauma / hypovolaemia-induced bone marrow suppression (11).

Metabolic Effects

Albumin also plays a role in energy supply to the tissues. In health, energy is obtained from glucose but in the critically ill, including those bordering on SIRS, plasma protein (of which albumin constitutes two thirds) are broken down by the relatively inefficient Urea Cycle, directing energy away from protein synthesis and tissue repair (12).

Adverse Events

It should be remembered that albumin is produced from human blood and despite the precautions taken, may theoretically transmit infection, although there are no such cases reported in the world literature. An investigation into adverse events associated

with albumin administration in 1998-2000 confirmed that they are rare. Not surprisingly the observed incidence of non-fatal and fatal adverse events during 1998-2000, after publication of the Cochrane report, was approximately five times that for 1990-1997. This large increase is primarily attributed to reduced under reporting rather than a true increase in the frequency of adverse events.

In the three years following the report there were a total of 198 non-fatal and 13 fatal adverse events reported to 10 major suppliers of therapeutic albumin. Of the 13 fatalities only 3 were judged to be possibly related to albumin and, of the 198 non-fatal events, only 7.1% were classified as probably related to albumin administration. There were no absolute cases and potential mechanisms of these detrimental effects were not examined. Between 1990-2000, 112 million albumin doses were distributed worldwide; no death with a high probability attributable to albumin administration was documented. This investigation concluded that human albumin is remarkably safe (13).

Clinical Evidence

The Cochrane Report and its fall out

In 1998 the Cochrane Injuries Group reviewed albumin usage and specifically quantified the effect on mortality when administered in critically ill patients with hypovolaemia, burns or hypoalbuminaemia. It was carried out as a systematic review of 30 randomised controlled trials up to March 1998, reporting 1419 patients, which compared albumin or plasma protein fraction to nothing or administration of a crystalloid solution. They included studies that had compared different levels of albumin supplementation. The results found that for each patient category the risk of death in the albumin group was higher than in the comparison groups and that there were six additional deaths for every one hundred patients treated. They concluded that the use of human albumin in critically ill patients be urgently reviewed (1). On the strength of this, warnings were made by the Committee on Safety of Medicines in UK (CSM) and the Food and Drug Agency in the USA (FDA), warning of the potential dangers of giving albumin.

A flood of papers then followed, some criticising the review, others supporting it. Nadel *et al* (5) argued that the Cochrane study comprised of trials that predominately looked at haemodynamic variables, not mortality, and that none of the trials specifically included children. Following the treatment of 410 children with meningococcal septicaemia using 4.5% Human Albumin solution at volumes of 80ml/Kg (range 20-200), they reported that they had a lower than predicted case fatality ratio and

no deaths from pulmonary oedema. They felt that the current practise of using albumin in septic children be continued until further trials were conducted.

McClelland (14) took a balanced view. He noted that in the trials used in the Cochrane review there had only been a small number of deaths and, therefore, the results should be interpreted with caution, a statement that had been accepted by the reviewing group. He agreed that the results did show some cause for concern but that further trials were needed. He also proposed that the Cochrane review group and dissenting clinicians combine to review the data again with a greater clinical input into data interpretation.

Offringa (15) examined how the systematic review had been carried out and concluded that the standard guidelines had been followed appropriately and that the review was scientifically robust, but, given that mortality was being specifically looked at, favourable effects of albumin in certain patients may have been obscured during the analysis and had potentially been overlooked. Although the review showed an increase in mortality with albumin, no plausible pathophysiological mechanism to explain this had been put forward. He concluded that the administration of albumin should be halted until further high quality clinical trials were available.

Shwe and Bhavnani (16) published a hospital audit carried out following an increase in the use of human albumin focussing on the clinical indications for its use, especially in the light of the Cochrane analysis. They found that 4.5% albumin was used non-specifically in patients with low serum albumin, and 20% albumin in patients with liver disease. Their literature search confirmed that advice regarding the use of albumin varied across Europe and was often conflicting: in one country there were only 2 indications for its use compared to 12 in another. Their conclusion was that a concerted effort was needed to identify those patients who may benefit from albumin administration.

