Commentary

Debate: Albumin administration should not be avoided

Simon P Allison and Dileep N Lobo

University Hospital, Queen's Medical Centre, Nottingham, UK

Received: 11 January 2000
Accepted: 21 April 2000
Published: 15 May 2000

Crit Care 2000, **4**:147–150

The electronic version of the accompanying article can be found online at http://ccforum.com/content/4/3/151

Abstract

The recent Cochrane report on albumin administration is analysed and criticised on the grounds of clinical methodology, content and interpretation. Although it is naïve and illogical to treat hypoalbuminaemia with albumin infusions, a more balanced view on the use of albumin for resuscitation in acute hypovolaemia is necessary. Once the acute phase of critical illness is past, interstitial volume is often expanded causing oedema, with a low plasma volume. We argue for the use of salt-poor albumin solutions in this situation and conclude that, on current evidence, the assertion that albumin should be avoided in all situations is irrational and untenable.

Keywords: albumins, colloids, critical illness, crystalloids, hypovolaemia

Introduction

Meta-analyses and systematic reviews are useful, but potentially dangerous tools in the present age of evidence-based medicine. Evidence presented in such studies is graded as type Ia, and is more than likely to be accepted uncritically and to change clinical practice. The conduct of a systematic review or a meta-analysis is, therefore, a process of utmost scientific importance, and must be undertaken with the same care as a randomized controlled study [1]. Any meta-analysis is only as good as the studies included. Each study needs to be critically appraised and rated not only for its statistical methodology, but also for its clinical and physiological validity.

The systematic review of the use of albumin by the Cochrane Injuries Group [2] has rightly been criticized for a number of reasons. First, the media hype that accompanied it was inappropriate for a subject that requires rational scientific appraisal. Second, pooling data from studies on extremely heterogeneous groups of patients makes firm conclusions difficult. Third, although the authors were undoubtedly expert statisticians, none of them appeared to have much understanding or experience of the underlying pathophysiological problems being studied. Thus, although they were able to score the trials analyzed for their statistical validity, they appeared to take no account of the clinical and physiological validity of the studies being conducted. There was no comment, for example, on whether the fluids studied were titrated to accurate physiological end-points, or were merely given in absolute amounts, irrespective of the underlying physiology. Solutions of albumin, crystalloids or plasma substitutes cannot be treated like drugs of fixed dosage, and need to be titrated to desirable physiological end-points. This is because if they are given indiscriminately to individuals with a normal or excessive plasma volume, there are clearly grave risks of overloading the patient and increasing mortality.

A further major condemnation was the fact that the paper was published despite adverse referee criticism [3], and a number of paediatricians and burns specialists criticized

the inadequacy of the studies quoted from their own fields [4–6]. It is common practice, for example, to use albumin in the management of shock associated with meningococcal meningitis in children, and also in the postshock phase in severe burns. None of the studies in the review were designed with mortality as the primary end-point, and there was therefore no prerandomization stratification for mortality risk. Thus, conclusions concerning mortality can be only tentative at best.

It was perhaps the messianic rather than scientific method of its public presentation that antagonized many thoughtful clinicians. If, instead, its conclusions had been presented with caution and as a stimulus to further carefully conducted studies in specific groups of patients, then despite its limitations it would have served a useful purpose.

One might draw an analogy with the situation in the late 1970s and early 1980s concerning nutritional support. Critics such as Koretz [7] and Detsky *et al* [8] were rightly able to point to the lack of clear evidence that nutritional support was beneficial, and also to the poor quality of many of the studies conducted up to that point. Since that time, a whole flood of excellent studies has defined clear benefit in certain clinical circumstances and in certain groups of patients. Conversely, they have shown either no benefit or even harm in other groups. The clinical indications for this modality of treatment have therefore become much better defined. In the present discussion we make a plea for a similarly thoughtful approach to the use of albumin.

Clinical situations

There are three clinical situations in which albumin has been or should be considered: hypoalbuminaemia; resuscitation in acute hypovolaemia; and in hypovolaemia occurring after the acute phase of critical illness.

Hypoalbuminaemia

Use of albumin in hypoalbuminaemia is the ultimate naïveté, because hypoalbuminaemia bears no direct relationship to plasma or other fluid compartment volumes. It may occur in the presence of intravascular overload or deficit; it is also affected by dilution, disease and distributional factors. We may therefore dismiss the hypoalbuminaemia group of studies considered in the Cochrane report [2], because there must be few, if any, clinicians who would even consider using albumin merely to correct a serum albumin concentration. One might just as well say that all patients with hyponatraemia should be given salt solutions, irrespective of the patient's total extracellular sodium.

