

One in a series of reports concerning meetings on topics relevant to the clinical use of human serum albumin

Selected topics concerning Intravenous fluid therapy

from the 24th International Symposium on Intensive Care and Emergency Medicine held in Brussels, Belgium, 30th March – 2nd April, 2004.

Introduction

For the 24th International Symposium on Intensive Care and Emergency Medicine (ISICEM), the meeting moved away from its original central

Brussels location to the Exhibition and Convention Centre at Heysel, to the north of the city. Professor Jean-Louis Vincent, Chairman of the Symposium

welcomed delegates to the largest, annual medical conference in Belgium, with 5000 delegates expected in 2004.

The colloid versus crystalloid debate

The topic of the relative merits and demerits of crystalloids versus colloids for fluid resuscitation is a matter for regular discussion at the ISICEM. Although disputed, the findings of one meta-analysis of clinical reports (*Brit Med J*, 1998, **317**, 235–40) suggested that albumin as fluid resuscitation is harmful and its use should be restricted to controlled clinical trials. Despite the obvious shortcomings of this meta-analysis (see page 9) this opinion has influenced the crystalloid versus colloid debate for several years. However, at the 2004 meeting, of the ISICEM, Simon Finfer, on behalf of the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trial

Group, presented findings from the Saline versus Albumin Fluid Evaluation (SAFE) study. This large, prospective, double-blind, randomised study was designed specifically to compare the effects of two resuscitation fluids (4% albumin and saline) on 28-day all-cause mortality in intensive care unit (ICU) patients requiring intravascular volume resuscitation, with the hypothesis that there would be no difference in mortality at 28 days. The overall findings confirmed the hypothesis. A report of Dr Finfer's presentations, in the opening session of the Symposium and in the "Intravenous Fluids" session can be found later in this report (page 9).

As the artificial colloids, including the hydroxyethyl starch (HES) solutions have been developed to try to optimise their advantages and reduce their disadvantages, and as more is understood of the properties and effects of albumin and the effects of colloids, the colloid versus crystalloid debate has evolved into a discussion of the appropriate use of both types of fluids, using them to best therapeutic effect.

This was illustrated during the Symposium Pro:Con debate "Colloids are better than crystalloids", moderated by Wilfred Druml (Vienna, Austria).

For the proposal – "Colloids are better than crystalloids"

The "Pro" position in the debate was taken by Monty Mythen (London, UK). The primary objectives of fluid management, in terms of plasma volume expansion are to:

- Maintain an effective circulating blood volume
- Prevent inadequate tissue perfusion

The basic hypothesis in giving colloids as a plasma substitute is that they will remain in the intravascular space, whereas saline-type crystalloids will distribute throughout the extracellular

compartment, and glucose solution, which is essentially metabolised to water, will distribute throughout the full volume of total body water. The Starling equation concerns the balance between hydrostatic pressure and colloid osmotic pressure; if hydrostatic pressure is increased without elevating colloid osmotic

pressure, a greater flux of fluid is generated and, in consequence, oedema is increased.

Overall, it could be proposed that in discussing colloids versus crystalloids as plasma substitutes:

- Colloids are more efficient at resuscitating the intravascular space; they are more likely to remain in the intravascular space, although this is dependent upon molecular size and the state of the endothelial membrane.
- Colloids increase colloid osmotic pressure and reduce oedema.
- Colloids improve microcirculatory flow and are more anti- than pro-coagulant, so it could be hypothesised that trauma patients may be at a disadvantage, but sepsis patients might have a better chance of survival.

- Colloid usage reduces oedema-related morbidity following major surgery.

Although the SAFE study is important, it refers to critically ill patients in the ICU. It does not cover fluid usage during, for example, major surgery where higher molecular weight colloids are used more frequently, at least in Europe. In such situations the predicted mortality is probably nil, but outcome variables that are meaningful to the surgeon and the patient are nausea, anti-emetic usage and severe pain. In a study comparing two colloids, given in a blinded fashion, with Ringer's lactate (RL), Moretti *et al* (*Anesth Analg*, 2003, **96**, 611–7) showed the two colloids to be superior to crystalloid with respect to these three variables.

However, these conclusions are both disease- and context-sensitive.

Including the findings of the SAFE study, what is known to date and based on best available evidence:

- If the patient is at risk of haemorrhaging to death, and this is the overriding factor, it is probably better to use a crystalloid for immediate fluid resuscitation.
- If the patient is at risk of clotting, then colloids are possibly the better treatment option, though the evidence for this is less firm.
- If the patient has sepsis, then the probability is that a colloid is more suitable.
- If oedema-related morbidity following major surgery is the risk, there is some evidence from randomised clinical trials to prefer a colloid.

Against the proposal – “Colloids are better than crystalloids”

The “Con” presentation in the debate was given by Joachim Boldt (Ludwigshafen, Germany). Dr Druml expressed surprise at Professor Boldt taking the “Con” stance in this debate, as he is widely known for his work with colloids. In fact, Professor Mythen's and Professor Boldt's views concurred in this discussion.

Colloids find much more widespread use in Europe, while crystalloid use predominates in the USA. The American College of Surgeons (ACS) gives recommendations concerning fluid use in patients suffering from haemorrhage or hypovolaemia according to the extent of blood loss, but all the fluids recommended are crystalloids or crystalloids plus blood. The ACS does not recommend colloids in patients who are suffering from haemorrhage or hypovolaemia after major surgery.

If it is necessary to treat the intravascular space, colloids are superior. The interstitial space cannot be predictably treated with colloids; a saline-based crystalloid or glucose is more appropriate.

The objectives of volume replacement are firstly to stabilize the patient haemodynamically, with secondary considerations of fluid homeostasis and coagulation and then the side effects. The volume effects of crystalloids are largely lost by 2 hours from infusion, while those of hydroxyethyl starches (HES) are maintained over this time. Therefore, hypovolaemia is much better treated by colloids, because they do not leave the intravascular space so rapidly. Crystalloids move rapidly into the interstitium. It is necessary to replace 1L of blood loss with 4 to 6 litres of crystalloids to correct hypovolaemia. Professor Boldt does not recommend crystalloids as a volume replacement strategy in the critically ill the ICU, in

the operating theatre or in emergency management. The volumes involved to stabilise the patient are not an appropriate treatment for optimal therapy to replace severe hypovolaemic deficit.

Apart from the treatment of hypovolaemia and macrocirculatory disturbances, tissue perfusion is a consideration. Data from patients undergoing major abdominal surgery that compared colloid and crystalloid and measured oxygen tissue tension (Lang *et al*, *Anesth Analg*, 2001, **93** 405–9) showed that with HES there was an increase in tissue oxygenation, and with crystalloid (RL) there was a decrease. The haemodynamics were exactly the same in these patients.

It is important for the patient that circulation and oxygenation are well-managed, but what counts most for the doctors and patients is outcome. In the meta-analysis by Choi *et al* (*Crit Care Med*, 1998, **27**, 200–10), there

was a slight trend in favour of crystalloids in trauma patients. Velanovich (*Surgery* 1989, **105**, 65–71), in a meta-analysis of mortality associated with crystalloid versus colloid use (three studies, 96 patients) found that colloids had a beneficial effect on mortality in non-trauma patients, compared with crystalloids. These publications illustrate that findings are different in different patients and, as Professor Mythen had already said, the findings are disease-sensitive.

