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)
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>PLAIN LANGUAGE SUMMARY</td>
<td>2</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>2</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>2</td>
</tr>
<tr>
<td>RESULTS</td>
<td>2</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>3</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>4</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>4</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>8</td>
</tr>
<tr>
<td>NOTES</td>
<td>8</td>
</tr>
<tr>
<td>INDEX TERMS</td>
<td>8</td>
</tr>
</tbody>
</table>
Human albumin solution for resuscitation and volume expansion in critically ill patients

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

Contact address:

Editorial group: Cochrane Injuries Group.


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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
hypoproteinaemia 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% confi-
dence 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 sys-
tematic 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, allo-
cation 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 conceal-
ment 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 clini-
cal 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 hypoproteinaemia,
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 hypo-
albuminaemia because it is believed to be effective in replacing vol-
ume and supporting colloid oncotic pressure (Soni 1995). How-
ever, albumin is also believed to have anticoagulant properties, in-
hibiting platelet aggregation and enhancing the inhibition of fac-
tor Xa by antithrombin III (Soni 1995). Such anticoagulant activ-
ity might be detrimental in critically ill patients, particularly those
with haemorrhagic hypoproteinaemia. 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 extra-
vascular 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 ad-
ditional 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-proteinemia) 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 con-
rolled trials have been initiated and details of these trials are pre-

dented in the table of on-going studies. The largest of the on-going
trials is ‘SAFE,’ (Saline versus Albumin Fluid Evaluation), a ran-

domised 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.

ACKNOWLEDGEMENTS

We thank the Intensive Care National Audit & Research Centre in London for help with identifying trials for this review and for their extensive hand searching activities. We are grateful to AJ Woottie for providing unpublished trial data from the trial that was registered in the Medical Editors’ Trial Amnesty. We thank Elizabeth Bryant, Information Officer at Centeon Limited, and Martin O’Folpe at Bio Products Limited, for searching their databases for albumin trials. We thank Anne Greenough for re-examining individual patient records in order to provide data on mortality. We are also grateful to Peter Sandercock for his assistance in the editorial process.

REFERENCES

References to studies included in this review

Bland 1973 [published data only]

Bland 1976 [published data only]

Boldt 1993 [published data only]

Boutros 1979 [published data only]

Brown 1988 [published data only]

Ernest 1999 [published data only]

Ernest 2001 [published data only]

Foley 1990 [published data only]

Gallagher 1985 [published data only]

Golub 1994 [published data only]

Goodwin 1983 [published data only]

Greenhalgh 1995 [published data only]

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Greenough 1993 (published and unpublished data)

Grundmann 1982 (published data only)

Jelenko 1978 (published data only)


Kanarek 1992 (published data only)

Lowe 1977 (published data only)


Lucas 1978 (published data only)


McNulty 1985 (published data only)

Nielsen 1985 (published data only)


Oca 1999 (published data only)
Oca MJ, Nelson M, Donn SM. Randomized trial of normal saline (NS) versus 5% albumin (ALB) for the treatment of neonatal hypotension. Pediatric Research. 1999;45:#1265.

Pockaj 1994 (published data only)

Prien 1990 (published data only)
Rackow 1983 [published data only]

Rubin 1997 [published data only]

Shah 1977 [published data only]

Skillman 1975 [published data only]

So 1997 [published data only]

Tollosrud 1995 [published data only]

Virgilio 1979 [published data only]

Woititz 1998 [unpublished data only]


Wojtysiak 1992 [published data only]


Woods 1993 [published data only]

Zetterstrom 1981a [published data only]

Zetterstrom 1981b [published data only]

References to studies excluded from this review

Artru 1989

Brehme 1993

Carlon 1979

Fiorica 1991

Goslinga 1992

Goslinga H, Eijenbach V, Heuvelmans JH, van de Nes JC, Kurk RM, Bezemer PD. Individualized hemodilution in acute brain infarct using a 20% albumin solution and

Grundmann 1985

Grundmann 1986

Hauser 1980

Lagonidis 1995

Lennihan 2000

Magder 1999

Martin 1999

Metildi 1984

Steinberg 1989

Tomita 1994

**References to studies awaiting assessment**

**Lundstrom 2000**

**References to ongoing studies**

**French**

French J, et al. SAFE (Saline vs Albumin Fluid Evaluation). The Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australian Red Cross Blood Services and the Institute for International Health.

**Martin**
Bioimpedance measures of albumin effects in ALI. Ongoing study Starting date of trial not provided. Contact reviewer for more information.

Martin G. Bioimpedance measures of albumin effects in acute lung injury.

**Additional references**

**ABPI 1998**

**Egger 1997**

**Fleck 1985**

**Goldwasser 1999**

**McClelland 1999**

**Oxman 1994**

**Schulz 1996**

**Soni 1995**
References to other published versions of this review

CIGAR 1998

* Indicates the major publication for the study

**SOURCES OF SUPPORT**

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**Internal sources of support**
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**NOTES**
Please note that this review was also published in the *BMJ* 1998;317:235-240.

**INDEX TERMS**

**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