Human albumin solution for resuscitation and volume expansion in critically ill patients (Review)

The Albumin Reviewers (Alderson P, Bunn F, Lefebvre C, Li Wan Po A, Li L, Roberts I, Schierhout G)

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[Intervention Review]

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ABSTRACT

Background

Human albumin solutions are used in a range of medical and surgical problems. Licensed indications are the emergency treatment of shock and other conditions where restoration of blood volume is urgent, burns, and hypoproteinaemia. Human albumin solutions are more expensive than other colloids and crystalloids.

Objectives

To quantify the effect on mortality of human albumin and plasma protein fraction (PPF) administration in the management of critically ill patients.

Search strategy

We searched the Cochrane Injuries Group trials register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and BIDS Index to Scientific and Technical Proceedings. Reference lists of trials and review articles were checked, and authors of identified trials were contacted. The search was last updated in November 2002.

Selection criteria

Randomised controlled trials comparing albumin/PPF with no albumin/PPF, or with a crystalloid solution, in critically ill patients with hypovolaemia, burns or hypoalbuminaemia.

Data collection and analysis

We collected data on the participants, albumin solution used, mortality at the end of follow up, and quality of allocation concealment. Analysis was stratified according to patient type.

Main results

We found 31 trials meeting the inclusion criteria and reporting death as an outcome. There were 177 deaths among 1519 trial participants.

For each patient category the risk of death in the albumin treated group was higher than in the comparison group. For hypovolaemia the relative risk of death following albumin administration was 1.46 (95% confidence interval 0.97 to 2.22), for burns the relative risk was 2.40 (1.11 to 5.19), and for hypoalbuminaemia the relative risk was 1.38 (0.94 to 2.03). The pooled relative risk of death with albumin administration was 1.52 (1.17 to 1.99). Overall, the risk of death in patients receiving albumin was 14% compared to 9% in the control groups, an increase in the risk of death of 5% (2% to 8%). These data suggest that for every 20 critically ill patients treated with albumin there is one additional death.

Reviewers' conclusions

There is no evidence that albumin administration reduces the risk of death in critically ill patients with hypovolaemia, burns or hypoalbuminaemia, and a strong suggestion that it may increase the risk of death. These data suggest that the use of human albumin in critically ill patients should be urgently reviewed and that it should not be used outside the context of a rigorously conducted randomised controlled trial.

PLAIN LANGUAGE SUMMARY

Synopsis

No evidence that giving human albumin to replace lost blood in critically ill or injured people improves survival, and some evidence it may do harm

Trauma, burns or surgery can cause people to lose large amounts of blood. Fluid replacement, giving fluids intravenously (into a vein), is used to help restore blood volume and reduce the risk of dying. Blood products (including human albumin), non-blood products or combinations can be used. The review of trials found no evidence that albumin reduces the risk of dying. Further, there is evidence that albumin may increase the risk of death in people who are critically ill.

BACKGROUND

In patients with acute and chronic illness, serum albumin concentration is inversely related to mortality risk. A systematic review of cohort studies meeting specified criteria estimated that, for each 2.5 g/L decrement in serum albumin concentration, the risk of death increases by between 24% and 56% (Goldwasser 1997). The association persists after adjusting for other known risk factors and pre-existing illness, suggesting a direct protective effect of the albumin molecule (Goldwasser 1997). Largely as a result of these observations, human albumin solutions are now used in the management of a diverse range of medical and surgical problems. Published indications for human albumin solution include the emergency treatment of shock and other conditions where restoration of blood volume is urgent, the acute management of burns, and clinical situations associated with hypoproteinaemia (ABPI 1998).

In comparison with other colloidal solutions and with crystalloid solutions, human albumin solutions are expensive (McClelland 1990). Volume for volume human albumin solution is twice as expensive as hydroxyethyl starch, and over thirty times more expensive than crystalloid solutions such as sodium chloride or Ringer's lactate. Because of the high cost and limited availability of human albumin, it is particularly important that its use should be restricted to the indications for which it has shown to be effective. To assess the effectiveness and safety of human albumin solutions in the management of critically ill patients, particularly those with hypovolaemia from injury or surgery, burns and hypoproteinaemia, a systematic review of randomised controlled trials was conducted.

OBJECTIVES

To quantify the effect on mortality of human albumin administration in the management of critically ill patients.

RESULTS

In each of the patient categories the risk of death in the albumin treated group was higher than in the comparison group. For hypovolaemia the relative risk of death following albumin administration was 1.46 (95% confidence interval 0.97, 2.22), for burns the relative risk was 2.40 (1.11, 5.19), and for hypoalbuminaemia the relative risk was 1.38 (0.94, 2.03). There was no substantial heterogeneity between the trials in the various categories (chi-square = 17.74, df = 24, p =/>0.2). The pooled relative risk of death with albumin administration was 1.52 (1.17, 1.99). Overall, the risk of death in patients receiving albumin was 14% and the risk of death in patients not receiving albumin was 9%. When the analyses were repeated using a random effects model, the pooled relative risk with albumin administration was 1.35 (1.04, 1.76).

