

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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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.

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.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We sought to identify all randomised controlled trials of human albumin or plasma protein fraction (PPF) administration (albumin/PPF versus no albumin/PPF, or a crystalloid solution).

Types of participants

Critically ill patients with hypovolaemia, burns or hypoproteinaemia. Trials involving patients receiving pre-operative volume loading or haemodilution, and trials of albumin administration during paracentesis, were excluded.

Types of intervention

Human albumin solution or plasma protein fraction (PPF).

Types of outcome measures

The principal outcome measure was mortality from all causes assessed at the end of the follow up period scheduled for each trial.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

Trials were identified by computerised searches of CENTRAL, the Cochrane Controlled Trials Register, and MEDLINE using

the following search terms: Exploded MeSH terms ALBUMINS, PLASMA SUBSTITUTES, AND PLASMA and the free text terms: volume next replacement, human next albumin, frozen next plasma, fresh next plasma, plasma next protein, low next albumin, and hypoalbumin*. EMBASE was searched using a search strategy developed by Carol Lefebvre, information scientist at the UK Cochrane Centre, and a copy of this can be obtained from the Review Group Co-ordinator.

Trials were also identified using BIDS Index to Scientific and Technical Proceedings and by hand searching 29 international journals and the proceedings of several international meetings on fluid resuscitation; by checking the reference lists of all trials and review articles; and by contacting the authors of all identified trials asking them about any other published or unpublished trials that may have been conducted. There were no language restrictions. To identify unpublished trials we searched the register of the Medical Editors' Trial Amnesty, and contacted the Medical Directors of Bio Products Laboratory (Zenalb), Centeon Limited (Albuminar), and Alpha Therapeutic UK Limited (Albutein).

An updated search was carried out using the following electronic databases and search strategies in September 2002. Searches of web-based trials databases and the internet in general were also carried out.

Cochrane Injuries Group Trials Register 09/2002

#1 (albumin* or colloid* or ppf or dextran* or gelatin* or gentran* or haemacell* or hemacell* or hetastarch* or pentastarch* or pentaspan)
#2 (volume or fluid*) and (resuscitat* or restor* or replac*)
#3 #1 and #2

Cochrane Central Register of Controlled Trials 2002 issue 3 (CD)

Pubmed to 2002/09

(<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>)

National Research Register 2002 issue 3

#1 explode "Fluid Therapy" / all SUBHEADINGS
#2 explode "Albumins" / all SUBHEADINGS
#3 explode "Plasma Substitutes" / all SUBHEADINGS
#4 explode "Saline Solution Isotonic" / all SUBHEADINGS
#5 explode "Isotonic Solutions" / all SUBHEADINGS
#6 explode "Colloids" / all SUBHEADINGS
#7 colloid* or albumin* or dextran* or gelatin* or gentran* or h?emacel* or pentastarch* or pentaspan* or hetastarch*
#8 crystalloid* or ringer* or hartman* or sodium* or potassium* or salin*
#9 ppf or (plasma next protein*)
#10 (fluid near therap*) or (fluid near restor*) or (fluid near substitut*) or (fluid near resuscitat*) or (fluid near replac*)
#11 (volume near therap*) or (volume near restor*) or (volume near substitut*) or (volume near resuscitat*) or (volume near replac*)

#12 (#7 in ti) or (#7 in ab) or (#8 in ti) or (#8 in ab) or (#9 in ti) or (#9 in ab) or (#10 in ti) or (#10 in ab) or (#11 in ti) or (#11 in ab)

#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 RCT filter (Clarke 2001)

#15 #13 and #14

EMBASE to 2002 September week 1 (OVID)

#1 exp Fluid Therapy/

#2 exp Albumin/

#3 exp Plasma Substitute/

#4 exp Colloid/

#5 exp Isotonic Solution/

#6 (colloid\$ or albumin\$ or dextran\$ or gelatin\$ or gentran\$ or haemacel\$ or hemacel\$ or pentastarch\$ or pentaspan\$ or hetastarch\$).ti,ab.

#7 (crystalloid\$ or ringer\$ or hartman\$ or salin\$).ti,ab.

#8 (ppf or plasma next protein\$).ti,ab.

#9 ((fluid adj5 therap\$) or (fluid adj5 restor\$) or (fluid adj5 substitut\$) or (fluid adj5 resuscitat\$) or (fluid adj5 replac\$)).ti,ab.

#10 ((volume adj5 therap\$) or (volume adj5 restor\$) or (volume adj5 substitut\$) or (volume adj5 resuscitat\$) or (volume adj5 replac\$)).ti,ab.

#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

#12 exp Randomized Controlled Trial/

#13 randomi\$ or (single adj blind\$) or (double adj blind\$) or (controlled adj trial\$)

#14 #12 or #13

#15 #14 and #11

Science Citation Index to September 2002 (Web of Science)

(colloid OR colloids OR albumin OR albumins OR plasma substitut* OR plasma protein* OR ppf OR dextran OR gelatin* OR gentran* OR hemacel* OR haemacel* OR pentastarch* OR pentaspan* OR hetastarch*) AND (fluid* OR volume*) AND trial*

METHODS OF THE REVIEW

One reviewer (a different person for different databases) scanned the titles and abstracts of reports identified by electronic searching to produce a list of possibly relevant reports. Two reviewers (PA and IR) then checked this list to determine which articles to retrieve in full. Disagreements were resolved by discussion.

The same two reviewers then applied the selection criteria, again resolving disagreements by discussion. They then both extracted data on study design, allocation concealment, participants, interventions and mortality. One reviewer (IR) put the data into Review Manager while the other (PA) checked it against his data extraction.

Where clarification on any aspect of the study was needed one reviewer sought to contact the author of the trial.

