

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

Albumin infusion is associated with reduced survival - results of meta-analyses

Report of a Pro-Con debate conducted as part of the 22nd International Symposium on Intensive Care and Emergency Medicine, held in Brussels in March 2002.

This debate gave an opportunity Ian Roberts (UK), the main author of the published Cochrane Injuries Group meta-analyses concerning albumin (*Brit Med J*, 1998, **317**, 235) and Mahlon Wilkes (USA) to present and discuss their findings.

Pro:

Dr Roberts proposed that agreement could not be reached about the effects of albumin on mortality in critically ill patients, because there is no evidence. He would not say unequivocally that albumin is harmful, but with the amount of information currently available we cannot know. The only way the question will be resolved is not by debating what little evidence there is, but through prospective randomised controlled trials (RCT) to provide the information.

The Cochrane Injuries Group's interest is in bringing together information from RCT about the effectiveness of various interventions, and interest in albumin was originally sparked when an intensive care specialist, Neil Soni, wrote an editorial in the *British Medical Journal*, in 1995 entitled "Albumin is not all its cracked up to be". He asserted that use of albumin was more to do with word association and treatment of items marked on the pathology form than with scientific medical management.

The Cochrane Group conducted a systematic search for all the RCT of the effect of human serum albumin (HSA) on mortality in critically ill patients with hypovolaemia, burns and hypoproteinaemia, the three licensed indications for albumin use. Dr Roberts did not describe further the criteria on which the trials were selected for inclusion in these meta-analyses, but directly presented the findings that have been published in the *British Medical Journal*.

Trials in hypovolaemic patients

In the 13 trials in hypovolaemia, the confidence intervals in all trials were very wide, but most are compatible with either a slight benefit or a slight harm resulting from albumin use. However, combining the results to try to reduce the impact of random variability between trials, the pooled relative risk (RR) for the effect of albumin is 1.46 (Confidence Interval [CI] 0.97-2.22). The point estimate is on the harm side but the CI is wide so this is not clear cut evidence that albumin is harmful, but there is no evidence that albumin is beneficial.

Trials in burns patients

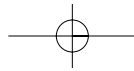
A similar comparison of three small trials of albumin versus no colloids in burns, again showed a wide confidence interval, but the pooled RR is 2.40 (CI 1.11-5.19). The CI

now excludes the null value, but these were not high quality trials and poor quality trials are often biased; it cannot be said that this is clear-cut evidence that albumin is harmful, but again there is no evidence of benefit.

Trials in hypoalbuminaemic patients

There were eight trials of albumin versus no colloid in patients with hypoalbuminaemia, and in each the RR is towards the "harm" side with a pooled RR of 1.69 (CI 1.07-2.67). These are still not necessarily the best quality trials and therefore it cannot be said that albumin is clearly harmful, but certainly there is no evidence of benefit in this indication from these eight trials.

These findings are of concern because, if they are added together (although some would dispute the validity of doing so), 14% of patients treated with albumin died compared with 8% in the control groups, an absolute difference in the risk of death of 6%. If this was a real result, there could be six additional deaths for every 100 patients treated. This would not be detected or detectable in normal clinical practice and that is why RCT are needed. The Cochrane Group concluded that albumin could be harmful and that RCT should be done to find out one way or the other.



Dr Roberts considers that the results of the meta-analysis are fairly straightforward:

- there is little evidence at all,
- such evidence as is available is not of high quality,
- if it is added together it shows no evidence of benefit of albumin and a suggestion of harm.

It can be divided different ways, different interpretations can be devised, but in essence there is little information.

The Cochrane Group, in preparing meta-analyses, seeks information from both published and unpublished sources, including data submitted to licensing authorities by manufacturers. Pointing out that the government was, essentially, the largest manufacturer of albumin in the UK (via national the Blood Transfusion service), Dr Roberts described the difficulties the Cochrane Group had encountered in obtaining information given in confidence by the industry to the licensing authorities. He also described the reactions provoked by the publication of this meta-analysis, in the intensive care community, government circles and the plasma products industry. After publication of the Cochrane Group's review, use of albumin fell sharply.

The Intensive Care Society of Australia and New Zealand responded to the review by instigating a large RCT, the Saline versus Albumin Fluid Evaluation (SAFE) study, to look the effects of human albumin or saline on 28-day mortality in critically ill patients. This is planning to recruit in the order of 7000 patients and will be really important in providing the evidence needed. Dr Roberts concluded by recommending that doctors not listen to propaganda, but wait for results of this large and important study.

Con:

In response, Dr Wilkes advocated the view that albumin infusion is not associated with reduced survival, with the contentions that:



Mahlon Wilkes

- The Cochrane meta-analysis is unreliable because it is based on a small, biased subset of the total evidence - therefore it is not so much that evidence is lacking, but that all evidence was not considered by the Group
- No overall effect of albumin on survival has been demonstrated in a larger, more reliable meta-analysis
- Higher quality trials suggest survival benefit
- Harm due to albumin is mechanistically implausible and inconsistent with the superb long-term safety record of albumin
- Based on extensive evidence, albumin reduces morbidity and this effect is also inconsistent with harm.