The analyses were repeated, including only the 13 trials with deaths in at least one arm in which allocation concealment involved a method that would be expected to reduce the risk of foreknowledge

of treatment allocation (pharmacy controlled randomisation or serially numbered sealed opaque envelopes). For hypovolaemia the relative risk of death with albumin administration was 1.39 (0.80, 2.40), for burns the relative risk was 2.47 (0.69, 8.79), and for hypoalbuminaemia the relative risk was 1.71 (0.92, 3.18). There was no substantial heterogeneity between the trials in the various categories (chi-square = 2.40, df = 12, p =/>0.2) and the pooled relative risk of death with albumin administration was 1.61 (1.09, 2.38).

DISCUSSION

There is no evidence that albumin reduces mortality and a strong suggestion that it may increase the risk of death in patients with hypovolaemia, burns and hypoproteinaemia. Overall, the risk of death in patients treated with albumin is about 5% (95% confidence interval 2%, 8%) higher than in patients not given albumin.

Mortality was selected as the outcome measure in this systematic review for several reasons. In the context of critical illness, death or survival is a clinically relevant outcome that is of immediate importance to patients, and data on death are reported in nearly all studies. Furthermore, one might expect that mortality data would be less prone to measurement error or biased reporting than would data on pathophysiological outcomes. The use of a pathophysiological end point as a surrogate for an adverse outcome assumes a direct relationship between the two, an assumption that may sometimes be inappropriate. Finally, when trials collect data on a number of physiological end points, there is the potential for bias due to the selective publication of end points showing striking treatment effects. Because we obtained mortality data for all but four of the included trials, the likelihood of bias due to selective publication of trial outcomes is minimal.

Although publication bias is a potent threat to the validity of systematic reviews, it is unlikely to have had an important impact in this study. There was no evidence of funnel plot asymmetry on visual inspection. In some of the trials included in this review, allocation concealment was inadequate or was unclear. As a result, it is possible that more severely ill patients were preferentially allocated to the albumin treated group which may account for the increased mortality risk in this group. Nevertheless, when the analyses were repeated including only those trials in which allocation concealment involved a method that would be expected to reduce the risk of foreknowledge of treatment allocation, the point estimates were little different.

To what extent are the results of this review of 31 relatively small randomised trials of albumin administration generalisable to clinical practice? We believe that this is a matter for judgement by the responsible clinician faced with an individual patient (Oxman 1994). However, an advantage of an overview such as ours is that since it includes many studies, the results are based on a wide range of patients. Because the results are consistent across the studies, they might reasonably be taken to apply to this wide variety of patients (Oxman 1994). Moreover, the randomised evidence that we have brought together is, as far as we can ensure, the totality of the available randomised evidence compared to no colloid for the use of albumin in hypovolaemia, burns and hypoalbuminaemia, the indications for which albumin is currently licensed.

Is there a plausible mechanism by which human albumin might increase mortality? Albumin is used in hypovolaemia and hypoalbuminaemia because it is believed to be effective in replacing volume and supporting colloid oncotic pressure (Soni 1995). However, albumin is also believed to have anticoagulant properties, inhibiting platelet aggregation and enhancing the inhibition of factor Xa by antithrombin III (Soni 1995). Such anticoagulant activity might be detrimental in critically ill patients, particularly those with haemorrhagic hypovolaemia. Furthermore, albumin has been shown to distribute across the capillary membrane, a process that is accelerated in critically ill patients (Fleck 1985). It has been suggested that increased leakage of albumin into the extravascular spaces might reduce the oncotic pressure difference across the capillary wall, making oedema more likely (Fleck 1985).

Because this meta-analysis was based on 31 relatively small trials in which there were only a small number of deaths, the results must be interpreted with caution. Nevertheless, we believe that a reasonable conclusion from these results is that the use of human albumin in the management of critically ill patients should be reviewed. A strong argument could be made that human albumin should not be used outside the context of a properly concealed and otherwise rigorously conducted randomised controlled trial with mortality as the end point. Until such data become available, there is also a case for a review of the licensed indications for albumin use.

This systematic review was updated in November 2001. One additional trial was identified and included (Bland 1973). This trial compared albumin and dextrose infusions in new-born infants with low cord serum protein levels who were considered to be at risk of respiratory distress. This trial meets the eligibility criteria for the review (hypo-proteinameia) but had been overlooked in the original search. However, the inclusion of this trial does not change the conclusions of the review.

Since the review was first published a number of randomised controlled trials have been initiated and details of these trials are presented in the table of on-going studies. The largest of the on-going trials is 'SAFE,' (Saline versus Albumin Fluid Evaluation), a randomised controlled trial of albumin administration in critically ill patients. Funded primarily by the Australian National Health and Medical Research Council, the New Zealand Research council and directly by Australian State and Federal Government agencies, SAFE aims to recruit some 7000 critically ill patients and should provide the evidence needed to resolve the current uncertainty

about albumin.

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* *Indicates the major publication for the study*

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NOTES

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INDEX TERMS

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MeSH check words

Human