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Editorial

The Cochrane 1998 Albumin Review – not all it was cracked up to be

In 1995 Neil Soni wrote an Editorial in the *British Medical Journal* [1] entitled 'Wonderful albumin? – not all it was cracked up to be'. In doing so, he lit the fuse that resulted in the explosion caused by the publication of the Cochrane Injuries Group Albumin Reviewers' (CIGAR) meta-analysis 3 years later [2]. Soni was asked by the *BMJ* to peer review the CIGAR review, and his opinion, which was overruled, was that it should not be published. The CIGAR review appeared in the *BMJ* on 25 July 1998, and the conclusions were described by the Editor as 'suitably tentative'. The main one was that albumin in critical illness kills more people than it saves. The media immediately seized on this clear message and trumpeted it abroad before most doctors had read the review. On 24 July 1998, *The Times* (London) reported that the review 'suggests that up to 30 000 patients in Britain alone have died because they were treated with human albumin solution'. Seldom has an article in a medical journal provoked so great an impact or caused so much concern, presumably to patients, and certainly to doctors in intensive care units. Ian Roberts, the review's principal author, had warned the UK Department of Health of the mortality findings the previous April and later accused it of dragging its feet for not responding. This resulted in the *Observer* (London) headline on 26 July 1998, which stated '300 die as health chiefs dither'. Commenting on the results of CIGAR, Roberts was reported as saying, 'We were amazed but totally confident we are accurate … having studied all the evidence I am sure we are right'. Events since then have shown that he did not study all the evidence and may well have been wrong.

The Cochrane reviewers said that the clinical use of albumin should be confined to a large blinded randomized clinical trial; no such trial has been started in Europe in the ensuing 4 years, which is not surprising in view of the media's response and the comments by Iain Chalmers, the Director of the UK Cochrane Centre, who let it be known that not only would he refuse to take part in such a trial, but also he would sue any doctor who gave him an infusion of albumin. Two years later he took encouragement from the prospect of patients seeking redress in the courts for clinical negligence if the guidelines based on evidence such as that of the CIGAR review were transgressed [3]. Subsequently, two members of the Cochrane Collaboration wrote an Editorial in the *BMJ* [4], saying the Cochrane reviews were widely cited in guidelines for healthcare and that the *BMJ*, in common with other journals, recommended their editorialists to refer to relevant Cochrane reviews where these exist. Thus any editorial concerning albumin is now expected to quote the CIGAR review (which was updated in 2001 [5] with minor changes and no alteration in its conclusions) and, it is implied, to accept its conclusions. In this way, the Cochrane review is disseminated as received wisdom. The current position is that if one accepts these guidelines, albumin should not be used in the treatment of hypovolaemic patients who are critically ill as it has been shown in the CIGAR review to involve a 5% excess mortality rate. How likely is this to be true?

Physiology of albumin

Albumin is usually thought of as an important constituent of plasma, but in health it is predominantly extravascular, permeating the interstitial fluid of the tissues at concentrations which are mostly 25–30% of the plasma concentration. Normal capillaries allow about 5% of the plasma albumin content to escape each hour, so that the entire plasma content leaves the blood stream every 24 h and is replaced by an equivalent amount through the lymphatic system. In contrast to acute-phase proteins whose concentrations rise in response to stress and injury, the plasma albumin concentration falls, partly due to reduced liver synthesis and probably partly to redistribution. The only one of the many physiological properties of albumin which is of importance in this context is that, volume for volume, 4.5% albumin is approximately four times as effective in expanding the plasma

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volume as sodium-containing crystalloids. This attribute accounts for its continuous use by paediatric intensivists since the 1998 review – they, more than most, are wary of large infusions of isotonic sodium in neonates and infants.