Resuscitation in acute hypovolaemia

Here again, in the adult patient there is no evidence in most situations that albumin solutions are any better than crystalloids or plasma substitutes. Indeed, at face value the results of the Cochrane report [2] are open to the interpretation either that there is no difference between albumin and other solutions, or that albumin gives a worse outcome, but not that albumin is potentially superior to any other solutions.

Another systematic review of colloids (including albumin) versus crystalloids [9] included methodological quality assessment of 17 trials on 814 patients, with mortality data. That review rightly concluded that, although the mortality results tended to favour the crystalloid group, an excess mortality in the colloid group could not be inferred on statistical analysis. It also suggested that colloids caused less pulmonary oedema than crystalloids, with a relative risk (95% confidence interval) of 0.84 (0.25–2.45). That review excluded studies in which hypertonic crystalloids were used in order to avoid the confounding influence of these solutions. Trial quality was assessed by evaluating the randomization procedure, population description, blinding, documentation of cointerventions and whether patient selection was consecutive. On this basis, only 11 out of the 17 studies had a validity score of 8 or more (worst possible score 0; best possible score 16). The authors of that review also assessed the use of physiological end-points such as tissue perfusion and oncotic pressure.

It is argued that, during the acute phase of critical illness, the transcapillary escape rate of albumin is high, and therefore administered albumin is not retained within the circulation for a sufficient length of time to be useful, and may accumulate in the tissues, causing adverse effects. Even here one should be cautious because there were some studies quoted in the Cochrane report that measured the physiological consequences of giving albumin versus crystalloid solutions, and appeared to show superior physiological effects of giving albumin without any detriment in terms of mortality [10,11].

The papers with the largest relative risk of death in the albumin group [12–14], and which therefore weighted the meta-analysis of the Cochrane Injuries Group [2], are either open to major criticism in terms of physiological and clinical methodology or are so small and with so few deaths that mortality figures in the studies themselves were statistically insignificant. The small study by Zetterstrom [12], with its relative risk of 5.0, had only two deaths out of 18 in the entire study, both in the albumin group. The study of Woods and Kelley [13] had only one death in 69 patients, but the relative risk was 2.61. This paper was included by the Cochrane reviewers in the hypovolaemia group even though the authors categorically state that 'thirty-four treatment group patients ($n=37$) received albumin for low levels postoperatively' [13], clearly indicating that the study should have been analyzed in the hypoalbuminaemia group. In none of these studies was mortality cited as a primary or even a secondary end-point.

The paper with the largest excess mortality, by Lucas *et al* [14], showed that this was predominantly due to cardiopulmonary failure. In that study, albumin was added to a standardized fluid resuscitation regimen in the protocol group, rather than being substituted for other fluids. This meant that the protocol group received higher volumes of fluids than did the control individuals, and it is hardly surprising therefore that there was an excess mortality in a group that was clearly given excessive fluid. It is of note that the albumin group received the same salt load as the nonalbumin group in phase 1, and a greater than average salt load in phases 2 and 3 of the resuscitation process. Patients in the albumin group also received more whole blood and fresh frozen plasma than did the control individuals. In fact, not unexpectedly, the measured plasma volume in the albumin group was, on average, 1294 ml greater than the theoretically expected volume.

As Webb [15] recently indicated, most of the papers discussed in the Cochrane study were designed to assess the effects of various fluids on physiological variables, and were not designed to assess mortality. He pointed out that a randomized controlled trial comparing one colloid with one crystalloid would require over 6500 patients to detect an excess mortality from colloid of 4% on the basis of the data presented in the Cochrane review. He concluded 'I cannot see how we can make a meaningful statement on comparative mortality.'

Although current evidence does not favour the use of albumin in acute resuscitation in most situations, the proper scientific view should be that the jury is still out, particularly in paediatrics. As some have pointed out, however, the way in which the Cochrane report was presented and interpreted has made the setting up of careful trials more rather than less difficult.