Relative risks and 95% confidence intervals for mortality were calculated for each trial on an intention to treat basis. Heterogeneity between trials was tested using a Chi-squared test, where p less than or equal to 0.05 was taken to indicate significant heterogeneity. As long as statistical heterogeneity did not exist, for dichotomous data, summary relative risks and 95% confidence intervals were calculated using a fixed effects model. In the event of statistical heterogeneity, if the source of heterogeneity could obviously be related to patient type, or allocation concealment, we stratified the analyses on that dimension.

DESCRIPTION OF STUDIES

A total of 36 randomised controlled trials were identified that met the study inclusion criteria. Mortality data were available either from the published report or on contact with the authors of 31 of these trials. The five trials for which mortality data could not be obtained [McNulty 1993; Skillman 1975; Ernest 1999; Ernest 2001; Oca 1999] included a total of 124 randomised patients, comprising 8% of the total number of randomised patients in all trials meeting the study inclusion criteria. One of the trials was an unpublished trial registered in the Medical Editors' Trial Amnesty. Further details about this trial, including data on mortality, were obtained directly from the trialist. In six trials there were no deaths in either the intervention or comparison groups. The trial by Lucas et al was reported in five publications. An early report gave the mortality data for 52 randomised patients, 27 allocated to receive albumin, 25 allocated to receive no albumin [Lucas 1978]. Subsequent publications indicated that recruitment to the trial continued until 94 patients were randomised. Mortality data for all the 94 patients were not published, nor were they available on contact with the author. Consequently the outcome data for the 52 patients are presented. For the 25 included trials in which there were one or more deaths in either the intervention or control groups, 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) in 13 trials, was unclear in eight trials, and inadequate in four trials.

METHODOLOGICAL QUALITY

Bland 1973

Randomised control trial. Therapy cards were randomised in pairs matched for weight. Method of allocation concealment was not described.

Bland 1976

This study is reported as randomised but the method of allocating random numbers and method of allocation concealment are unknown.

Boldt 1993

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

Boutros 1979

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

Brown 1988

The random sequence was generated using random number tables. No allocation concealment.

Ernest 1999

Randomisation was done by the hospital chart number (odd/even).

Ernest 2001

Randomisation was done by the hospital record number (odd/even).

Foley 1990

Patients were randomly assigned to either a treatment or non treatment group by medical record number.

Gallagher 1985

Randomisation and allocation concealment were by computerised system.

Golub 1994

Random sequence was computer generated. Allocation concealment was by the use of sealed opaque envelopes.

Goodwin 1983

Randomisation was according to random number tables. The methods of allocation concealment were unknown.

Greenhalgh 1995

Randomisation scheme controlled by the pharmacy

Greenough 1993

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

Grundmann 1982

The study is reported as prospectively randomised, but the methods of randomisation and allocation concealment are unknown.

Jelenko 1978

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

Kanarek 1992

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

Lowe 1977

The method of allocating random numbers is unknown. Sealed envelopes were used to ensure allocation concealment.

Lucas 1978

Allocation was based on the last digit of each patient's case number. Ninety four patients were randomised in total but the number of deaths was not reported in the final report. However, in a preliminary report, based on 52 of the randomised patients, deaths were reported.

McNulty 1993

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

Nielsen 1985

This study is reported as randomised but the method of allocation concealment is not described.

Nilsson 1980

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

Oca 1999

Randomisation was done by sequentially numbered, sealed, opaque envelopes.

Pockaj 1994

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

Prien 1990

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

Rackow 1983

Randomisation was according to a pre-determined randomisation schedule, but the methods and the allocation concealment are unknown.

Rubin 1997

Allocation concealment was by a sealed opaque envelope system in the hospital pharmacy.

Shah 1977

Randomised controlled trial. Allocation by sealed envelope.

Skillman 1975

The study is reported as randomised but the method of randomisation and allocation concealment are unknown.

So 1997

Randomised controlled trial. Allocation concealment was by computerised system.

Tollofsrud 1995

The method of generating random numbers is unknown. Allocation concealment was by sealed opaque envelopes.

Virgilio 1979

Randomisation was determined using random number tables. Methods of allocation concealment are unknown.

Woittiez 1998

Randomised controlled trial. Allocation concealment was by the use of sealed opaque envelopes.

Wojtysiak 1992

Randomisation was determined using random number tables. Allocation concealment was inadequate.

Woods 1993

Patients with even hospital numbers were allocated to the group receiving albumin, while those with odd hospital numbers were allocated to the group not receiving supplemental albumin.

Zetterstrom 1981a

Patients were randomly divided into two groups. Allocation concealment was by the use of sealed opaque envelopes.

Zetterstrom 1981b

Patients were randomly divided into two groups. Allocation concealment was by the use of sealed opaque envelopes.

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). How-

ever, 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-proteinaemia) 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.

REVIEWERS' CONCLUSIONS

Implications for practice

It would seem reasonable to conclude from these results that the use of human albumin in the management of critically ill patients should be urgently reviewed.

Implications for research

A strong argument could be made that 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.

NOTES

Please note that this review was also published in the BMJ 1998;317:235-240.

POTENTIAL CONFLICT OF INTEREST

None known.