Commenting on the CIGAR review as it was published, the *BMJ*'s Science Editor [6] wrote that in hypovolaemic shock the increased capillary permeability allowed albumin to escape from the circulation and attract water into the extracellular fluid, resulting in life-threatening pulmonary oedema. Comments such as this overlook the fact that the control groups in the hypovolaemic patients in some of the randomized clinical trials were given large volumes of whole blood, fresh frozen plasma and platelets, and no one has suggested that the albumin in these acts differently, as far as capillary leakage is concerned, from processed albumin.

Processed albumin

A possible cause of harm due to albumin is that during its processing both organic and inorganic substances may be formed or added. This was certainly true until the last 15–20 years and the UK product, which was known as Plasma Protein Fraction, was associated with a 1% incidence rate of febrile reactions or hypotensive states. Since then modern fractionating has resulted in a product with a much reduced frequency of adverse reactions. The Human Albumin produced by the Bio Products Laboratory in England was reported by Matejtschuk and colleagues [7] to be associated with one adverse reaction in 17 000 infusions of the 4.5% solution and one in 78 000 of the 20% product. There were no deaths. Under-reporting is inevitable in such surveys, but they include patients undergoing plasmapheresis who received large volumes of albumin and were closely monitored: deaths and serious reactions would certainly not have been overlooked.

Explanations for the excess albumin mortality rate

I contend that there are two reasons for the 5% extra mortality rate attributed to albumin in the CIGAR review. The first is found in the constitution of the seven Cochrane collaborators who comprised the Injuries Group. Not one of them had ever had ultimate clinical responsibility for critically ill adults in an intensive care ward. This may account for them overlooking or disregarding important matters in, for instance, the trial by Lucas and colleagues [8] as described in my *Lancet* Viewpoint paper [9]. By overlooking the fact that deaths were only reported in patients in both groups who had survived 24 h, the CIGAR reviewers failed to realize that this meant that all the deaths in both the albumin and control arms that occurred during resuscitation and surgery were excluded from the mortality rates they documented. The mortality of the 26 victims in the control group who suffered gunshot and knife wounds necessitating an average of one-and-a-half blood volume replacement is given in CIGAR as nil. Any clinician familiar with this type of work would know that this is not remotely likely, yet the CIGAR team accepted it uncritically.

The second reason was the choice as an end-point of deaths from all causes by the end of follow-up. Roberts, in rejecting various indices of disturbed cardiovascular function, wrote, 'the use of a pathophysiological end point as a substitute for an adverse outcome, assumes a direct relationship between the two that may sometimes be inappropriate'. This is true, but it applies equally to deaths that occur in the hypovolaemia randomly controlled trials, days and sometimes weeks after infusions of albumin: it strains credulity to link the death of a victim of a gunshot wound that penetrates his colon and causes widespread faecal peritonitis with albumin given during resuscitation. Furthermore, deaths following major arterial surgery are obviously likely to be associated with preoperative cardiovascular disease and the incidence of this in the small numbers of several of the trials was higher in the albumin groups than the controls [9].

In the CIGAR review there were 38 deaths in the 256 patients in the albumin arms. If the Lucas trial is excepted, not one of the authors of the other randomized clinical trials implicated albumin as a cause of death. The seven deaths in the trial reported by Lucas and colleagues were said to be due to heart failure and pulmonary oedema [8,10]. This is precisely what any contemporary intensive care doctor would expect if a group of young men were given an average of 600 mL 25% albumin a day for up to 5 days, plus 4 L crystalloids, at a time during which they were in a phase of positive water and sodium balance and gaining weight. In this manner, abuse of albumin given for hypoalbuminaemia was accepted by the Cochrane team as use of albumin for hypovolaemia and assigned a relative risk of death of 13.9 – exactly equal to the sum of all the relative risks of the other six trials purporting to indicate harm – with a relative risk of death of >1.

The Zetterström trial [11] is the most egregious example of the tenuous evidence linking albumin to mortality in the CIGAR review. Five per cent albumin was given to the 9 patients in the albumin arm during aortic surgery and for 20 h thereafter. Of these 9 patients, 2 died, aged 80 and 70 yr, on the 4th and 38th postoperative days. I wrote to Zetterström recently and in his reply he expressed his astonishment

that deaths days and weeks after receiving albumin for replacement of perioperative losses of albumin could be linked.