Dr Roberts had mentioned the trials that were included in the Cochrane meta-analysis. There were five trials specifically considered and excluded, and overall those trials favoured albumin. Dr Wilkes said that they were excluded on an ad hoc basis in that the exclusions were not consistent with the stated trial selection criteria of the meta-analysis. Furthermore, the Cochrane collaborators omitted 10 trials which overall favoured albumin; those trials had conformed with the stated trial selection criteria.

In the five trials excluded on an ad hoc basis the pooled RR is 0.93 (0.73-1.20), with three of the five favouring albumin. When the 10 trials that conformed with the stated trial collection criteria, that

is they concern hypovolaemia, burns and hypoalbuminaemia, are considered, they fairly strongly suggest a reduction in mortality associated with albumin administration (pooled RR 0.78 (0.57-1.06) (Figure 1).

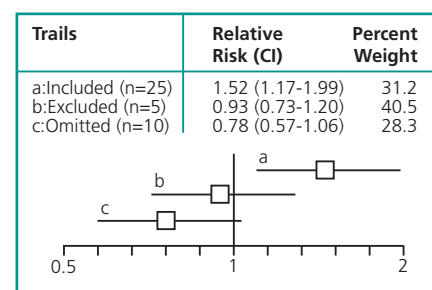
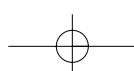


Figure 1 Relative risk of mortality associated with albumin administration in trials included, excluded and omitted by the Cochrane Injuries Group.

Comparing the findings of the 25 included versus the five excluded and 10 omitted trials (Figure 1), there is a large disparity in the point estimates of relative risk. There is a strong suggestion of harm from the 25 included trials, while the excluded and omitted trials suggest the opposite. A critical point is that the excluded and the omitted trials were more than twice as large as the included trials in terms of median number of patients per trial; consequently, they account for the majority of the weight of meta-analytic evidence. The included trials account for 31.2% of the total weight of available evidence in the combined meta-analysis.

Wilkes and Navickis published their own meta-analysis in 2001 (*Ann Intern Med*, 2001, **135**, 149) of randomised trials of albumin, versus crystalloid, no albumin or lower dose albumin. They considered papers concerning all indications, with no particular exclusion rules applied. Thus, all the trials considered by the Cochrane Group were included, together with additional trials.

Wilkes and Navickis found no statistically significant overall effect on survival, pooled RR 1.10



(CI 0.95-1.27). While in different indications there were RR greater or less than 1, there were no categories of clinical indications in which there was a statistically significant overall effect of albumin on mortality. Dr Wilkes argued that the overall results are contaminated by the contribution of poorer quality trials to which Dr Roberts had already alluded. Trial quality makes a substantial difference to the findings of meta-analyses. Higher quality trials are:

- blinded,
- have mortality as an endpoint,
- have no crossover, or
- include more than 100 patients.

Mortality endpoint

Trials designed to assess mortality as an endpoint rather than physiological variables are more likely to have an adequate follow up period and safeguards to avoid detection bias.

Crossover

It was the practice in some trials of attempting to rescue the control group patients by switching them to albumin if their clinical condition deteriorated. On an intention-to-treat analysis, the switched patients would retain their control group assignment and the net effect would be to spuriously reduce the apparent mortality rate in the control group.

Large trials

Larger studies are usually recognised to be more rigorously designed and conducted and, overall, more reliable.

Considering the highest quality trials, in all six of the subsets defined by the presence of two more attributes indicative of higher quality, RR is substantially below 1, consistently pointing toward a possible survival benefit associated with albumin (Figure 2).

Quality Attributes	Trials	Relative Risk (CI)
Blinded + Mortality Endpoint	2	0.59 (0.35-1.00)
Blinded + No Crossover	5	0.64 (0.40-1.04)
Blinded + 100 or more Patients	2	0.54 (0.31-0.92)
Mortality Endpoint + No Crossover	14	0.89 (0.73-1.07)
Mortality Endpoint + 100 or more Patients	8	0.93 (0.76-1.14)
No Crossover + 100 or more Patients	8	0.85 (0.68-1.06)

Figure 2 Relative risk associated with albumin administration - meta-analysis of higher quality trials.

Dr Wilkes would argue that this more recent published meta-analysis is more reliable than that of the Cochrane Injuries Group, because of:

- The comprehensiveness of included trials
Considering the trials with one or more deaths, which are those that contribute to relative risk calculations, there were 43 considered by Wilkes and Navickis and 25 considered by the Cochrane Group, including 3000 and 1300 patients, respectively.
- The quality of included trials
The proportion of blinded trials was greater in Wilkes and Navickis meta-analysis; a higher proportion had mortality as a protocol-defined study endpoint, a slightly higher proportion had no crossover and twice as many trials included 100 or more patients.