In 2001, Wilkes *et al* (17) hypothesised that albumin administration is not associated with excess mortality. They looked at 55 randomised controlled trials comparing albumin with crystalloid, no albumin and lower doses of albumin, using an end point of the relative risk for death. Included trials were those that were randomised and had mortality data available; no restrictions on clinical indications were enforced. Using broad inclusion criteria and meta analyses they aimed to rule out bias which they felt the Cochrane report had potentially included. The data from the selected trials was independently extracted and differences in interpretation resolved by discussion. The results from the 55 trials covered 3504 patients including 525 deaths and found that

there was no evidence to suggest that albumin significantly affected mortality in any category looked at (trauma, sepsis or burns).

In 2003 a further systematic review by Haynes *et al* (18) included 79 studies and 4755 patients although there were no trauma studies or attempts at quantitative meta-analysis. The studies used were based around sepsis, elective surgery including cardiac surgery and burns, where albumin administration was compared to crystalloid, no albumin or lower dose albumin. Though no significant treatment effect was found in a quarter of the trials, they concluded that albumin could be beneficial in certain clinical settings. Lower fluid requirements, higher COP, reduced pulmonary oedema and less abnormalities in haemostasis was found, compared with a synthetic colloid in cardiac surgery and crystalloid in septic patients. In non-cardiac surgery albumin use required less fluid volume and pulmonary and intestinal oedema was less compared to crystalloid use. Albumin reduced morbidity in hypoalbuminaemia, and in ascitic patients reduced haemodynamic derangements, and morbidity.

Saline vs. Albumin Fluid Evaluation (SAFE) Study

In answer to the questions raised by the Cochrane review on the use of albumin, Finfer *et al* (19) undertook the SAFE trial, publishing the results in 2004. They carried out a multi-centred, double blind controlled trial based in Australia and New Zealand.

Intravenous 0.9% sodium chloride or 4% human albumin was randomly allocated to critically ill adults requiring fluid resuscitation in the ICU. The primary outcome measure was mortality at 28 days and secondary outcomes included length of ICU and hospital stay, organ dysfunction and other physiological measures in response to fluid therapy. Patients with severe sepsis and acute respiratory distress syndrome at study entry were identified to allow for subgroup analysis. Patients who had cardiac surgery were excluded from the trial as the mortality in this group is known to be < 1% and their inclusion would significantly increase the number of patients to be studied without demonstrating a mortality benefit in either fluid group. Patients admitted to ICU due to burns or following liver transplants were also excluded as the accepted treatment protocols for these conditions include albumin containing fluids. A total of 6997 patients were recruited, 3497 received albumin and 3500 normal saline, both groups had similar baseline characteristics and received similar intensive care interventions. In the albumin group there were 726 deaths compared to 729 in the normal saline group (relative risk of death,

0.99; 95 % confidence intervals, 0.91 -1.09; P=0.87). The results showed that albumin and normal saline had a similar outcome at 28 days in both mortality and each of the secondary outcomes studied. No significant difference was established. In certain subgroup analysis, for example the severe sepsis group, albumin administration inferred a possible decrease in mortality (relative risk of death 0.87: 95% confidence interval, 0.74 - 1.02). This data was to be interpreted with caution as these differences and others, occurred in the subgroups with small patient numbers, those that were based on biological mechanisms and in the groups established prior to the study, which were all areas of potential bias. This study concluded that albumin and normal saline should be considered clinically equivalent treatments for intravascular volume resuscitation in a heterogeneous population of patients in the ICU (20-22), although no advantage of albumin over crystalloid was demonstrated.

Conclusion

Throughout these trials, debates and reviews it is evident that albumin has a place in medical practice. Its positive properties of increasing COP, being an anti oxidant and free radical scavenger as well as transporting and binding drugs and toxins give us the mechanisms by which it may be beneficial. Clinically the decrease in mortality and morbidity demonstrated in the treatment of such groups as septic children, hypoalbuminaemic patients, burns and post operative patients, confers a potential benefit of albumin in a more highly selected population of critically ill patients.

The initial concern of an increase in mortality following the Cochrane study has been allayed for now, but it should be noted that no significant benefit in the use of albumin has been shown and there is no evidence supporting the use of albumin in trauma resuscitation over other fluids.

There remains a requirement for further, well constructed, clinical trials examining the use of albumin in different clinical settings. In the meantime, should albumin be part of our fluid resuscitation protocol? If so, when, how much and of what strength? The jury is still out.

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