Discussion

In discussion, Professor Boldt said that while many thousands of patients are needed for a study of adequate power to detect a difference in mortality as an outcome, he doubted that mortality was an appropriate outcome for determining the best way to treat patients. There is the criticism that there is no evidence to show that colloids are superior to crystalloids, and therefore crystalloids should be used on the basis of cost. Some 90% of therapeutic approaches in the ICU are not evidence based,

but there are many small studies demonstrating that colloids are superior to crystalloids.

In answer to a question about whether crystalloids or colloids should be used, Professor Mythen replied that colloids should be used for plasma volume expansion. The important thing is probably timing and dosage, rather than which fluid is used. Professor Boldt said that he thought the appropriate answer to whether one should use colloids or crystalloids is “Yes”.

An overview of intravenous fluids

Professor Mythen also introduced the session on intravenous fluids moderated by Duncan Wyncoll (London, UK) and Per-Olof Grände (Lund, Sweden).

The amount of water in the body approximates to 45L in a 70kg person, of which two-thirds, some 30L, is intracellular and of the extracellular compartment, two-thirds is interstitial; of the intravascular water, two-thirds is plasma and one third is contained in blood cells. Colloids are usually thought of as staying within the intravascular compartment, saline-type crystalloids distribute throughout the 15L of the extracellular compartment, while infused glucose solutions, metabolised to water, distribute through the full 45L volume. This is not necessarily borne out when it comes to clinical studies that involve disease states.

Crystalloids are usually discussed in terms of their osmolarity, pH and electrolyte composition. Colloids are discussed in terms of their various qualities, but the main focus is on their relative costs.

Polydispersity and molecular size

The synthetic colloids have various recognisably different qualities, some of which can be explained by their polydispersity and their relative molecular size. If it is postulated that the vascular endothelium is a semi-permeable membrane with pores of a particular size, then increased colloid molecular size is attractive because there should be prolonged intravascular retention, particularly if the reflection coefficient changes and a leaky endothelium develops, as in sepsis. However, larger molecular size is associated with fewer particles per unit volume and, therefore, inferior plasma volume expanding capacity.

For albumin, which has historically been accepted as the gold standard colloid, even though many consider it is not an ideal, the molecule is seen as being slightly larger than the pores in the vascular endothelium. Decreased molecular size, relative to albumin, results in shortened intravascular retention, but many more particles per unit volume and, therefore, a plasma volume expander.

Gelatins

Gelatins are derived from hydrolysis of bovine collagen. Two major forms are the succinylated gelatins (Gelifusine) and urea-linked or polygeline compounds (Haemaccel). They are of relatively low molecular weight, (35kDa) and excretion is via the kidneys.

Gelatins are favoured in the UK because they are relatively inexpensive compared with, for example, human albumin solution. Gelatins tend to be used as a primary resuscitation fluid, because they plasma volume expand, transiently drawing water into the intravascular space, but because of low intravascular retention this is a relatively short term effect and they can not be regarded as a long term plasma substitute.

Side effects of gelatins include anaphylactoid /anaphylactic reactions; the FDA in the USA have never approved gelatins, primarily because of concerns of these reactions in the early trials. Other side effects include varying coagulopathies and effects on fibronectin.

Dextrans

Dextrans are commonly used in some parts of the world as the primary synthetic plasma substitute. They are a bacterial product, derived by fermentation of sucrose by a certain strain of *Leuconostoc* bacteria with subsequent chemical cleavage and fractionation. There are two major forms, Dextran 40 (low molecular weight) and Dextran 70, which is used as a plasma substitute. Dextrans are metabolised by dextranases in the reticuloendothelial cells and excreted via the gut and kidney.

Dextran 40 has low intravascular retention, whereas Dextran 70 has a slightly longer retention than albumin. There are a number of side effects (Box 1), which are the reasons some do not consider them a good plasma substitute, but they have no effects on blood cross-matching.

Starches

Starches are the most commonly used synthetic plasma substitutes in the world and are produced by hydroxyethyl substitution of amylopectin, a D-glucose polymer, derived from maize or potatoes.

The hydroxyethyl starches (HES) are usually referred to by their weight average molecular weight (high,

- *Anaphylaxis / anaphylactoid reactions; these can be avoided by dextran hapten 1 pretreatment, and it has been demonstrated that with this pretreatment, dextrans may be some of the safest fluids*
- *Coagulopathy; however, some use dextrans for deep-vein thrombosis prophylaxis to utilise this effect*
- *Renal dysfunction*

Box 1 Side effects of dextrans

medium or low molecular weight starches), although it is important to note that the low molecular weight starches are still quite high molecular weight compared to, for example, albumin. A high degree of hydroxyethyl substitution in the molecule protects against enzyme breakdown in the body.

The high molecular weight starches (450/0.6), which are now considered old-fashioned (“dinosaur starches”), are still used in the USA and Canada. In Europe, over last decade there has been a trend to using the pentastarches of medium molecular weight (220/0.5) and now there is a move towards a relatively low molecular weight HES (130/0.4).

HES tend to be slightly more expensive than gelatins, but cost considerably less than human albumin, although albumin is free of charge in a number of countries. In

relation to polydispersity, the newest preparations are said to be designed to remove the very small and the very large particles, and are theoretically superior preparations, designed as plasma substitutes with intravascular retention. HES are associated with a number of side effects (Box 2).

- *Anaphylactoid / anaphylactic reactions*
- *Coagulopathy*
- *Renal dysfunction*
- *Tissue deposits and severe itching*

Box 2 Side effects of hydroxyethyl starches (HES)

The clinical significance of the impact of these colloids on coagulation is not known. Bunn *et al* (*The Cochrane Library*, Issue 4, 2000) found no difference in terms of clinically significant outcomes from a survey of the available literature covering 46 trials and 2884 patients. The information on the amount of blood transfused was available in 23 of the trials, however this was reported in a variety of different ways that made combining the data in a meta-analysis unfeasible. The trials were considered of poor quality; only six trials mentioned blinding and only four of the trials included over 100 patients. Thus, larger trials are needed to detect clinically significant differences in mortality.

Fluid composition

The composition of fluids has become a discussion point; so-called normal saline is hyperchloraemic, but RL solution has a lower osmolarity, a lower sodium concentration and more physiological chloride level (Table 1). In the USA and Canada, a high molecular weight HES has been reformulated in something more similar to RL than to normal saline (Hextend®), with a lower chloride content than normal saline and some calcium and magnesium.

Electrolytes (mmol/L)	Normal saline	Ringer's Lactate	Hextend
Na+	154	130	143
K+	0	4	3
Ca++	0	2.7	5
Mg++	0	0	0.9
Cl-	154	109	124
Lactate -	0	28	28

Table 1 Composition of some common fluids

In a Phase III study, Gan *et al*, *Anesth Analg*, 1999, 5, 992–8) have shown that the formulation of colloids can be important. Two groups of patients received exactly the same HES, one formulated in saline, one in Hextend®;

of the 56 of 120 patients who received a red blood cell (RBC) transfusion, there was a statistically significant 1L difference in estimated blood loss (Figure 1).