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Internal sources of support

- Institute of Child Health, University College London UK

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* Indicates the major publication for the study

TABLES

Characteristics of included studies

Study	Bland 1973
Methods	Randomised controlled trial. Therapy cards were randomised in pairs matched for weight. Method of allocation concealment not fully described.
Participants	Newborn infants considered at high risk for developing respiratory distress. Those with a cord serum protein level less than 4.6g/100ml and at least one of the following; birthweight less than 2500g, gestational age less than 37 weeks, arterial pH less than 7.25.
Interventions	1) Intervention (n=50) received 8ml/kg 25% salt poor albumin. 2) Control group (n=50) received 8ml/kg 5% dextrose in water.
Outcomes	Deaths reported within 28 days.
Notes	
Allocation concealment	B

Study	Bland 1976
Methods	Randomised controlled trial. Method of allocation concealment not fully described.
Participants	Premature infants (less than 37 weeks gestation), with hypoproteinaemia (cord serum total protein of 4.6g/100ml or less).
Interventions	1) Intervention group (n=14) received 8ml/kg salt-poor albumin. 2) Comparison group (n=13) received 8ml/kg glucose in water.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	B

Study	Boldt 1993
Methods	Randomised controlled trial. Method of allocation concealment not described in published report. Authors were contacted and confirmed the use of sealed opaque envelopes.
Participants	Men undergoing elective aortocoronary bypass grafting, who had a pulmonary capillary wedge pressure of less than 5mmHg after induction of anaesthesia.
Interventions	1) Intervention (n=15): Albumin 5%. 2) Control (n=15): No additional volume.
Outcomes	Deaths not reported. Authors were contacted and confirmed that there were no deaths in the albumin nor the control group.
Notes	Follow-up to 1 day.
Allocation concealment	A

Study	Boutros 1979
Methods	Randomised controlled trial. Method of allocation concealment not fully described.
Participants	Participants were undergoing major operative procedures on the abdominal aorta.
Interventions	1) Intervention group (n=17) received albumin in 5% dextrose

Characteristics of included studies (Continued)

2) Control group (n=17) received 5% dextrose in lactated Ringers and 5% dextrose in 0.45 NaCl . Allocated fluids were used on admission to ICU, following surgery.

Outcomes	Deaths reported.
Notes	Follow-up to 48 hours after the end of the operation.
Allocation concealment	B

Study **Brown 1988**

Methods	Randomised controlled trial. Patients entered into the study were assigned to one of two treatment groups by a table of random numbers. Method of allocation concealment not described. Author contacted - no allocation concealment.
Participants	All patients who required central TPN and had hypoalbuminaemia (serum albumin concentration below 3.0g/dl). Patients who were thermally injured, had nephrotic syndrome or required protein restriction were excluded.
Interventions	1) The intervention group received central TPN plus normal serum albumin (n=33). 2) The control group (n=34) received central TPN alone.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	C

Study **Ernest 1999**

Methods	Randomised controlled trial, not blinded.
Participants	18 septic, critically ill patients where a fluid infusion was clinically indicated.
Interventions	1) 5% albumin (n=9) 2) normal saline (n=9)
Outcomes	Information on death not collected.
Notes	Follow up for about an hour after infusion
Allocation concealment	C

Study **Ernest 2001**

Methods	Randomised controlled trial, not blinded
Participants	40 postoperative cardiac surgical patients.
Interventions	1) 5% albumin (n=23) 2) normal saline (n=17)
Outcomes	Information on death not collected.
Notes	Follow up for 40 minutes after infusion. Trial conducted in 1992.
Allocation concealment	C

Study **Foley 1990**

Methods	Patients were randomly assigned to either a treatment or non-treatment group by medical record number.
Participants	Hypoalbuminaemic (serum albumin <25g/L) critically ill patients. Potential subjects with Child's class C cirrhosis were excluded.
Interventions	1) The treatment group (n=18) received 25-50g per day of 25% albumin in addition to full nutritional support with parenteral nutrition. Albumin administration was continued daily until serum albumin levels exceeded 25 g/L after which patients received additional albumin as needed to keep the albumin level at 25 g/L or higher.

Characteristics of included studies (Continued)

	2) The non treatment group (n=22) received no exogenous concentrated albumin.
Outcomes	Deaths reported.
Notes	Follow up to discharge.
Allocation concealment	C

Study Gallagher 1985

Methods	Randomised controlled trial. Method of allocation concealment not described. Author contacted - allocation concealment by computerised system - patient details were entered before treatment assignment was revealed.
Participants	Patients after coronary artery bypass graft surgery.
Interventions	1) Treatment group received 5% albumin (n=5) 2) The control group received lactated Ringers (n=5).
Outcomes	Deaths were not reported. Author contacted and confirmed that there were no deaths in either group.
Notes	Follow-up to 1 day.
Allocation concealment	A

Study Golub 1994

Methods	Computer randomisation - method of allocation concealment not described. Author contacted and confirmed that allocation concealment was by the use of sealed opaque envelopes.
Participants	Patients in the surgical intensive care unit of a community hospital with circulating albumin concentrations of <3.0g/dL.
Interventions	1) The treatment group (n=116) received 37.5g/day of albumin until the circulating albumin concentration increased to 3.0g/dL. 2) The control group received no supplemental albumin. Both groups received standard nutritional support.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	A

Study Goodwin 1983

Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	79 thermally injured patients. No other inclusion criteria were reported. All of the participants were previously healthy young adults.
Interventions	1) The treatment group (n=40) group received 2.5% albumin in Ringer's lactate 2) The control group (n=39) Ringers lactate. Allocated fluid was used throughout resuscitation.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	B

Study Greenhalgh 1995

Methods	Method of random allocation not described. Author contacted and confirmed the use of a randomisation scheme controlled by the pharmacy.
Participants	Patients aged 18 years or younger with acute burns.
Interventions	1) High albumin group (n=34): Patients were supplemented with human albumin to maintain serum levels between 2.5 and 3.5g/dL. Albumin was supplied as a continuous drip of 25% human albumin at a rate

Characteristics of included studies (Continued)

of 3-10mL/hour. Supplementation was discontinued if serum albumin levels remained >2.5 g/dL without supplementation or if intravenous support was discontinued.

