

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

This review should be cited as: The Albumin Reviewers (Alderson P, Bunn F, Lefebvre C, Li WP, Li L, Schierhout G). Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev* 2004; (4): CD001208, pub2. DOI: 10.1002/14651858.CD001208.pub2.

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 August 2004.

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 32 trials meeting the inclusion criteria and reporting death as an outcome. There were 1632 deaths among 8452 trial participants. For hypovolaemia, the relative risk of death following albumin administration was 1.01 (95% confidence interval 0.92-1.10). This estimate was heavily influenced by the results of the SAFE trial, which contributed 91% of the information (based on the weights in the meta-analysis). 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 ($\chi^2 = 21.86$, $df = 25$, $p = 0.64$). The pooled relative risk of death with albumin administration was 1.04 (0.95-1.13).

Conclusions. For patients with hypovolaemia there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline. There is no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminaemia. The possibility that there may be highly

selected populations of critically ill patients in which albumin may be indicated remains open to question. However, in view of the absence of evidence of a mortality benefit from albumin and the increased cost of albumin compared to alternatives such as saline, it would seem reasonable that albumin should only be used within the context of well concealed and adequately powered randomised controlled trial.

Plain language summary. There is no evidence that giving human albumin to replace lost blood in critically ill or injured people improves survival when compared to giving saline.

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 hopefully 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. Albumin is very expensive in which case it may be better to use cheaper alternatives such as saline for fluid resuscitation.

Summarising evidence from poorly conducted trials helps identifying important priorities for new randomised trials: the methodologist's point of view

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The Cochrane review first published in 1998

In 1998 the Cochrane Injuries Group published the results of a systematic review (SR) of human albumin administration in critically ill patients. After publication in the Cochrane Library results were also reported in the *British Medical Journal* showing that when data from the 30 randomised controlled trials up to then available are considered together, the risk of death was 14% in patients receiving albumin and 8% in those not receiving albumin. This suggests that for every 17 critically ill patients treated with albumin there is one extra death¹.

The results were widely reported in the television and print media throughout the world and stimulated an immediate response from the drug regulatory agencies, the plasma product industry and the medical profession. Despite vigorous attempts by the industry to limit the effects of the SR on albumin sales, the use of albumin declined steeply, showing that evidence from SRs can have an important effect on clinical care.

The review has been updated in 2004 and in the last issue of the Cochrane Library (Issue 3, 2006) 37 randomised

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controlled trials have been identified with mortality data available for 32, totalling approximately 8500 patients². This story resembles that of the effects of antibiotic prophylaxis in intensive care that was discussed in the previous edition of the Cochrane Corner. At issue, however, is not uncertainty about a beneficial but about a harmful effect. Let's consider the various SRs in detail. Between 1989 and 2005 eight different SRs have been reported³. The first two SRs (Velanovic et al., 1989 and Bisonni et al., 1991) (see ref. 3) compared crystalloid and colloid fluid resuscitation in heterogeneous seriously ill patients finding a trend toward increasing mortality with colloids. Wade in 1997 (see ref. 3) found no difference in mortality between trauma patients receiving hypertonic saline and those receiving isotonic crystalloid. In 1998 Schierhout et al. also observed a trend toward increasing mortality, but not in all subgroups examined. In 1998 the Cochrane review was first published showing a statistically significant increased risk of mortality in patients who received albumin.

Why results from systematic reviews can diverge?

As the number of SRs increases, more contradictions among them are inevitable. SRs can diverge in two fundamental ways. First, the actual results can differ because of the trials that are available or selected. Second, the results may be very similar but the authors may interpret the results quite differently. In reviewing some of the SRs quoted previously one can be struck by the similarity of results and the differences in the interpretations. Reasons for this may include different interpretations of point estimates and confidence intervals, *a priori* beliefs, knowledge of pathophysiology, variable costs considerations and conflicts of interests.

As funding may influence how research findings are interpreted, it is of pivotal importance that report of SRs are fully transparent as of the different steps that authors undertake from the definition of the SRs question to the selection of studies and the criteria used to interpret the results. Cochrane reviews are ahead in this area as authors have to publish their protocol before undertaking their review and, once published in the Cochrane Library, reviews are open to public scrutiny and can be modified in subsequent updated when errors are detected or more data become available.

The impact of the Cochrane review on clinical research

Since its first publication the main message of this Cochrane review is that there is not good evidence to warrant the use of albumin in critically ill patients, as it may not only be infective but also harmful. As said before, the Cochrane review had a measurable impact in reducing the use of albumin in critically ill patients immediately after its publication. The methodological weaknesses of the available studies and their heterogeneous populations and variable treatment regimens suggest

that investigators should undertake larger, more rigorous studies based on current physiological rationale and modern randomised trials methods. On the basis of the Cochrane review reported here the Australian and New Zealand Intensive Care Society began a new large scale trial designed to enrol over 7000 patients. At least another large scale trial has been designed in Australia following the meta-analysis by Wade and attempting to evaluate not only mortality but also long term neurological sequelae of fluid choice. Other trials testing more specific hypothesis have also been launched as results of the Cochrane and other SRs in this area.

This example indicates that rigorous SRs of randomised trials can be a valuable tool to inform practice. It also indicates that their results can help to design trials in a more appropriate way and with more realistic expectations of benefits and harms. It also teaches us that, while physiological rationale often guides clinical practice, it is necessary to acknowledge when well conducted trials do not confirm the expectations, and be ready to revisit theories in the light of empirical data.

References

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No evidence supports the use of albumin in critically ill patients, but large areas of uncertainty make mandatory the production of new high quality data: the clinician's point of view

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A variety of circumstances like trauma, burns or surgery can lead to large blood loss. Fluid replacement is used to try to replace lost blood in order to maintain blood

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pressure and improve survival. Blood products, non-blood products or combinations are used, including colloid or crystalloid solutions.

Human albumin solutions are licensed for use in the emergency treatment of shock and other conditions where restoration of blood volume is urgent.

At present there is no evidence from randomised controlled trials that resuscitation with albumin and plasma protein fraction (PPF) improves survival, compared with resuscitation with cheaper alternatives such as saline, in patients with hypovolaemia, burns and hypoalbuminaemia. As human albumin is not associated with an improvement in survival, and it is more expensive than colloids and crystalloids, it is hard to see

how their continued use in these patients can be justified. However, present evidence does not rule out the possibility that there may be highly selective populations of critically ill patients in which albumin may be indicated. The poor methodological quality of the trials conducted in this field makes further evidence from high quality adequately powered randomised controlled trials urgently needed.

Therefore, in spite of the important meaning of this review, in view of the absence of evidence of a mortality benefit from albumin and the increased cost of albumin compared to alternatives such as saline, it would seem reasonable that albumin should only be used within the context of high quality clinical trials.