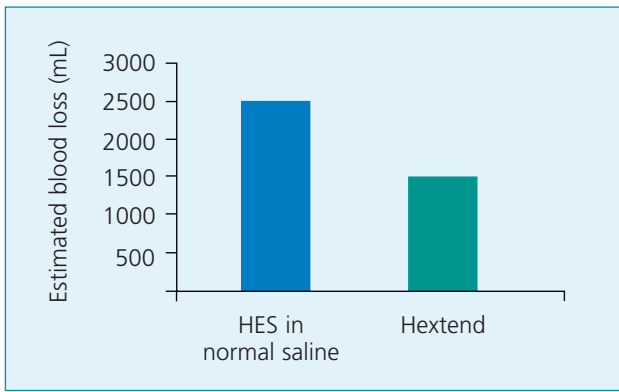


Figure 1 Estimated blood loss in 120 patients requiring red blood cell transfusions

Ex vivo experiments have compared a range of fluids in mixing experiments, diluting volunteers' blood by 60% with, normal saline, RL, high molecular weight starch in saline or in balanced electrolytes, medium molecular weight in balanced

would clot if the electrolytes were kept to normal concentrations.

In summary, Professor Mythen said that all these substances are good fluids and it should be appreciated that they make an important

contribution to the ability to save lives in medicine, whether they are crystalloids or colloids. However:

- They are drugs; they have varying pharmacodynamics and kinetics.
- All have an adverse event profile, including the crystalloids.
- There are no clinically significant differences – depending on the context and the question posed in a study.
- Timing and dosage are possibly more important than which fluid is used.
- The formulation may be more important than the colloid.

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Albumin and respiratory function

Neil Soni (London, UK)

Dr Soni suggested that it was worth reviewing the recent history of albumin. Some 15 years ago, the debate was "colloid versus crystalloid" and for those in favour of colloid, the only substance likely to be used would be albumin; it was the gold standard, it was what should be used and it was considered necessary to use it. Then, over several years it was found that perhaps albumin was not as useful as had previously been considered and the focus shifted to when it would be appropriate to use albumin.

However, evidence based medicine as proposed by the Cochrane Collaboration (*Br Med J*, 1998, 317, 235–40) suggested albumin was dangerous. Only now, with evidence from the SAFE study (page 9) has it been clearly shown that their evidence base was totally inadequate, it should not have been used, the Cochrane collaboration was flawed in their analysis and, in Dr Soni's opinion, the British Medical Journal should never

have published it. Therefore, it has taken 5 years to get back to the position of considering what albumin should be used for, and when.

Properties of albumin

Apart from the biochemical properties of albumin, including potential anti-oxidant and anti-inflammatory properties, albumin has a number of properties related to:

- Binding and transport of certain molecules including drugs,
 - Colloid osmotic pressure,
 - Microvascular integrity,
 - Anticoagulation,
 - Free radical scavenging,
- all of which suggest that there should be a place for albumin in clinical practice.

At one time it was considered that albumin levels should be within a normal range. A distribution analysis of 694 patients on admission to an intensive treatment unit (ITU) showed that more than 95% of these patients had albumin

levels below the lower laboratory limit for the institution. This observation has been made frequently, and so comparing levels on admission to the ITU is not necessarily useful. However, albumin levels fall following ITU admission, as recorded by McCluskey *et al* (*Anaesthesia*, 1996, 81, 724–7), particularly in non-survivors (Figure 2).

Albumin and colloid osmotic pressure (COP)

It is known from Starling's equation that albumin should influence COP, and that it is also known that it does so in normal individuals. A problem,

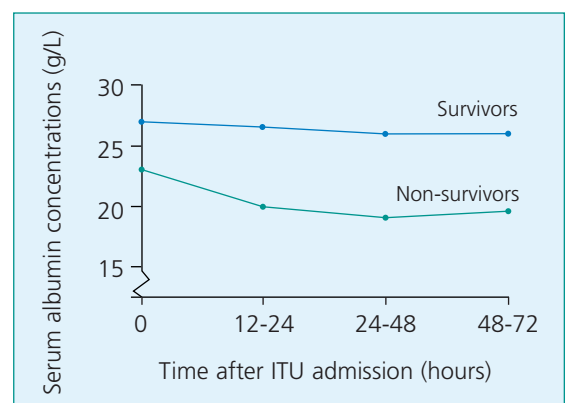


Figure 2 Mean albumin levels during the first 72 hours following admission to ITU in survivors and non-survivors

until relatively recently, was that measurements of serum albumin were flawed in that many laboratory methods did not accurately measure values below 20g/dL. Margaron's work has shown that there is no obvious relationship between albumin

serum levels and COP in septic patients.

Margaron, working with Dr Soni's group in London demonstrated the changes in COP in septic controls compared to controls (Margaron and

Soni, *Brit J Anaesth*, 2004, **92**(6), 821–6). A bolus of 40g albumin, given in 200mL, produced a marked change in COP, but this declined and continued to decline with time. This decline occurred more markedly in septic patients than in controls.

Microvascular integrity

Using ¹²⁵I radiolabelled albumin, Margaron and Soni (*J Appl Physiol*, 2002, **92**, 2139–45) examined whether albumin can actually stabilise membranes and change permeability. Transcapillary escape rates (TER) were measured over a 90-minute baseline period, then a bolus of albumin was given to see if the change in plasma albumin concentration had an impact

on the rate of movement of albumin out of the circulation. Albumin did not appear to influence microvascular permeability in the 12 septic patients studied, in contrast to animal work, which strongly suggested that albumin has an impact on TER.

Hoegerle *et al* (*Nuklearmedizin*, 2001, **40**, 44–50), studying patients with acute lung injury/acute respiratory

distress syndrome (ALI / ARDS), showed that microvascular permeability to albumin correlates with disease severity and has a negative correlation with survival, but there was no correlation between permeability and what are considered to be the sequelae of illness or of fluid movement, such as oxygenation, duration of disease or plasmin/anti-plasmin relationships.

Effects in lung injury

Powers *et al* (*Crit Care Med*, 2003, **31** 2355–63) using albumin in a rodent model in which resuscitated shock primes for increased lung injury in response to a small dose of instilled lipopolysaccharide (LPS), demonstrated changes in transpulmonary flux, bronchoalveolar lavage (BAL) neutrophil movement and histopathological injury. The authors concluded that albumin attenuates lung injury in this rat sepsis model due to reduced neutrophil sequestration and antioxidant effects, and suggested that 25% albumin could be useful as an anti-inflammatory agent in neutrophil-mediated disease

To investigate this theory, a 200mL bolus of 20% albumin, was given to 24 septic patients with monitoring of the cardiovascular system and oxygenation over the following 4 hours. An increase in cardiac index (CI) was seen in the first minutes after bolus injection, which declined over the next 30 minutes and had almost disappeared by 4 hours. This was reflected in the wedge pressure, which increased and then declined as the albumin re-distributed. There was a marginal change in PaO₂ almost immediately that appeared to correlate with the haemodynamics, which then deteriorated and was undetectable after 4 hours.

Kuper (personal communication) attempted to influence COP by giving albumin to rapidly redistribute fluid into the intravascular space and then remove the fluid by diuresis, which might be considered a "last resort" approach. The inspired oxygen ratio was studied in 14 acutely ill patients with ALI, given a bolus of fluid. There was an increase in oxygenation, as measured by PaO₂/FiO₂ after

5 minutes in some patients, but then a return to baseline values at 4 hours. The cardiac output correlated with the changes in PaO₂/FiO₂, increasing rapidly then deteriorating. There were no correlations with central venous pressure (CVP) rise, extravascular lung water, with basal albumin or the albumin rise in albumin levels. Professor Slutsky discussed the effects of more long-term administration of albumin on oxygenation later in the session.

It can be concluded that:

- Albumin levels are a function of illness.
- Permeability is reflection of illness.
- Neutrophil sequestration and antioxidant effects of albumin are observed, but there is no great body of knowledge, nor is it known how this can be applied to clinical practice.
- A short-term effect of albumin on oxygenation has been demonstrated, but this is very short term and seems more haemodynamic than related to any real change in fluid shifts.