In the Viewpoint paper [9], I concluded that all the evidence relating to hypovolaemia was flawed. Roberts was sent the draft by the *Lancet* before publication and his response was printed with it [12]. His reply failed to refute any of the allegations, although it was considered satisfactory by Chalmers, Offringa and Gotzsche – all members of the Cochrane Collaboration. For one who had described his group's review as 'a strong argument for preparing *scientifically defensible* (my italics) syntheses of the evidence of RCTs (randomized clinical trials) in medicine', Roberts's response was no surprise. All criticisms of the CIGAR review during the previous 4 years had been met with a response from him and other Cochrane collaborators which was both dismissive and evasive.

The Brussels debate – an opportunity missed

The opportunity to defend the CIGAR review scientifically came in a Pro/Con debate in March 2002 in Brussels, Belgium, at the 22nd International Symposium of Intensive Care and Emergency Medicine. The motion was 'Albumin Infusion is Associated with Reduced Survival: Results of Meta-analyses'. Speaking against the motion was Mahlon Wilkes, who (along with Navickis) had published a wider meta-analysis [13], including all the randomized clinical trials in the CIGAR review, together with 18 other randomized clinical trials. All but two of these, Wilkes claimed, complied with the CIGAR criteria for inclusion but had either been overlooked or excluded by the Cochrane group.

In the seven highest quality trials in the hypovolaemia category the pooled relative risk was 0.87 (CI 0.67–1.14) implying a tendency to benefit from albumin in contrast with the CIGAR figures of 1.46 (0.97–2.2) implying the opposite.

If ever there were an opportunity for reasoned debate this was it – the first time that the oft-repeated claim from Roberts (and every other member of the Cochrane Collaboration who had entered the debate) that there was no evidence of benefit from albumin had been challenged. What happened was a travesty of a confrontation because Roberts refused to step into the ring and spent two-thirds of his time reiterating what he called 'politics' by which he meant his dealings in 1998 with the UK government, the Bio Products laboratory, the plasma products industry and doctors. All of this had been documented at the time and had recently been resurrected in a paper with Frances Bunn who is one of the Cochrane Injuries group [14]. In doing so, he evaded the challenge of the Wilkes meta-analysis, but he can no longer claim that there is no evidence that albumin may confer benefit in critical illness.

The international impact of CIGAR

If the *BMJ* had published the Cochrane meta-analysis with qualified editorial comment, the explosion in July 1998 would not have erupted. Instead, the review received then and ever since unquestioning and enthusiastic support from Richard Smith, its Editor. Exactly a month earlier he had given a lecture to the Royal College of Psychiatrists in which he was reported to have said [15] that only 5% of articles published in medical journals reached minimum standards of scientific soundness and clinical relevance. The CIGAR review was assessed by one or two editors, two practising doctors experienced in assessing peer reviews (usually physicians) and a statistician [16], all of whom read every word. Clearly these five decided that CIGAR was one of the 5% of articles submitted to the *BMJ* that was scientifically sound.

The international impact of this has been considerable. The European Union has adopted a revised *Core Summary of Product Characteristics* for albumin and the UK a more restrictive one. The Scottish National Blood Transfusion Service has, according to Chalmers, advised that CIGAR provides convincing evidence that albumin is associated with a higher mortality than crystalloids in critical illness. In the USA, the Food and Drugs Administration and the University Healthcare System Consortium have both quoted the Cochrane review as evidence of the increased mortality attributable to albumin in critical illness and the Consortium has issued guidelines for fluid resuscitation accordingly [17].