It is to be hoped that the recent paper by Sort *et al* [16] will be the first of many such trials that will define the indications for this expensive form of treatment in a more rational manner. They studied the effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. They randomly assigned 126 patients with cirrhosis and spontaneous bacterial peritonitis to treatment with intravenous cefotaxime (63 patients) or cefotaxime and intravenous albumin (63 patients). Mortality in the first group was 41%, and 22% in the albumin group. The difference was significant ($P=0.03$). The incidence of renal impairment was also reduced in the albumin group. That study did not compare the use of albumin with crystalloids or plasma substitutes. However, because both of these contain large amounts of sodium, which might be expected to have adverse effects in cirrhotic persons with ascites, this is perhaps a theoretical rather than a relevant clinical consideration.

The contention that albumin should be avoided in acute hypovolaemia is therefore a dogmatic and untrue generalization.

Plasma hypovolaemia after the acute phase of critical illness

One of the problems of resuscitation with crystalloids, or even the plasma substitutes, which all have a high sodium content, is that circulatory function is maintained at the expense of interstitial salt and water overload. The effect of acute illness and injury on salt and water retention have been known for many years [17,18]. Acutely ill patients are unable to excrete an excess salt and water load, and the return of a sodium diuresis is the first herald of recovery and convalescence.

One of the major arguments for the use of salt-poor albumin in resuscitation is that the circulation might be maintained without incurring a large interstitial salt overload. In the majority of patients, however, who make a good recovery, this overload is excreted spontaneously in the postacute period. Those patients who suffer persisting complications, however, continue to retain salt and water and to become increasingly oedematous. We have shown [19], for example, that patients, who are referred for nutritional support in the postacute phase and who are oedematous, have an average salt and water overload equivalent to 10 l extracellular fluid. This of itself may have adverse effects on pulmonary and gastrointestinal function. Such patients are often those with major complications of gastrointestinal surgery, with dehiscent wounds, intra-abdominal abscesses, fistulae and continuing losses of serous fluids. Many of these patients combine interstitial overload with a low plasma volume, leading to a low renal plasma flow. These patients are not only unable to diurese their salt and water overload because of renal responses to plasma hypovolaemia, but are also diuretic resistant. The logical treatment of such patients is the use of salt-poor concentrated albumin in a dose that is titrated carefully to physiological end-points such as central venous pressure, pulse rate, blood pressure, and urinary salt and water excretion.

Plasma substitutes contain high sodium concentrations and have a shorter half-life than plasma or albumin in the circulation. It seems, therefore, less appropriate to use these in the postacute phase. Compounding the salt excess with crystalloid is certainly inappropriate and merely worsens the oedema. Our own experience of the use of salt-poor albumin under these circumstances is that the diuresis ensues immediately with improved cardiovascular parameters. We have also found, in our clinical experience, that such patients only require 200–400 ml of 20% salt-poor albumin over 48 h. Once the plasma volume has been restored, no further administration of albumin is necessary, thereby indicating that the albumin is retained within the circulation, rather than leaking out continuously as it might do in the acute phase of illness.

It is common practice in some burns centres to use albumin during the postacute phase [6]. Many years ago we reported data on fluid and electrolyte balance in burned patients during the weeks after injury, and described the appropriate use of plasma and whole blood to sustain the intravascular volume at a level where salt and water diuresis occurred [20]. The Cochrane report [2] did not even mention the postacute situation, in which there are few formal studies. Doctors whose main experience is in intensive or critical care rarely have to deal with this postacute problem, and because most of the literature concerning the use of crystalloid, colloids and albumin emanates from this group, it is hardly surprising that it has received little or no attention, despite the fact that it is an important and common clinical entity. Studies comparing salt-poor albumin and plasma substitutes, titrated to physiological end-points, are needed in this situation.

Conclusion

We make a plea for a more thoughtful approach to the therapeutic use of albumin solutions.

There is no physiological logic in using albumin simply for hypoalbuminaemia, because it is plasma volume rather than protein concentration that is most clinically relevant.

In acute resuscitation, we accept that the weight of literature suggests at least that albumin has no advantage over crystalloid or other colloids in most cases, although there may be specific instances in adults and in children where its use may be beneficial, and one recent paper [16] concerning its use in peritonitis in cirrhotic persons showed a clear reduction in mortality. To regard this subject as closed by the Cochrane report would be unfortunate in the extreme, and we express the hope that further careful studies will be published in this area.

Finally, during the postacute phase of major illness, there are many patients who are left with an interstitial salt and water overload combined with a low plasma volume, in which the use of concentrated salt-poor albumin is the most logical treatment. Although clinical experience with the use of albumin in this group of patients is encouraging, formal studies are required to compare the use of albumin with that of the less expensive plasma substitutes.