In relation to lung injury, the premise for using albumin is as follows:

- If oxygenation is low due to interstitial oedema, permeability allows fluid into the wrong sites. If the COP is low, this gives the potential for manipulation to move the fluid and improve lung function.

The overwhelming conclusion is that there is much that remains unknown of how albumin can best be used in clinical practice. It is time that progress was made in investigating aspects of albumin use in a focussed

way, rather than whether it kills people or not as suggested by the Cochrane Collaboration.

Dr Soni suggested that the lesson learned is that evidence based

medicine used badly is an appalling and dangerous tool, and far more dangerous than albumin.

Albumin may protect the lungs

Arthur S Slutsky (Toronto, Canada)

An animal study and a human study go some way to addressing the issue of whether albumin may protect the lungs.

The factors influencing outcome of acute lung injury following sepsis or blood loss are:

- Initial fluid resuscitation during shock – local and systemic inflammatory patterns are affected by the initiation of the shock itself and there are potential effects of the fluid and the way in which it is given.
- Later mechanical ventilation strategies – lung recovery or further damage.

Many patients who develop shock or sepsis require mechanical ventilation. Over the last few years there have been studies that have demonstrated that mechanical ventilation can cause the type of injury known as biotrauma. This involves release of mediators from the lung that can potentially cause further damage within the lung and also release

cytokines and other mediators into the systemic circulation that can affect organ function.

Selection of an appropriate fluid for use in association with mechanical ventilation requires consideration of their advantages and disadvantages (Table 2).

Preclinical study

The question arises as to whether albumin can protect the lung, by its effect on oncotic pressure, by decreasing interstitial fluid in the lung, and by an anti-inflammatory or antioxidant effect. This provided the hypothesis for an animal study, that albumin resuscitation following septic or haemorrhagic shock may be protective against ventilator-induced acute lung injury.

Zhang *et al* (*Crit Care Med*, 2003, **31**, 1515–22) studied rats with two forms of shock, either endotoxic shock induced by intravenous *Escherichia coli* LPS, or haemorrhagic shock induced over 1 hour by bleeding to a mean arterial pressure (MAP) of 40 mmHg. Plasma cytokines were

measured 1 hour after fluid resuscitation was given with RL solution, 5% albumin or 25% albumin. Animals were sacrificed and their lungs removed and ventilated, *ex vivo* for 2 hours, without perfusion. Bronchoalveolar lavage (BAL) fluid was sampled after 2 hours of ventilation for cytokine measurement. The major study endpoints were:

- Cytokines in plasma and BAL
 - H₂O₂ in plasma and BAL
 - Lung wet/dry weight ratio
- Professor Slutsky presented data only on the haemorrhagic shock study; the endotoxic shock study showed no impact of albumin in that group.

Approximately 12mL of blood was withdrawn from all animals. As expected, the volume of fluids required to achieve a controlled mean blood pressure was significantly smaller in the albumin-treated groups than in the RL-treated animals. Resuscitation was performed to a MAP of approximately 80 mm Hg and was relatively well maintained with all three solutions, with the same findings in the endotoxic shock model.

Examination of BAL after 2 hours of *ex vivo* ventilation following resuscitation showed a significant decrease in tumour necrosis factor (TNF) α , a pro-inflammatory cytokine, in the 25% albumin group and a tendency to a decrease with 5% albumin. There was no change in interleukin (IL)-6 and a fall in macrophage inflammatory protein

	Advantages	Disadvantages
Crystalloids, RL, normal saline	Replace interstitial fluid deficit; volume expansion	75–90% will lodge in the extravascular compartments → oedema
Synthetic colloids	Maintain fluid intravascularly	Coagulation disorders, allergies
Albumin	Maintain fluid intravascularly, anticoagulant, antioxidant*/drug binding */ biochemical properties * – clinical relevance unknown	Cost

Table 2 Advantages and disadvantages of resuscitation fluids

(MIP)-2, in the albumin groups and an increase in IL-10, an anti-inflammatory cytokine, in these groups. At the end of the resuscitation period, and a delay of 1 hour, there were decreases in plasma TNF, IL-6 and MIP-2 and increases in IL-10 in plasma of albumin-treated animals. These data suggest that the type of fluid can have an impact on cytokines released both into the circulation and then subsequently on BAL, although the levels in BAL prior to mechanical ventilation were not known.

There were significant decreases in plasma hydrogen peroxide (H_2O_2) and BAL H_2O_2 (Figure 3) in the animals with haemorrhagic shock in both albumin groups, but no change in endotoxin group. There were small but significant decreases in lung wet/dry weight ratios, associated with both albumin solutions, suggesting the lungs were dryer.

These data suggest that albumin at 5% and 25% could have an impact on various aspects of inflammatory responses in the lung and could have

an impact on lung wet/dry weight ratio; therefore, albumin might be beneficial in haemorrhagic shock, but not in endotoxic shock.

Clinical evidence

Martin *et al* (*Crit Care Med*, 2002, 30, 2175–82) addressed the question of whether diuresis and colloid replacement in hypoproteinaemic patients with ALI would improve pulmonary physiology in a prospective, double-blind, placebo-controlled study. Thirty-seven patients, with ALI and total protein ≤ 5.0 g/dL were randomised to 25g albumin every 8 hours with a continuous infusion of furosemide, or dual placebo with the treatment targeted to diuresis, weight loss, total protein.

In the group treated with albumin, there was increase in total protein that levelled off at approximately

6g/dL (Figure 4). The study protocol required that, once the protein levels exceeded 6g/dL, albumin infusions were stopped. In the placebo there was a much slower increase in total protein levels.

Significant weight losses were achieved. Over the 5 days of treatment, albumin-treated patients lost approximately 10kg of body weight compared with slightly over 4kg in the placebo group. Treatment was not associated with

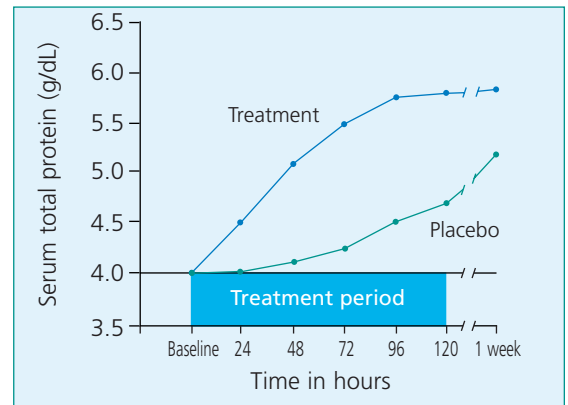


Figure 4 Serum total protein in ALI patients treated with albumin/furosemide or placebo for 5 days

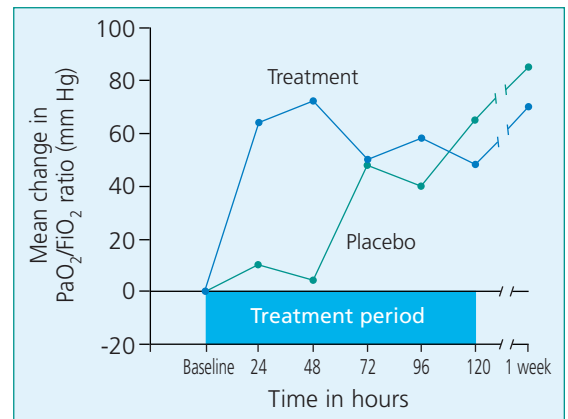


Figure 5 Change in PaO_2/FiO_2 ratio in ALI patients receiving albumin/furosemide or RL

major problems in terms of haemodynamics in the albumin group. Over the 5-day study period there was essentially no change in MAP in the placebo group, but there appeared to be an increase in MAP in patients who received albumin and furosemide that was statistically significant only at the end of 5 days.