2) Low albumin group (n=36): Patients were not given albumin supplementation unless levels dropped <1.5 g/dL. During burn shock, patients were allowed to receive albumin if they had levels <2.0 g/dL and were receiving >4 mL/Kg/% burn fluid resuscitation.

Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	A

Study **Greenough 1993**

Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.
Participants	Infants between 24 and 34 weeks gestational age, who were ventilator dependent, and had a serum albumin level of less than or equal to 30g/l.
Interventions	1) Intervention group (n=20) received 5ml/kg 20% salt-poor human albumin. 2) Control group (n=20) received 5ml/kg of the infant's maintenance fluids.
Outcomes	Deaths were not reported. Author contacted and provided data on deaths.
Notes	Follow-up to 24 hours after infusion.
Allocation concealment	A

Study **Grundmann 1982**

Methods	Randomised controlled trial. Method of allocation concealment not fully described.
Participants	Participants were undergoing partial gastrectomy. The average age was 50 years (range 19-84).
Interventions	1) Intervention group (n=14) group received human albumin 2) Control group (n=6) details of crystalloid were not reported. Allocated fluid was continued for 4 days after operation.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	B

Study **Jelenko 1978**

Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Participants had burns covering more than 20% of body surface.
Interventions	1) Intervention group (n=7) received albumin in hypertonic saline (240MeQ Na+, 120 MeQ Chloride, 120 MeQ lactate, 3.5torr/liter); 2) Control group (n=7) received hypertonic saline (240MeQ Na+, 120 MeQ Chloride, 120 MeQ lactate). Allocated fluid was used to the end of resuscitation.
Outcomes	Deaths reported.
Notes	Follow-up to 5 days.
Allocation concealment	B

Study **Kanarek 1992**

Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.
Participants	Sick premature newborn infants whose serum albumin was less than 3g/dL
Interventions	1) Intervention group (n=12) received TPN with added albumin.

Characteristics of included studies (Continued)

	2)Control group (n=12) received no added albumin.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	A

Study Lowe 1977

Methods	Randomised controlled trial. The solutions were randomised by opening a sealed envelope containing a card denoting the appropriate fluid.
Participants	Participants were undergoing emergency laparotomy for acute abdominal trauma.
Interventions	1) Intervention group (n=57) received 50g albumin in 200ml in Ringers lactate; 2) Crystalloid group (n=84) received Ringer's lactate. Allocated fluid was used throughout the pre- and intra-operative period.
Outcomes	Deaths reported.
Notes	Follow-up to 5 days post-operatively. Data on the 30 participants with chest injuries who were left out of the Lowe 1977 report, but included in Moss 1981, have been included in the meta-analysis.
Allocation concealment	A

Study Lucas 1978

Methods	Randomised controlled trial. Randomisation was based on the last digit of each patient's case number.
Participants	52 seriously injured patients.
Interventions	1) Intervention group (n=27) received supplemental salt-poor albumin totalling a maximum of 150g during operation and 150g per day over the next five days. 2) Control group (n=25) received standard resuscitation regimen but no supplemental albumin.
Outcomes	Deaths reported.
Notes	In the final report of 94 randomised patients deaths were not reported. However, in this preliminary report of 52 injured patients deaths were reported.
Allocation concealment	C

Study McNulty 1993

Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Patients following elective cardiopulmonary bypass.
Interventions	1)Intervention group (n=14) received 5% albumin. 2)Control group (n=14) received isotonic crystalloid.
Outcomes	Deaths not reported.
Notes	Length of follow-up unspecified.
Allocation concealment	B

Study Nielsen 1985

Methods	Randomized controlled trial. Method of allocation concealment not described.
Participants	Patients admitted for reconstructive surgery of the abdominal aorta. Twenty six patients were randomised.
Interventions	1) Intervention (n=13): 80 g of albumin administered in units of 100 ml 20% human serum albumin on the day of the operation and 20 g albumin daily on the following three postoperative days. 2) Control group (n=13): no supplemental albumin.
Outcomes	Deaths not reported. Author when contacted confirmed that there were no deaths in either group.

Characteristics of included studies (Continued)

Notes	Follow-up 4 days.
Allocation concealment	B
Study	Nilsson 1980
Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.
Participants	Patients with colorectal cancer undergoing elective surgery with resection of the tumour and primary anastomosis.
Interventions	1) Intervention group (n=29) received 20-25g per day of albumin (as 5% albumin or 20% albumin) for three days, starting on the day after the operation. 2) Control group (n=30) received no albumin.
Outcomes	Deaths reported.
Notes	Follow up to discharge.
Allocation concealment	A
Study	Oca 1999
Methods	Randomised controlled trial. Allocation concealment was by the use of sealed opaque sequentially numbered envelopes. Information obtained on contact with the author.
Participants	24 neonates being treated for hypotension. Hypotension was defined as an oscilometric mean arterial blood pressure <30 mmHg for at least 30 minutes. Exclusion criteria consisted of proven sepsis, life-threatening congenital abnormalities, congenital hear disease, unresolved thoracic air leak, insulin-requiring maternal diabetes mellitus or treatment with high-frequency ventilation.
Interventions	1) 5% albumin (n=11) 2) normal saline (n=13)
Outcomes	Mean arterial blood pressure.
Notes	Follow-up to discharge
Allocation concealment	A
Study	Pockaj 1994
Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Participants required fluid resuscitation as a result of vascular leak syndrome associated with Interleukin-2 therapy for metastatic cancer.
Interventions	1) Intervention group (n=54) received 5% albumin n 154meq/L NaCl; 2) Control group (n=53) received 0.9% normal saline with 154Meq/L NaCl.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	B
Study	Prien 1990
Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Patients undergoing hemipancreato-duodenectomy (Whipple's operation).
Interventions	1) Intervention group (n=6) received 20% human albumin to maintain central venous pressure at the pre-operative level. 2) Control group (n=6) received Ringer's lactate.
Outcomes	Deaths reported.