Benefits and harmful effects of the Cochrane Albumin Review

CIGAR has belatedly resulted in the setting up of the SAFE (Saline versus Albumin Fluid Evaluation) randomized controlled trial in Australia and New Zealand. To date this has recruited 1300 patients and is on target to achieve its aim of 7000 patients by 2004 [18]. Unfortunately it is restricted to adults so will not provide guidance about the safety and possible benefits of albumin in those cases where it still finds staunch supporters. Roberts can and does take credit for the SAFE study and if it shows no increased mortality attributable to albumin, he will remain unabashed. In the event that albumin is shown to benefit some classes of critical illness this will be more difficult. The CIGAR review certainly made clinicians more critical in their attitudes to fluid therapy and clearly many stopped using albumin, an act which may or may not turn out to have been justified.

If the allegations in my Viewpoint paper [9] and in this Editorial are valid, it follows that the Cochrane Albumin Review is a work of disrepute and that Neil Soni's assessment of it was correct [1]. If the result of the Wilkes meta-analysis [13] is supported by future trials, the Cochrane review will have harmed and not benefited critically ill patients.

As matters now stand, the real harm it is doing is to the Cochrane Collaboration itself because of the stubborn reluctance of its Injuries Group and their fellow collaborators to acknowledge they may have been wrong. If the 1998 Cochrane Albumin Review remains posted in the Cochrane Library, it will call into question the validity of all of the other Cochrane meta-analyses.

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References

1. Soni N. Wonderful albumin? – not all it was cracked up to be. *BMJ* 1995; **310**: 887–888.
2. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; **317**: 235–240.
3. Chalmers I. A patient's attitude to the use of research evidence for guiding individual choices and decisions in healthcare. *Clinical Risk* 2000; **6**: 227–230.
4. Clarke M, Langhorne P. Revisiting the Cochrane Collaboration. *BMJ* 2001; **323**: 821.
5. Cochrane Review. Human albumin for resuscitation and volume expansion in critically ill patients. In: *The Cochrane Library*, Issue 3. Oxford Update Software, 2000.
6. Berger A. Why albumin may not work. *BMJ* 1998; **317**: 240.
7. Matejtschuk P, Dash CH, Gascoigne EW. Production of human albumin solution: a continually developing colloid. *Br J Anaesth* 2000; **85**: 887–895.
8. Weaver DW, Ledgerwood AM, Lucas CE, Higgins R, Bouwman DL, Johnson SD. Pulmonary effects of albumen resuscitation from severe hypotensive shock. *Arch Surg* 1978; **113**: 387–392.
9. Horsey P. Albumin and hypovolaemia: is the Cochrane evidence to be trusted? *Lancet* 2002; **359**: 70–72.
10. Kovalik SG, Ledgerwood AM, Lucas CE, *et al.* Impaired pulmonary function after albumin resuscitation from shock. *J Trauma* 1980; **21**: 275–279.
11. Zetterström H. Albumin treatment following major surgery II: effects on postoperative lung function and circulatory adaptation. *Acta Anaesthesiol Scand* 1981; **25**: 133–141.
12. Roberts I. Albumin and hypovolaemia: time to move on and generate new evidence. *Lancet* 2002; **359**: 72–73.
13. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomised, controlled trials. *Ann Intern Med* 2001; **135**: 149–164.
14. Roberts I, Bunn F. Egg on their faces. The story of human albumin solution. *Eval Health Prof* 2002; **25**: 130–138.
15. Boseley S. Medical studies 'rubbish'. *The Guardian* 1998, 24 June, 5.
16. Smith R. *Why I published 'the albumin paper': confession of a buccaneering editor*. 8th World Congress of Intensive Critical Care, November 2001, Sydney, Australia.
17. Vermeulon LC Jr, Ratko TA, Erstad BL, Brecher ME, Matuszewski KA. A paradigm for consensus. The University Hospitals Consortium guidelines for the use of albumin, non protein colloid and crystalloid solutions. *Arch Intern Med* 1995; **155**: 373–379.
18. Australian Red Cross Blood Service. Unpublished data.