There was a major change in the PaO_2/FiO_2 ratio in the first 48 hours in the albumin group, but after 3 days there was essentially no difference between the placebo and the treatment group (Figure 5). Therefore, this regimen could improve oxygenation.

Although the study was not powered to assess clinical outcomes, there was no difference in mortality in the two groups. There was little difference in terms of the number of patients requiring mechanical ventilation, but the active treatment group had a

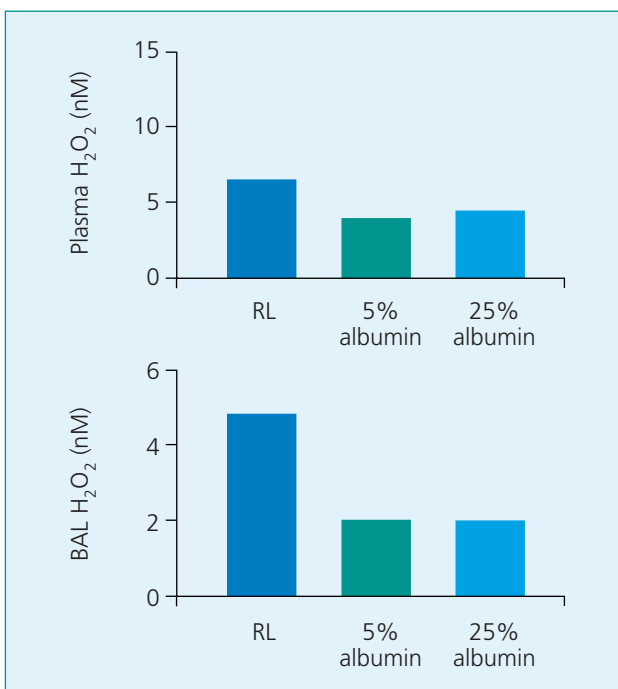


Figure 3 Plasma and BAL hydrogen peroxide (H_2O_2) concentrations in a rodent model of haemorrhagic shock after fluid resuscitation with Ringer's Lactate (RL), 5% albumin or 25% albumin

median of 5.5 more ventilator-free days than the placebo group. This was not statistically significant, but was a strong tendency and similarly there was a tendency toward improvement in length of ICU stay in actively treated patients.

Conclusions

- Animal studies suggest some improvement in ventilator-induced injury with albumin resuscitation in the haemorrhagic shock model, but not in an endotoxin model.

- There is evidence of some beneficial effect on lung function in hypoproteinaemic ALI patients, especially in the first 48 hours although the improvement in oxygenation did not persist to the fifth day of study.
- There was a suggestion of increase in ventilator-free days in the albumin-treated group, which would be an important clinical endpoint.

- Utility of albumin in this context will be determined from large randomised clinical trials (RCTs).

Professor Slutsky said that he did not consider that either of these studies should affect the immediate treatment of patients in the ICU. Large RCT results will inform that decision, but these data suggest trials that can be done.

The SAFE study

Simon Finfer (Sydney, Australia)

Dr Finfer presented the results of the Saline versus Albumin Fluid Evaluation (SAFE) study, speaking on behalf of the collaborators in the study conducted by the Australia and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group, The Australian Red Cross Blood Service and the George Institute for International Health University of Sydney, Australia.

Background

Fluid resuscitation is the cornerstone of intensive care practice, although whether the choice of fluid influences mortality is unknown. There have been no adequately powered trials concerning this issue and current best evidence is from meta-analyses. Important amongst these is that published by the Cochrane group in the British Medical Journal in 1998 (327, 235–40), which covered 24 studies and a total of 1419 patients and limited the indications for albumin to hypovolaemia, hypoalbuminaemia and burns. The meta-analysis concluded there was an increased relative risk of death associated with albumin in each of those groups with an overall excess

mortality of 6%. The studies used any albumin containing-fluid, some of the studies were very old and some used plasma protein fraction, so essentially a number of different drugs were compared in different populations. The accompanying editorial in the British Medical Journal suggested that the use of albumin should be halted outside of large controlled trials.

A subsequent meta-analysis by Wilkes and Navickis (*Ann Intern Med*, 2001, 135, 149–64) included 55 trials and a total of 3504 patients; the analysis placed no restriction on the clinical indication for albumin and, therefore the trials were not restricted to those of critically ill patients. This second analysis concluded there was no difference in mortality associated with the use of albumin.

These two conflicting findings left clinicians with substantial uncertainty concerning the role and safety of albumin in the critically ill. As a result, the saline versus albumin fluid (SAFE) evaluation was undertaken with the objective:

- To compare the effects of two resuscitation fluids (4% albumin and saline) on 28-day all-cause

mortality in ICU patients requiring intravascular volume resuscitation, with the hypothesis that there would be no difference in mortality at 28 days.

The study was funded predominantly by government money, in the form of peer-reviewed grants from the Australian National Health and Medical Research Council, the Health Research Council of New Zealand and by direct grants from all Australian States and Territories and from some New Zealand Hospitals. There was only one commercial funder, CSL Ltd, a publicly listed company that fractionates blood and supplies blood products in Australia, New Zealand and in other countries. No funding bodies had any say in the design of the study, they had no role in data collection or analysis, and they have had no role in deciding on the publication and presentation process.

Study design

The study was a multicentre, randomised, concealed, stratified, double-blind, controlled trial, conducted in 7000 patients in 16 ICUs in Australia and New Zealand over 18 months. This number of patients was calculated to be sufficient to provide

90% power to detect a 3% difference in absolute mortality from an estimated baseline mortality of 15%. The study was approved by the independent ethics committees of the University of Sydney and each of the participating institutions.

The SAFE study was totally a web-based study. All randomisation, data collection, query collection and real-time query resolution was handled through a password-protected encrypted website. In addition, the fluid distribution was handled through the website.

Patient eligibility

The main inclusion criteria were:

- In the opinion of the treating clinician, the patient had a need for intravascular fluid resuscitation.
- The treating doctor had substantial uncertainty over which was the best fluid to administer to that patient.
- No absolute indication or contra-indication for either albumin or saline existed.
- Informed consent given, if competent, or otherwise delayed consent was allowed.

The main exclusion criteria were:

- Age less than 18 years.
- Patients admitted to the ICU with burns.
- Patients admitted to the ICU following cardiac surgery or liver transplantation surgery.
- Patients with allergy or religious objection to albumin (as a blood-derived product).
- Patients moribund and expected to die.

The pre-defined patient subgroups were those patients admitted to the ICU for treatment of trauma, and those fulfilling the criteria of severe

sepsis or ARDS at the time of randomisation.

Blinding procedures

The study treatments in the form of 4% albumin (as Albumex) or saline were manufactured by CSL Ltd at their plant in Australia. The study was blinded by the use of specially designed and manufactured materials. Both treatments were filled into standard 500mL glass bottles, which were then sealed within a carton. A yellow opaque window on both sides of the container allowed the clinicians administering the fluid to see the level of the fluid, but they could not tell whether it was albumin or saline. The fluid was administered via a green giving set, which also prevented the clinicians distinguishing the fluid; any parts of the giving set where it might have been possible to see the frothing within the fluid, were obscured with black plastic material. This blinding system was tested in a formal study prior to initiating the trial and was found to be successful in concealing the nature of the resuscitation fluid.