Characteristics of included studies (Continued)

Notes Length of follow-up unspecified.

Allocation concealment B

Study Rackow 1983

Methods Randomised controlled trial. Method of allocation concealment not described.

Participants Participants were above 18 years of age, and had any one of the following pre-determined indicators of shock: systolic blood pressure of 90mmHg or less, a cardiac index of less than 2.2L./min.m2, a serum arterial lactate greater than 18mg/dl and WP less than 15mmHg.

Interventions 1) Intervention group (n= 9) received 5% albumin
2) Control group (n=8) received 0.9% NaCl. Allocated fluid was given as needed until the end of resuscitation.

Outcomes Deaths reported.

Notes Follow-up to discharge.

Allocation concealment B

Study Rubin 1997

Methods Patients were randomised using "a closed envelope system in the pharmacy".

Participants Patients with hypoalbuminaemia (<2.5g/dL) who required TPN for at least six days, were not pregnant or under age, and did not have metastatic cancer, cirrhosis, or nephrotic syndrome.

Interventions 1) Intervention group (n=16) 25g on normal serum albumin
2) Control group (n=15) 100 mL of normal saline placebo over a 1 hour period daily.

Outcomes Deaths reported.

Notes Follow-up to discharge.

Allocation concealment A

Study Shah 1977

Methods Randomised controlled trial. allocation by sealed envelope.

Participants Patients with severe, multiple trauma and a systolic blood pressure of less than 90mmHg. All patients were adults and both sexes were included.

Interventions 1) Intervention group (n=9) 5% salt-poor albumin in Ringers lactate
2) Control group (n=11) Ringer's lactate for resuscitation, volume infused guided by physiological parameters.

Outcomes Death reported.

Notes Length of follow-up not stated.

Allocation concealment A

Study Skillman 1975

Methods Randomised controlled trial. Method of allocation concealment not described.

Participants Participants were undergoing elective abdominal reconstructive surgery.

Interventions 1) Intervention group received 25% concentrated salt-poor albumin and 5% albumin in saline.
2) Control group received Ringer's lactate with 5% dextrose. Allocated fluid was given intra-operatively. All patients received crystalloids only for pre-loading before surgery.

Outcomes Deaths were not reported. Author could not be contacted.

Notes Follow-up to 1 day.

Allocation concealment B

Characteristics of included studies (Continued)

Study	So 1997
Methods	Randomised controlled trial. Method of allocation concealment not described. Author contacted and confirmed that allocation concealment was by computer randomisation. Details of patient were entered before group allocation revealed.
Participants	Pre-term infants weighing 540 to 1959g at birth, with gestational ages of 23 to 34 weeks, who developed hypotension within the first two hours of life.
Interventions	1) Intervention group (n=32) were given 5% albumin at a dose of 10mg/Kg by slow intravenous infusion over 30 minutes. 2) Control group (n=31) were given 0.9%NaCl at a dose of 10mg/kg by slow intravenous infusion over 30 minutes.
Outcomes	Deaths reported.
Notes	Follow up to discharge.
Allocation concealment	A

Study	Tollofsrud 1995
Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.
Participants	Patients undergoing elective coronary artery bypass surgery. Patients with left ventricular ejection fraction less than 40%, valvular heart disease, ventricular aneurysm, arrhythmia, diabetes mellitus, renal failure or lung disease were excluded.
Interventions	1) Intervention group (n=10) received albumin 40mg/ml whenever fluid was required to stabilise haemodynamics. 2) Control group (n=10) received Ringers acetate.
Outcomes	Deaths reported.
Notes	Follow-up to 48 hours.
Allocation concealment	A

Study	Virgilio 1979
Methods	Randomised controlled trial. Method of allocation concealment not described.
Participants	Participants were undergoing abdominal aortic surgery.
Interventions	1) Intervention group (n=15) received 5% albumin in Ringer's lactate 2) Control group (n=14) received Ringers lactate. Allocated fluid was used during operation for maintenance of pre-defined physiological parameters, and the resuscitation was continued with the allocated fluid until the day following the operation. This was followed by 5% dextrose in half-normal saline, with potassium chloride as needed.
Outcomes	Deaths reported.
Notes	Follow-up 2 and a half weeks.
Allocation concealment	B

Study	Woittiez 1998
Methods	Randomised controlled trial. Allocation concealment by sealed opaque envelopes.
Participants	Post-operative intensive care patients.
Interventions	1) Intervention group (n=15) received 20% albumin. 2) Control group (n=16) received 0.9% NaCl.
Outcomes	Unpublished data on deaths were provided by the trialist.
Notes	Length of follow-up unspecified.

Characteristics of included studies (Continued)

Allocation concealment A

Study	Wojtysiak 1992
Methods	Randomised controlled trial. Table of random numbers was used to generate the random sequence. Method of allocation concealment not described in published report. The author was contacted and indicated that there was inadequate allocation concealment.
Participants	Patients between the ages of 18 and 75 years who were to receive parenteral nutrition and had a serum albumin concentration <3.0 g/dL. Patients were excluded if they had renal impairment, liver impairment or were haemodynamically unstable.
Interventions	1) Intervention group (n= 15) had 25g of human albumin added to each litre of parenteral nutrition. 2) Control group (n=15) had no supplemental albumin.
Outcomes	Deaths not reported in published report. Author when contacted confirmed that there were no deaths in either group.
Notes	Follow-up to 5 days.
Allocation concealment	C