Dr Wilkes said that his meta-analysis was funded by the PPTA, which certainly has an economic stake in that it represents albumin suppliers, but the PPTA's support was in the form of an unrestricted grant and the organisation had no role in the design, conduct, creation of the review or its approval processes. The Cochrane Group meta-analysis was supported by the UK NHS, who have an economic stake in both supplying and paying for albumin, but it is not disclosed what the role, if any, of the NHS has been in the original meta-analysis and its subsequent update.

The safety record of albumin

If there were harm from albumin, how might that occur?

The Cochrane Group suggested two possible mechanisms:

- Promoting oedema during vascular leak
- Increasing bleeding by an anticoagulant effect

However, The Society of Critical Care Medicine Task Force concluded in its published 1999 recommendations on fluid resuscitation of adult patients with sepsis: "Clinical studies in patients with septic shock and the acute respiratory distress syndrome have not found evidence of increased lung water or compromised lung function with administration of colloids" and De Jonge and Levi (*Crit Care Med*, 2001, **29**, 1261) could not identify "any report on an increased bleeding tendency related to the infusion of albumin".

Apart from these recent conclusions, the safety record of albumin and the history of investigation of albumin safety go back 60 years. A recent pharmacovigilance study (von Hoegen and Waller, *Crit Care Med*, 2001, **29**, 994) has reviewed the 100 million albumin doses distributed worldwide between 1990 and 1997. In that time, the incidence of spontaneously reported serious adverse events (SAE) has been 1.29 per million doses, with no deaths "probably" attributable to albumin, and the incidence of fatal SAE "possibly" related to albumin was 5.24 per 100 million. The authors conclude that both fatal and nonfatal serious adverse events in albumin recipients are very rare.

These data suggest that both mortality and morbidity are low in association with albumin administration, and in addressing the issue "what is the benefit" one has to consider morbidity, which is clinically relevant and a more sensitive endpoint than mortality.

Of RCT showing a *significant within-study difference* between albumin and control, the only one with mortality as an endpoint (Sort *et al*, *N Engl J Med*, 1999, **341**, 403) showed a significant survival difference favouring albumin, while 16 of 17 which showed a statistically significant within study difference in morbidity favoured albumin (Table 1).

Endpoint	Total	Albumin superior
Mortality	1	1
Morbidity	17	16*

Table 1 Randomised clinical trials showing significant within-study difference between albumin and control.

* In the exceptional study (Lucas *et al*, *J Trauma*, 1978, **18**, 564), the excess morbidity has been recognised as being more related to fluid overload than albumin *per se*.

As Dr Wilkes had proposed in an earlier session, this postulated albumin morbidity benefit can be confirmed by meta-analysis. A new meta-analysis, not yet published, considered the same group of trials as before but looked at morbidity rather than survival. In the 56 RCT published and unpublished in which morbidity data are available, the morbidity is significantly lower overall in albumin recipients (0.93, CI 0.90-0.96), and this significant morbidity benefit is seen in four of the five subsets of trials defined by the presence of higher quality

attributes. He also referred to the meta-analysis conducted in collaboration with Professor Vincent and Dr Marc-Jacques Dubois and Dr Navickis, focussing on controlled trials of albumin therapy to correct hypoalbuminaemia. In the meta-analytical regression, as the albumin dose increases, as reflected by the attained albumin level during therapy, there is a progressively stronger evidence of morbidity benefit associated with albumin therapy.

Dr Wilkes also welcomed the SAFE trial being conducted in Australia and New Zealand and concluded that - with reference to the title of the debate:

- Albumin is not harmful
- Albumin does not increase mortality
- Higher quality trials suggest survival benefit, which merits further investigation
- Based on extensive evidence, albumin reduces morbidity

Discussion

Dr Roberts said in considering poor quality evidence, he saw no point in discussing which trials should be included and which should not. There is clearly uncertainty, which can only be resolved by a large, rigorously conducted RCT. The wrong approach is to contest poor quality evidence. There is no clear evidence that albumin is beneficial and it is very expensive. Patients

should receive treatments not because they do no harm but because they have been shown to be of benefit and this does not, at the moment, apply to albumin. RCT are the appropriate way forward. He asserted that this is all that the Cochrane Group has ever advocated. Such trials are now in progress and are to be welcomed.

Dr Wilkes would certainly not contest the view that there is a role for trials such as the SAFE trial. However, he cannot support the premise that the issue is one of dissecting the same evidence different ways to get different results, because he considers that the Cochrane Group considered only one third of the evidence. Some of the evidence excluded, for whatever reason, was of better quality than that included and that larger pool of evidence allowed analysis in greater detail of the effects of trial quality. If the original BMJ Cochrane paper is read, the position stated there was that there was a strong argument that albumin should only be used in the context of randomised trials, so Dr Roberts and his collaborators had taken the position that albumin should not be freely available for clinical use as it has been for 60 years. Dr Wilkes does not believe that that position is supported by the totality of evidence.

The presenters had the opportunity to review and to comment on this manuscript before publication

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