Four of these bottles were packaged into a cardboard container, such that the initial request and any subsequent request to the website to obtain resuscitation fluid for a patient, supplied 2 L of fluid. These were then sealed into a further cardboard box, each identified by a unique six-digit code which allowed the website to track the box. Thus, it was possible to ensure that the fluids were being distributed in a timely fashion within the ICU and the patient received the same fluid type throughout their ICU stay.

Patient randomisation was carried out centrally, via the website, using a minimisation algorithm. The treatment assignment was concealed both

before and after randomisation. Randomisation was stratified by treating institution and by the diagnosis of trauma.

Treatment

- The treating physicians decided both the amount and the rate of fluid administration according to each patient's clinical status and response to treatment.
- The allocated study treatment was used for all fluid resuscitation in the ICU, until death or discharge or 28 days following randomisation.
- Patients who were re-admitted to the ICU within the 28-day study period, continued to receive the fluid to which they were assigned by the initial randomisation. Use of any other fluid in this time precluded entry of that patient into the study.
- Administration of intravenous fluids outside the ICU was not controlled.
- Central venous pressure monitoring, pulmonary artery catheterisation and all other aspects of patient care were performed at the discretion of the treating clinicians.

Outcome measures and interim analyses

The primary outcome measures are summarised in Box 3. Two interim analyses were pre-planned, carried

Primary outcome measure

- *Death from all causes at 28 days following randomisation*

Secondary outcome measures

- *Survival time during the first 28 days*
- *Proportion of patients with new organ failures*
- *Duration of mechanical ventilation*
- *Duration of renal replacement therapy*
- *Duration of ICU and hospital stay*

Box 3 Outcome measures in the SAFE study

out by an independent statistician, following recruitment of 2333 (33%) and 4666 (67%) patients. These analyses were reviewed by the independent data monitoring committee, chaired by Professor Sir Richard Peto. On both occasions the committee said the trial should continue.

Results

As planned, 7000 patients were randomised. In error, three patients were randomised twice within the 28-day study period; they received the fluid they were allocated by their first randomisation and were analysed only in the group in which they were first randomised. Therefore, data from 6997 patients were analysed.

There was a 0.7% loss to follow up in albumin group and 1.1% loss to follow up in saline group. The majority of these were due to refusal or withdrawal of consent. Primary outcome measures could, therefore, be analysed in 99.3% of patients in the albumin group and in 98.9% of patients in the saline group.

The patient groups were well matched at baseline, for age, gender and for reason for admission to ICU. Patients were also well matched for physiological variables, in relation to the need for fluid resuscitation, cardiovascular status (heart rate, mean arterial pressure, central venous pressure), urine output and baseline serum albumin levels. Comparable percentages of patients in both groups were receiving mechanical ventilation and renal replacement

therapy. Just under 4% of patients in both groups and received albumin in the 72 hours prior to randomisation.

Volumes of study fluid administered

In the albumin group on day 1 just under 1200mL was administered and on day 2,600mL. As expected during the first 4 days of the study, more study fluid was administered to the patients who were assigned to saline. Overall the ratio of albumin to saline in these first 4 days was 1L albumin to 1.38L of saline. The mean difference per randomised patient for the first 4 days was 749mL. There was an increase in the mean volume of packed RBC administered to patients assigned albumin. The mean difference per randomised patient for the first 4 days was 71.0mL.

Overall, over the first 4 days, the patients assigned to saline had a greater mean net daily positive fluid balance. The mean difference per randomised patient over the first four days was 956mL.

Markers of response to resuscitation

- At baseline, MAP was essentially identical in the two groups, remained so through the first four days of the study and thereafter.
- The heart rate was very similar at baseline; albumin patients had a slightly lower heart rate on day 1, but the difference resolved during the next 4 days.
- At baseline there was a 0.4mm Hg difference in CVP between the two groups, the higher value in the albumin group, and this difference

increased over the following days. On the first 2 days of the study the mean difference was 1.2mmHg, subsequently 0.77 and 0.6mm Hg ($P < 0.001$ for all differences). In an individual patient, such a difference probably means little, but does represent difference of approximately 10%. For those who take a broad view in blood pressure research, this may be important.

- The serum albumin concentration increased in the group assigned to albumin and was significantly different to those assigned saline.

Primary outcome measurement

There were 726 deaths in the patients assigned to albumin, a mortality rate of 20.9%, and 729 deaths in the saline patients, a mortality rate of 21.1%. The absolute difference for albumin versus saline was a -0.17% difference in mortality (95% confidence interval [CI] -2.08 to $+1.75\%$).

- The relative risk (RR) of death in patients assigned to albumin was 0.99 ($P = 0.87$).
- The Kaplan Meier curves for all cause mortality, albumin versus saline, are essentially identical for the two groups, showing that there was no difference in mortality and no difference in the time to death in those who died.

Secondary outcomes

There were no differences in the days of mechanical ventilation or days of renal replacement therapy between the two groups (Table 3)

There was no difference between the two groups in the percentages of patients developing new single or multiple organ failures.

	Albumin	Saline	P
Days of mechanical ventilation	4.5±6.1	4.3±5.7	0.74
Days of renal replacement therapy	0.48±2.28	0.39±2.0	0.41

Table 3 Days of supportive therapy in ICU patients assigned to albumin or saline (mean ± SD)

Relative risks (RR) of death in patient subgroups according to fluid assignment

Patients with trauma

Table 4 summarises mortality rates in patients with and without trauma. The RR of death for patients with trauma assigned to albumin versus saline was 1.36 (95% CI, 0.99–1.86, $P=0.55$) and without trauma, 0.96 (95% CI, 0.88–1.06).

Patients with sepsis

Despite the opinion that colloids should not be given in the first 48–72 hours to patients with sepsis or capillary leak-inducing syndrome, in this study albumin was given to those assigned albumin from the moment they entered ICU and for their entire time in the ICU. Mortality in patients with and without sepsis is summarised in Table 5. The RR for death in patients with sepsis assigned to albumin versus saline was 0.87 (95% CI, 0.74–1.02). Although the CI spans unity, and the P value is >0.05 , there is no evidence of harm associated with albumin. In patients without sepsis, the RR for death, albumin versus saline, was 1.05, with a wider 95% CI, 0.94–1.17.

Patients with ARDS

In patients with ARDS, the RR of death for patients assigned albumin versus saline was 0.93 (95% CI, 0.61–1.41) and for those without ARDS, 1.00 (95% CI 0.91–1.01).

Discussion of subgroup findings

The study was originally powered to answer the question whether there was, overall, a 3% or greater increase in mortality associated with albumin use. It was not powered to look at the subgroups. However, this is, in effect, a 1200 patient study of albumin versus saline in patients with severe

	Albumin	Saline
Mortality in patients with trauma	81/596 (13.6%)	59/590 (10%)
Mortality in patients without trauma	641/2831 (22.64%)	656/2830 (23.18%)
Mortality in patients with trauma and TBI	59/240 (24.58%)	38/252 (15.07%)
Mortality in patients with trauma but no TBI	22/356 (6.17%)	21/338 (6.21%)

Table 4 Mortality in patients with and without trauma, and with trauma with and without traumatic brain injury (TBI) in relation to assigned fluid

	Albumin	Saline
Mortality in patients with severe sepsis	185/603 (30.67%)	217/615 (35.28%)
Mortality in patients without severe sepsis	518/2734 (18.94%)	492/2720 (18.08%)

Table 5 Mortality in patients with and without severe sepsis in relation to assigned fluid

sepsis, larger than any other study in severe sepsis, and therefore provides the best evidence so far and merits further investigation.