Study	Woods 1993
Methods	Randomised controlled trial. Patients with even hospital numbers were randomised to the group receiving albumin while those patients with odd hospital numbers were randomised to the group not receiving supplemental albumin.
Participants	Patients undergoing surgery for abdominal aortic aneurysm, aortoiliac or aortofemoral bypass.
Interventions	1) Intervention group (n=37): albumin was replaced to a level greater than or equal to 3.5 g/dL. 2) Control group (n=32): received no supplemental albumin.
Outcomes	Deaths reported.
Notes	Follow-up to discharge.
Allocation concealment	C

Study	Zetterstrom 1981a
Methods	The patients were randomly divided into two groups. The method of allocation concealment is not described. Author was contacted and confirmed the use of sealed opaque envelopes.
Participants	Adult patients undergoing elective major abdominal surgery.
Interventions	1) Intervention group (n=15) 2) Control group (n=15) A similar schedule of fluid therapy and blood replacement was followed in the intervention and control groups. However, the albumin group received a 20% solution of human albumin intravenously according to the following scheme: At the end of the operation: 100ml. Postoperatively on the day of the operation: 200-300 ml. First day after the operation: 200 ml. Following 3 days 100 ml each day.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	A

Study	Zetterstrom 1981b
Methods	Patients were randomly divided into two groups. Method of allocation concealment was not described. Author was contacted and confirmed the use of sealed opaque envelopes.
Participants	Patients undergoing elective reconstruction of the abdominal aorta.
Interventions	1) Intervention group (n=9) 2) Control group (n=9) Postoperatively, the aim of fluid administration was to keep the pulmonary arterial occlusion pressure equal to the preoperative level. When lower values were recorded, the patients in the control group were given a balanced electrolyte solution of the Ringer type, whereas the albumin patients received a 5% solution of human albumin.
Outcomes	Deaths reported.
Notes	Length of follow-up unspecified.
Allocation concealment	A

Characteristics of excluded studies

Study	Reason for exclusion
Artru 1989	Intervention to control intracranial pressure not directed at fluid resuscitation.
Brehme 1993	Intervention directed at haemodilution, not at volume replacement.
Carlson 1979	Randomised controlled trial of pre-operative volume expansion during anaesthesia.
Fiorica 1991	Not a randomised trial. The first 18 patients received standard maintenance crystalloid solution. The next 10 consecutive patients received 100g of a concentrated 25% albumin solution.
Goslinga 1992	Intervention directed at haemodilution, not volume replacement.
Grundmann 1985	This was a randomised controlled trial of 220 patients, 106 were given albumin when their colloid osmotic pressure (COP) fell below 24 cm water and 114 were given albumin when their COP fell below 29 cm water. Patients were not randomised to albumin or no albumin, nor were they randomised to supplemental albumin versus normal amounts of albumin, rather, this was a trial of different criteria for albumin supplementation. It is unlikely therefore that the two arms of the trial were comparable and hence the trial is excluded.
Grundmann 1986	This was a randomised controlled trial to examine whether postoperative human albumin supply is justified in intensive care patients in the case that the colloid osmotic pressure decreases below 26 centimetres of water. The therapy group received human albumin only if the colloid osmotic pressure dropped below 26 cm water. The control group also received albumin but only for resuscitation of cardiac output and central venous pressure. The trial was excluded because both intervention and control groups received albumin.
Hauser 1980	Cross-over trial.
Lagonidis 1995	Intervention was pre-loading for coronary artery bypass surgery.
Lennihan 2000	Participants had suffered subarachnoid hemorrhage and therefore did not meet the inclusion criteria.
Magder 1999	Participants were stable patients following cardiopulmonary bypass surgery and therefore did not meet the inclusion criteria.
Martin 1999	Intervention involved comparison of albumin with furosemide versus placebo therefore did not meet the inclusion criteria.
Metildi 1984	Participants were admissions to an intensive care and a trauma unit with adult respiratory distress syndrome and established pulmonary failure. Included both trauma and non-trauma patients and therefore did not meet the inclusion criteria for the review.
Steinberg 1989	Cross-over trial.

Characteristics of excluded studies (Continued)

Tomita 1994 Randomised controlled trial of normal versus high oncotic pressure following head injury. Patients were not randomised to albumin or no albumin. Albumin and furosemide were used together to achieve high oncotic pressure.

Characteristics of ongoing studies

Study	French
Trial name or title	SAFE (Saline vs Albumin Fluid Evaluation). A multi-centre randomised controlled trial of the effects of volume replacement with albumin compared to saline in critically ill patients.
Participants	Patients in intensive care units around Australia and New Zealand who require fluid resuscitation.
Interventions	Patients will be randomised to receive either 4% human albumin in normal saline or 0.9% saline.
Outcomes	Death, intensive care mortality, in-hospital mortality, time to discharge from ITU, no. of positive pressure ventilation-free days, renal failure.
Starting date	November 2001
Contact information	Julie French Senior Project Manager Institute for International Health University of Sydney PO Box 576 Newtown NSW 2042 jfrench@iih.usyd.edu.au
Notes	

Study	Martin
Trial name or title	Bioimpedance measures of albumin effects in ALI.
Participants	Hypoproteinemic patients with ALI or ARDS (total projected n=40, current n=24).
Interventions	Patients randomised to continuous infusion furosemide with or without blinded administration of albumin (25g of 25% albumin) for 3 days.
Outcomes	Powered for physiology (changes in weight, serum chemistries, oxygenation, hemodynamics) with additional outcome data (ventilator free days, ICU free days, organ failure, hospital LOS, mortality) to 28 days or hospital discharge (whichever is greater).
Starting date	
Contact information	Greg S Martin, M.D Pulmonary & Critical Care Medicine 80 Butler Steet , SE Grady Memorial Hospital, Suite 2D-004 Atlanta, GA 30335 USA Greg_Martin@emoryhealthcare.org
Notes	