The question to be addressed in each clinical situation is not only whether albumin is better than other fluids, but whether cheaper substitutes are just as effective and, therefore, more cost effective. We plead for an open-minded, thoughtful and scientific approach to this field, devoid of hyperbole or messianic fervour. We suggest that the view that albumin administration should be avoided in all situations is, on current evidence, untenable.

References

1. Sheldon TA: **Systematic reviews and meta-analyses: the value for surgery.** *Br J Surg* 1999, **86**:977–978.
2. Cochrane Injuries Group Albumin Reviewers: **Human albumin administration in critically ill patients: a systematic review of randomised controlled trials.** *Br Med J* 1998, **317**:235–240.
3. Soni N: **Human albumin administration in critically ill patients. Validity of review methods must be assessed.** *Br Med J* 1998, **317**:883–884.
4. Petros A, Schindler M, Pierce M, Jacobe S, Mok Q: **Evidence needs to be shown in paediatrics [letter].** *Br Med J* 1998, **317**:882.
5. Nadel S, Marriage S, De Munter C, Britto J, Habibi P, Levin M: **Review did not provide recommendations for alternate treatment.** *Br Med J* 1998, **317**:882–883.
6. Frame JD, Moiemem N: **Statisticians not trained in burns care should not evaluate data.** *Br Med J* 1998, **317**:884–885.
7. Koretz RL: **Is perioperative support of demonstrated value? Negative.** In: *Controversies in Gastroenterology*. Edited by Gitnick G. Edinburgh: Churchill Livingstone, 1984:253–261.
8. Detsky AS, Baker JP, O'Rourke K, Goel V: **Perioperative parenteral nutrition: a meta-analysis.** *Ann Intern Med* 1987, **107**:195–203.
9. Choi PT-L, Yip G, Quinonez LG, Cook DJ: **Crystalloids vs. colloids in fluid resuscitation: a systematic review.** *Crit Care Med* 1999, **27**:200–210.
10. Boutros AR, Ruess R, Olson L, Hoyt JL, Baker WH: **Comparison of hemodynamic, pulmonary, and renal effects of use of three types of fluids after major surgical procedures on the abdominal aorta.** *Crit Care Med* 1979, **7**:9–13.
11. Rackow EC, Falk JL, Fein IA, *et al*: **Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock.** *Crit Care Med* 1983; **11**:839–850.
12. Zetterstrom H: **Albumin treatment following major surgery. II: Effects on postoperative lung function and circulatory adaptation.** *Acta Anaesth Scand* 1981; **25**:133–141.
13. Woods MS, Kelley H: **Oncotic pressure, albumin and ileus: the effect of albumin replacement on postoperative ileus.** *Am Surg* 1993, **59**:758–763.
14. Lucas CE, Weaver D, Higgins RF, Ledgerwood AM, Johnson SD, Bouwman DL**: Effects of albumin versus non-albumin resuscitation on plasma volume and renal excretory function.** *J Trauma* 1978, **18**:565–570.
15. Webb AR: **Crystalloid or colloid for resuscitation. Are we any the wiser?** *Crit Care* 1999, **3**:R25–R28.
16. Sort P, Navasa M, Arroyo V, *et al*: **Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis.** *N Engl J Med* 1999, **341**:403–409.
17. Moore FD: *Metabolic Care of the Surgical Patient*. Philadelphia: Saunders, 1959.
18. Wilkinson AW, Billing BH, Nagy C, Stewart CP: **Excretion of chloride and sodium after surgical operations.** *Lancet* 1949, **i**:640–644.
19. Lobo DN, Bjarnason K, Field J, Rowlands BJ, Allison SP: **Changes in weight, fluid balance and serum albumin in patients referred for nutritional support.** *Clin Nutr* 1999, **18**:197–201.
20. Hinton P, Allison SP, Littlejohn S, Lloyd J: **Electrolyte changes after burn injury and effect of treatment.** *Lancet* 1973, **ii**:218–221.

Authors' affiliations: Simon P Allison (Clinical Nutrition Unit, University Hospital, Queen's Medical Centre, Nottingham, UK) and Dileep N Lobo (Section of Surgery, University Hospital, Queen's Medical Centre, Nottingham, UK)

Correspondence: S P Allison, Professor of Clinical Nutrition, Clinical Nutrition Unit, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK. Tel: +44 115 919 4427; fax: +44 115 919 4427; e-mail: simon.allison@mail.qmcuh-tr.trent.nhs.uk