The George Institute has considerable experience in conducting very large clinical trials and, with regard to the implications of the study results concerning the effects of albumin in patients with trauma or sepsis, the study collaborators there advised that the important thing was not to look at albumin versus saline in these groups, but to compare the treatment effects in patients with and without trauma and with and without sepsis, using a test for common relative risk.

The RR of death in patients with trauma assigned albumin versus saline is 1.36 and without trauma is 0.96. The P value for the test of common relative risk for the comparison between these values is 0.039.

The mortality in patients with and without trauma is summarised in Table 4, where it can be seen that the excess of 22 deaths in trauma patients assigned to albumin occurred in patients with trauma and brain injury. In patients with trauma, without brain injury, mortality rate was approximately 6.2% in both groups.

This finding conflicts with Choi *et al's* meta-analysis (*Crit Care Med*, 1999, 27, 200–10), which reported that colloids were worse for patients who had trauma. That meta-analysis considered five studies of patients with trauma and a total number of patients that generated the recommendation cautioning against the use of colloids was 302. In this study including approaching 700 patients with trauma but no TBI, there is no evidence of a different outcome.

There are a number of caveats in interpretation the differences in mortality in patients with trauma and brain injury (Table 4). This is a subgroup of a subgroup and there are not sufficient data on the baseline balance between the two groups to draw firm conclusions. The SAFE study was conducted as a large-scale pragmatic trial and it cannot yet be said that, in terms of all the factors pertaining to TBI patients, that there was a balance at baseline. Furthermore, 28-day all-cause mortality is the wrong outcome for assessing treatment effects in patients with TBI. Neurological recovery at least 6 months post-injury is much more appropriate as an endpoint. A follow-up analysis (SAFE-Brains), collecting and collating additional

baseline data and following all the patients by doing an extended Glasgow Outcome Score at 2 years post-randomisation is in progress.

For patients with severe sepsis versus those without severe sepsis (Table 5), the P value for the comparison of treatment effects (common relative risk) is 0.059. The difference between these two groups is just less than 5% (albumin versus saline in patients with severe sepsis), which may be an important clinical difference in a sepsis population, but it is necessary to determine whether this is a real difference or just a chance finding. However, there is a biological rationale for thinking that this is not a chance finding.

Conclusions

The conclusions of this major study are summarised in Box 4. As the collaborative group has a strict policy that public statements concerning the results of this or any of their other trials are made only when they are at publication standard, Dr Finfer would not discuss the impact of baseline albumin levels on outcome.

During the questions and discussion following his presentation, Dr Finfer made the following additional points:

The collaborators had wanted to include a synthetic colloid arm in the SAFE study, but there is no available starch in Australia, although there is in New Zealand. In Australia, the available fluids are dextrans, gelatin, albumin, which is supplied free to the hospitals, and crystalloids. Dextrans are clearly not something that could be used in such a study, and 40% of the hospitals involved in the study have banned use of gelatins. It would be valuable to collaborate with physicians in the rest of the world

who are able to look at a synthetic colloid.

Referring to the findings in trauma patients with TBI, there are data on cause of death for the 1400 deaths in the study. Assuming the follow-up study found identical baseline balances and the later mortality was still significantly different, if the cause of death in a proportion of those 1400 patients was refractory cranial hypertension, and there is no evidence anywhere in the literature to suggest benefit from the administration of albumin, then there would be enormous difficulty in executing such a follow-up study.

Although the analysis concerning patients with head injuries would take some time, Dr Finfer said he was finding it hard to advocate the use of albumin for any brain injury and he would not be prescribing it for TBI patients.

This trial was designed to determine whether albumin is safe and has done so. It has not been proven that, in a large heterogeneous population of patients given either all albumin or all saline, one or other is the better treatment. In such a population, there will be patients for whom albumin

would be beneficial and possibly patients for whom it is deleterious. One study never answers all the questions.

The SAFE study was performed successfully because it was designed as a large, pragmatic trial with limited data collection. Importantly, it was investigator-initiated, run and owned. All those people involved in the trial felt they were doing the trial for themselves rather than for someone else. There is a policy, which is strictly adhered to, of group authorship within the group, and large trials will only be published under the group name without any specific authors under the title of the paper.

The study shows that such a large-scale trial can be undertaken successfully in intensive care patients and possibly should be a model for future studies.

- *In a heterogeneous population of ICU patients, albumin is safe when given for all resuscitation in the ICU. The study measured mortality only to 28 days, but the Kaplan-Meier curve would indicate that any later effects would be unlikely.*
- *Use of either albumin or saline solution results in similar mortality, similar time to death in those who died, similar use of mechanical ventilation and renal replacement therapy, similar incidence of new organ failures and similar ICU and hospital length of stay.*
- *The safety of albumin in patients with trauma and brain injury is not established by the study.*
- *There is a possibility of benefit of albumin in patients with severe sepsis, but this must be investigated by an appropriately designed and powered study.*

Box 4 Conclusions of the SAFE study

Still a place for albumin?

Jean-Louis Vincent (Brussels, Belgium)

The SOAP study

During two weeks of May 2002, the purely observational Sepsis Occurrence in the Acutely ill Patient (SOAP) study recorded data from 3147 patients admitted to 198 centres. In the subsequent analysis, it has been noted that albumin was given to about 11% of patients, but with a wide international variation from 0% of patients in Finland to more than 20% in Greece. Albumin is more commonly used in Southern Europe and Belgium than other European countries.

Mortality was higher in patients receiving albumin, but they were also sicker, as reflected in their higher SAPS II scores (median 39, range 29–54 compared to 33, range 24–45 in non-albumin recipients). So there is no real surprise that albumin patients had lower survival rates than those that did not receive albumin. Multivariate logistic regression analysis, taking into account a number of variables in the study, showed albumin administration was one of a number of factors that may be associated with a worse outcome. Performing a propensity matched analysis, identifying 343 patients in each group who were well matched for baseline severity of disease and a number of other factors, the mortality curves separate after about 1 week. Observational studies, multivariate analysis and propensity matched analyses have their limitations, but nevertheless, the question arises whether albumin safe, in ICU patients. The ANZICS SAFE study, in 7000 patients, has now provided the answer.

Why would albumin be unsafe?

If albumin were unsafe, why would that be so? Discussion of the Cochrane Collaboration meta-analysis (*Br Med J*, 1998, **327**, 235–40) raised the following arguments:

- Perhaps, by remaining more in the intravascular space the albumin molecule may further increase plasma volume and result in more pulmonary oedema.
- Albumin may alter myocardial contractility by decreasing calcium availability.
- Albumin may leak from the intravascular into the interstitial space and thereby worsen interstitial oedema.
- There may be an increase blood losses, impaired water and sodium excretion and altered immune response.

None of these arguments is convincing and it is not known why albumin administration might be deleterious.

Why use albumin?