G R A P H S

Comparison 01. supplemental albumin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 deaths	31	1519	Relative Risk (Fixed) 95% CI	1.52 [1.17, 1.99]

I N D E X T E R M S

Medical Subject Headings (MeSH)

Blood Proteins [*therapeutic use]; Critical Illness [*therapy]; *Fluid Therapy; Plasma Substitutes [*therapeutic use]; Serum Albumin [therapeutic use; *therapeutic use]

MeSH check words

Human

C O V E R S H E E T

Title	Human albumin solution for resuscitation and volume expansion in critically ill patients
Authors	The Albumin Reviewers (Alderson P, Bunn F, Lefebvre C, Li Wan Po A, Li L, Roberts I, Schierhout G)
Contribution of author(s)	Phil Alderson (UK Cochrane Centre) searched The Cochrane Central Register of Controlled Trials for relevant trials, extracted the data from the trials, and commented on the paper; Frances Bunn (London School of Hygiene & Tropical Medicine) searched the Cochrane Injuries Group Specialised Register for relevant trials, obtained copies of relevant papers, wrote to authors for further information on allocation concealment, and commented on the paper; Carol Lefebvre (UK Cochrane Centre) designed the search strategies for The Cochrane Central Register of Controlled Trials and EMBASE, and searched these two databases for relevant trials; Leah Li (Institute of Child Health) did the funnel plot and the regression test of funnel plot asymmetry; Alain Li Wan Po (Centre for Evidence-Based Pharmacotherapy, University of Nottingham) helped to write the paper; Ian Roberts (London School of Hygiene & Tropical Medicine) designed the protocol, extracted data from the trials, contacted authors for unpublished data, and wrote the paper; Gillian Schierhout proposed the study hypothesis, and conducted preliminary searches of MEDLINE, EMBASE, and BIDS Index to Scientific and Technical Proceedings.
Issue protocol first published	/
Review first published	1998/3
Date of most recent amendment	25 February 2004
Date of most recent SUBSTANTIVE amendment	26 November 2001
What's New	An updated search for new trials was done in September 2002. One trial was found meeting the inclusion criteria but did not record data on mortality (Ernest 2001). Since the review was first published several new randomised control trials have been initiated. Details of these trials are given in the ongoing trials section.
Date new studies sought but none found	Information not supplied by author

Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 September 2002
Date authors' conclusions section amended	Information not supplied by author
DOI	10.1002/14651858.CD001208
Cochrane Library number	CD001208
Editorial group	Cochrane Injuries Group
Editorial group code	HM-INJ

COMMENTS AND CRITICISMS

Human albumin solution

Summary

1. It would be helpful to state that this review was published in the BMJ in 1998, to summarise the subsequent correspondence in print and on the BMJ website, and to note the respects (if any) in which this Cochrane review differs from the BMJ publication.
2. It would be valuable to summarise the report of the Committee for Safety of Medicines (CSM) on this review in the Comments and Criticisms section, with a rejoinder by the authors.
3. Because mortality was not the primary endpoint in any of the trials reviewed, it would be useful to note the primary outcomes of each trial, under 'characteristics of included trials'.
4. It would be helpful if the number of participants in each arm of each reviewed trial appeared under 'characteristics of included trials.'

Author's reply

1. We agree that it is important to direct the reader to other published versions of the review and will ensure that readers are alerted to the BMJ publication. We do not think it is appropriate to summarise the correspondence in response to this review, as to do so would run the risk of misrepresenting the views of the correspondents. At the time of first publication the Cochrane review was identical to the review published in the BMJ. However, the Cochrane review will be regularly updated to take account of new information from randomised controlled trials.
2. The Cochrane Database of Systematic Reviews is an international database and for this reason we believe that it would be inappropriate to give undue emphasis to the deliberations of the British Committee on Safety of Medicines (CSM).
3. Mortality was recorded in all but two of the trials included in our systematic review. However, we have no information on whether this was considered by the trialist to be the primary endpoint and would be interested to hear where the author of the comment found this information. How does the author of the comment define a primary endpoint? The concept of a primary endpoint implies a selection within the mind of the trialist of the most important endpoint. We would also ask whether it is appropriate that a process within the mind of a trialist should impact importantly on the estimation of the effect of albumin on mortality, and if so, what is the scientific basis for this.
4. We have included the number of participants in each arm of each reviewed trial in the section 'characteristics of included trials' as suggested.

Contributors

Author of comments: Dr Andrew Herxheimer

Author of Responses: Ian Roberts

Human albumin solution

Summary

I gather that a further trial - prompted by the review - is now planned and possibly underway in Australasia. If so, I think this should be mentioned, preferably with a link to a record for the trial on the meta-Register of Controlled Trials

Author's reply

Details of this ongoing trial are now in the on-going studies section.

Contributors

Author of comments: Iain Chalmers, UK

Author of response: Ian Roberts, UK

Human albumin solution

Summary

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

Summary of comment

1. In the hypovolaemia group, five randomised controlled trials were incorrectly included and should be deleted(1).
2. The Cochrane Albumin Review excluded or omitted extensive randomised controlled trials' evidence in the three categories of indications, namely, hypovolaemia, burns and hypoalbuminaemia(2) and this excluded and omitted evidence indicated that albumin may reduce rather than increase mortality.