Why should albumin be used if it is relatively expensive? Further insight is needed into the possible benefits of correction of hypoalbuminaemia. The Starling equation for water passage through the microvasculature relates filtration to permeability and driving pressure and explains why greater volumes of crystalloids than colloids are necessary to achieve the same resuscitation endpoints. Oedema may result from administration of crystalloids and occur throughout the body, leading to:

- Impaired gas exchange due to oedema in the lungs
- Limited oxygen availability
- Impaired wound healing
- Gut dysfunction due to oedema,

limiting possibilities for feeding the patient

- Myocardial dysfunction due heart oedema
- Cutaneous lesions
- Decubitous ulcers

No one has proven that giving colloids rather than crystalloids may avoid all these problems. Artificial colloids may achieve the same goals, while being cheaper, but are limitations to their use so that, in practice, many physicians still give their patients some albumin, some gelatin, some HES solutions and crystalloids.

Hypoalbuminaemia

Albumin is not only a natural product, it has carrying properties, antioxidant properties, good tolerance and can be easily monitored. Hypoalbuminaemia is associated with a number of unwanted consequences (Box 5).

- *Increased mortality rates*
- *Prolonged length of ICU stay*
- *Increased rates of readmission*
- *Anergy – pro inflammatory response*
- *Low T3 response*
- *Immobilization*
- *Diarrhoea*

Box 5 Adverse events associated with hypoalbuminaemia

Professor Vincent and colleagues (*Ann Surg*, 2003, **237**, 319–34) performed a meta-analysis of cohort studies and controlled trials reporting hypoalbuminaemia in acute illness. Data from more than 171,000 patients in 66 studies, including hospitalised patients in general, cardiac surgery, non-cardiac surgery or renal dysfunction, showed that in hypoalbuminaemic patients mortality

is increased globally by a factor greater than 2 and morbidity is increased by a factor of 1.78.

Other studies have shown hypoalbuminaemia is associated with length of hospital stay, with prolonged hospital stay and with resource utilisation. Djoussé *et al* (*Circulation*, 2002, **106**, 2919–24) in the Framingham Offspring Study found that hypoalbuminaemia increases the risk of myocardial infarction in the general population. Hypoalbuminaemia is also associated with greater degree of diastolic heart failure (Arques *et al*, *J Am Coll Cardiol*, 2003, **42**, 712–6), which would be logical as this condition is a consequence of oedema within the myocardium. Cancer specialists have found worse outcomes in hypoalbuminaemic patients with breast cancer.

Association does not imply a cause and effect relationship, but it is difficult to understand why hypoalbuminaemia would be advantageous. Hypoalbuminaemia can only result from decreased synthesis associated with re-prioritisation and increased production of acute phase reactants in the liver, gastrointestinal losses, renal losses, cutaneous losses and leaky capillaries in inflammation. Although some have suggested that hypoalbuminaemia is protective, none of these elements would be protective. Professor Vincent considers that hypoalbuminaemia may develop particularly in those patients have prolonged disease states. Evolution has not equipped us for prolonged illnesses; in nature the animal either dies fairly rapidly or recovers fairly rapidly

Very little is known about the possible implications of hypoalbuminaemia in

terms of pharmacokinetics of various agents including antibiotics.

Properties of albumin – preclinical studies

Apart from maintaining colloid osmotic pressure, some other properties of albumin had been discussed during the course of the Symposium session. The antioxidant potential of albumin and the influence on plasma free thiol levels has been described by Quinlan *et al* (*Clin Sci*, 1998, **95**, 459–65), but Lang *et al* (*Anesthesiology*, 2004, **100**, 51–8), using bovine aortic endothelial cells, showed that albumin may have antioxidant properties by mechanisms not related to thiols, including neutrophil binding or neutrophil-derived myeloperoxidase binding.

Anti-inflammatory effects of albumin have been investigated in studies by Horstick *et al* (*Shock*, 2001, **16**, 9–14). Intravital microscopy showed that administration of albumin could reduce the number of rolling leucocytes and adherent leucocytes in rat mesentery. Zhang and Frei (*Cardiovasc Res*, 2002, **55**, 820–9) showed a decreased expression of adhesion molecules in human aortic endothelial cells. Zhang *et al* (*Crit Care Med*, 2003, **31**, 1515–22) showed the antioxidant effects of albumin in a model of haemorrhagic shock. Platelet aggregation may be enhanced in the presence of hypoalbuminaemia and albumin may also have some anti-platelet and some anti-coagulant effects. Neurologists are also interested in the effects of albumin on stroke. Belayev *et al* (*Stroke*, 2001, **32**, 553–60) found a marked neuroprotective effect in a rodent model of stroke (middle cerebral artery occlusion in rats) even when albumin treatment was delayed up to 4 hours after the onset of ischaemia.

Compared with control vehicle-treated animals, albumin-treated animals showed:

- Much smaller infarction volume
- Dramatic reduction in brain swelling
- Improved neurological function after 24, 48 and 72 hours

Properties of albumin – clinical studies

There are clinical data to support these pre-clinical studies of albumin properties. Albumin administration may reduce mortality after coronary artery bypass graft (CABG) surgery. Discharge data from the Solucient Clinical Pathways Database, covering over 19,000 patients who had undergone CABG surgery, showed a lower incidence of mortality associated with albumin use (2.5%) compared with synthetic colloids (3%), equating to five lives saved for every 1000 patients (Sedrakyan *et al*, *Chest*, 2003, **123**, 1853–7). This was just an observational study, but the Odds Ratio for mortality associated with albumin was 0.8.

In the gastroenterology literature there are data showing that albumin administration in patients with ascites may limit the need for re-hospitalisation. In hepatorenal syndrome, albumin administration together with vasopressin derivatives (terlipressin) may improve renal function (Ortega *et al*, *Hepatology*, 2002, **36**, 941–8). In the transplant literature there is evidence that decreasing the oedema of the organs transplanted, by use of albumin, may have a beneficial effect.

These findings only emphasise how many questions remain to be answered about the consequences of hypoalbuminaemia and the possible benefits of albumin administration.

Perhaps the time will come when albumin is regarded not so much as a routine fluid solution, but as a valuable therapeutic substance.

Whilst working with Professor Vincent at the Erasmus University Hospital in Brussels, Marc-Jacques Dubois headed an investigation of albumin administration in hypoalbuminaemic critically ill patients in prospective, controlled, randomised pilot study. This study will shortly be submitted for publication.

Of the 1985 patients admitted to the ICU between March and December 2001, 100 were eligible for inclusion. Half received 300mL albumin 20% on first day and 200mL albumin 20% on the following days provided albumin levels were less than 3.1g/dL. Control patients received no albumin. The primary outcome measure was the effect on organ function as judged by the sequential organ function assessment (SOFA) scores on day 1 to day 7.

There was a greater reduction in SOFA scores in patients receiving albumin ($P=0.039$) and there was evidence from other findings that the gut of albumin recipients was somewhat less oedematous and enteral nutrition was better tolerated. This was a pilot study; Professor Vincent would like to conduct a larger, multicentre trial, but as yet lacks the financial resources to do so.

In summary:

- Albumin has many physiological properties.
- Hypoalbuminaemia is associated with higher morbidity and mortality rates.
- There is no evidence that hypoalbuminaemia is protective in any way.
- There is no place for *routine* administration of albumin in hypovolaemic states in ICU patients requiring volume administration in the broad sense.

- There is a good rationale for correction of hypoalbuminaemia in critically ill patients.
- There is a need for prospective randomised clinical trials to evaluate the effects on outcome of the correction of hypoalbuminaemia.

It is costly to correct hypoalbuminaemia, but there may be a benefit for acutely ill patients. Acutely ill patients tend to develop substantial oedema, which is also associated with substantial costs, so albumin administration should not be discarded too rapidly on the basis of price. Further studies are needed; the results of the SAFE study give a great deal of information, but there are still questions that remain unanswered.

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