(1) Horsey P Albumin and hypovolaemia - is the Cochrane evidence to be trusted? Lancet 2002 359 70-72

(2) Wilkes MM and Navickis RJ Patient survival after human albumin administration: a meta-analysis of randomised controlled trials. Annals of Internal Medicine 2001 135 149-164

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Author's reply

We are grateful to Dr Horsey for his thoughtful comments on our systematic review of albumin administration in critically ill patients. The comments were first made as a commentary in The Lancet (2002;359:70-72). Our response to these comments was published in the same issue (Lancet 2002:359:72-3). We are pleased that this discussion will now be available to readers of the Cochrane Library.

Dr Horsey feels that some of the trials included under the category 'hypovolaemia' would be more appropriate in a different category. We accept that in some clinical situations hypovolaemia and hypoalbuminaemia co-exist so that deciding which category would be most appropriate is a matter for judgement. Also, as Dr Horsey points out, the relationship between hypovolaemia and low blood pressure can be complicated, and the presence of the latter might not always signify the former. Nevertheless, our judgements about the categories were made without knowledge of the results of the trials and we are reluctant to change these post-hoc.

We are grateful to Dr Horsey for drawing our attention to the meta-analysis by Wilkes et al that was funded by the Plasma Protein Therapeutics Association. Because the inclusion criteria for the Cochrane Injuries Group Albumin Reviewer and the Wilkes reviews are different it does not follow that the two reviews should include the same trials.

We are pleased that our systematic review has stimulated so much interest from the intensive care community. However, it is a cause for concern that four years following the publication of our review, in which we concluded that there is no evidence that albumin administration reduced mortality in critically ill patients and a suggestion that it may increase mortality, that albumin continues to be used and promoted. Hopefully, the SAFE trial (www.safestudy.net) will provide the evidence needed to resolve this issue

Contributors

Comment: Dr PJ Horsey

Reply: Professor Ian Roberts

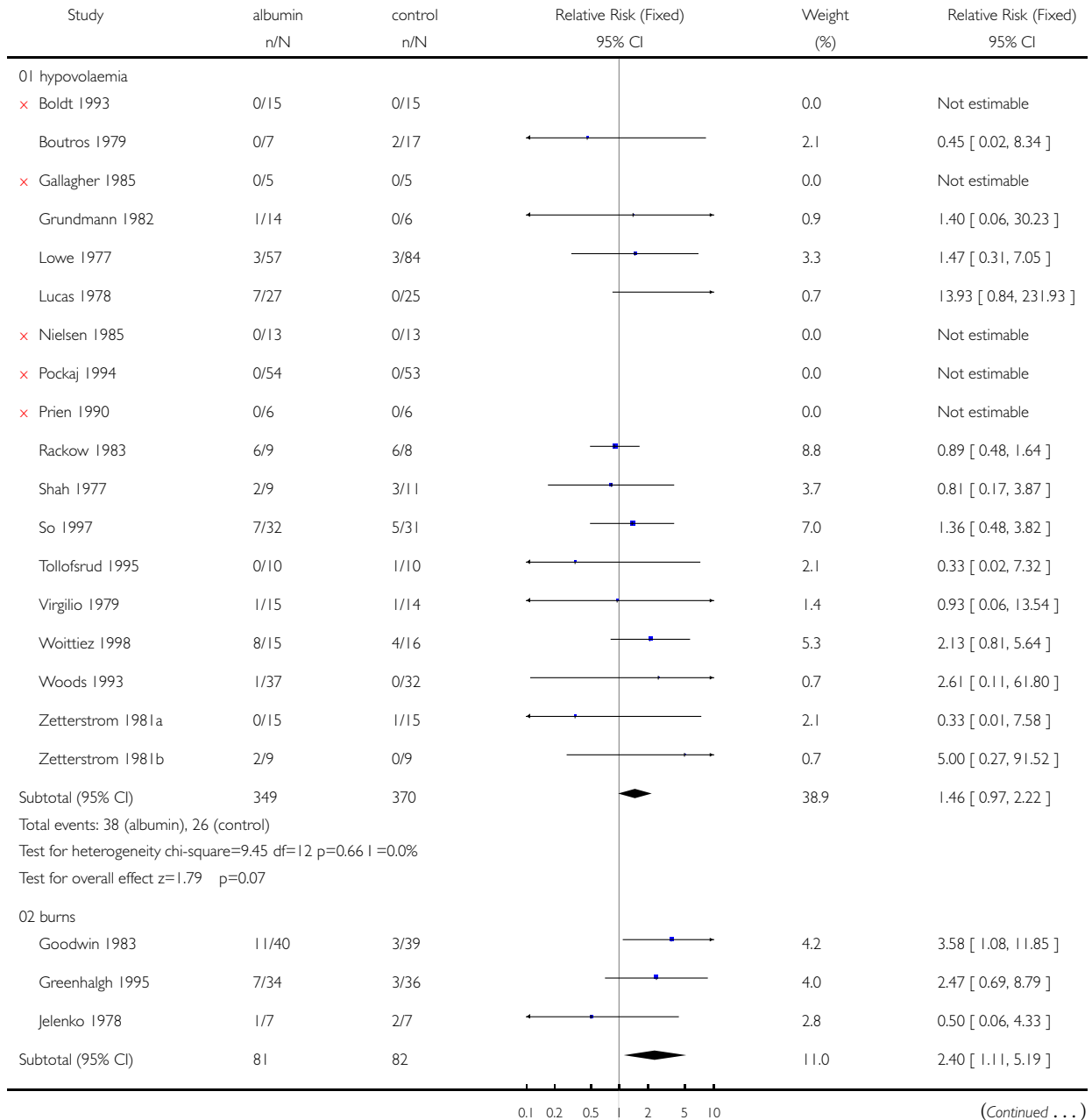
GRAPHS AND OTHER TABLES

Comparison 01. 01 deaths

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

Comparison: 01 supplemental albumin

Outcome: 01 deaths



(... Continued)

