

Crystalloid or colloid for resuscitation. Are we any the wiser?

Andrew R Webb

Address: Director of Intensive Care and Cardiac Services, University College London Hospitals, Mortimer Street, London, W1N 8AA. UK.
Tel: +44 20 7380 9008; fax +44 20 7636 3264;
email: a.webb@academic.uclh.nthames.nhs.uk

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Introduction

In the past year there has been an escalation of the age-old crystalloid–colloid debate as a result of the publication of several systematic reviews assessing the effect of various colloids versus various crystalloids on mortality. In 1998, an excess mortality of 4% for the colloid resuscitated patients was claimed for various colloids versus various crystalloids in various clinical scenarios [1]. A further systematic review, published in July 1998 from the same lead author, compared mortality in patients receiving human albumin solutions with those who did not and concluded there was a 6% excess mortality in the albumin group [2]. In 1999, a systematic review claimed no difference in mortality for colloid or crystalloid resuscitation where various colloids were compared to various crystalloids in various hypovolaemic insults [3]. This commentary seeks to analyse the systematic reviews critically and relate their findings to clinical practice in the modern intensive care unit.

Data presented in the systematic reviews

Crystalloid versus colloid in fluid resuscitation [1]

A total of 26 trials were selected comparing a variety of colloids carried in a variety of crystalloid solvents and compared to a variety of crystalloids, including 3.5% gelatine in the crystalloid group in one study [4]. Of these studies, mortality data were presented for 19 including 1315 patients. There was a claimed excess mortality of 4% in colloid group [95% confidence interval (CI) 0–8%] with a relative risk of 1.19 (95% CI 0.98–1.45).

Table 1 shows there was a bias towards inclusion of papers using albumin or dextran as the colloid. This is not surprising as these are the older colloids for which most comparative data exist. It is apparent that the only trials contributing to the mortality effect of colloid used albumin or dextran. The two dextran papers were by the

same authors [5,6] and both used hypertonic saline as the crystalloid in trauma resuscitation. It is not clear whether the colloid effect would be the same given with hypertonic crystalloid as the effect when given with isotonic crystalloid. In practice, there is an early, marked plasma volume expansion with hypertonic crystalloid which is not seen with isotonic crystalloid. This effect is short lived but may be maintained if colloid is used in addition. Furthermore, the current accepted view for fluid resuscitation in trauma is to secure haemostasis before full restoration of circulating volume since full early restoration promotes more bleeding. This is quite different to the management of other (non-haemorrhaging) critically ill patients where early restoration of circulating volume is considered to be an urgent goal.

The albumin papers included one using 5% (not 50% as stated in the review) albumin in acute respiratory distress syndrome (ARDS) [7] and one using a low concentration of albumin in burns patients [8]. In the series of Metildi *et al* [7] there was an imbalance of illness severity between the groups with an excess of septicaemic patients in the crystalloid group, the difference in illness severity accounting for the outcome differences. In the paper by Goodwin *et al* [8] albumin apparently contributed heavily to an excess mortality in the colloid group. Many burn centres contend that crystalloid resuscitation is as effective as albumin resuscitation, although argument persists over the role of larger molecular weight hydroxyethyl starches. In many burn centres, fluid resuscitation is guided by formulae rather than any physiological measurement. General intensive care units treating burned patients often discard the formula and resuscitate as they would for any hypovolaemic patient, guided by filling pressures and/or cardiac output measurements. Burned patients endure massive capillary leak for several days and it is easy to see why smaller molecular weight colloids (including albumin) may not be useful. It is more difficult to understand why a low concentration of albumin should contribute anything, particularly death.

Albumin versus no albumin [2]

The second systematic review of 30 trials with mortality data included 1419 patients with various concentrations of albumin, various hypovolaemic insults and hypoalbuminaemia included as an indication. There was a claimed excess mortality overall of 6% in albumin group (95% CI

Table 1**Colloids assessed in the 1998 systematic review**

Colloid	Papers	Patients	Colloid		Crystalloid		Papers contributing to excess mortality
	<i>n</i>	<i>n</i>	<i>n</i>	deaths	<i>n</i>	deaths	
Albumin	7	381	180	29	201	23	3 of 7
Gelatin	1	22	11	0	11	0	0 of 1
Hydroxyethyl starch	1	41	21	2	20	2	0 of 1
Dextran	7	652	351	96	301	56	2 of 7
Plasma	1	153	74	30	79	30	0 of 1
Mixed	2	66	48	11	28	7	0 of 2

3–9%) with a relative risk for hypovolaemia of 1.46 (95% CI 0.97–2.22) and for hypoalbuminaemia of 1.69 (95% CI 1.07–2.67).

It is worth noting that most of the studies using albumin supplementation in hypoalbuminaemia used parenteral nutrition fluids to which albumin had been added. Although visual compatibility has been established for the addition of albumin to total parenteral nutrition (TPN) there is an increased risk of bacterial and fungal contamination of the solution and concentrations >2.5% may increase particulate infusion [9]. Since albumin supplementation for hypoalbuminaemia is rare in modern critical care practice the systematic review supports current practice.

The search for papers using the indication of hypovolaemia produced 16 papers compared to seven using albumin in the first systematic review [1]. The paper by Metildi *et al* [7] was excluded from the second review (perhaps on the basis that the authors did not realise that ARDS patients receive fluid for hypovolaemia). The two papers from the first review using mixed colloids were included [10,11], but the data pertaining to albumin use only extracted. In two papers [12,13] included in both systematic reviews a proportion of the patients were excluded from one systematic review converting, in one case [12], a relative risk favouring colloid to a relative risk favouring control. It is of note that a further paper [8] was included in the second review that was not included in the first review. This raises questions on the search strategy.

If we consider the hypovolaemic patients in the albumin review, half the papers suggested benefit and half suggested an increased mortality. Of the seven papers suggesting an increased mortality with albumin, three had only one or two deaths in total [6,14,15] and two probably represented a different patient group from the others (one studying pre-term infants [16] and the other with a higher overall mortality [17]). It is also noteworthy that Zetterstrom's work contributed to both an excess albumin

mortality [14] and an excess non-albumin mortality [18] in the systematic review but these two papers were published back to back and were two parts of a single ongoing investigation. It is not particularly convincing that albumin kills if used in hypovolaemia.

The paper with the largest excess albumin mortality in the second review was the paper by Lucas *et al* [19]. This was a trauma study in which albumin was added to a standardised fluid resuscitation regimen in the protocol group. Thus patients were resuscitated to physiological goals with blood, fresh plasma and balanced electrolyte solutions in both treatment and control groups. There was no reduction of crystalloid solution in the protocol group to make space for the supplemental albumin. Patients died predominantly of cardiopulmonary failure, a recognised effect of excessive fluid resuscitation. It is by no means clear that the albumin supplementation contributed to the deaths, other than by the fluid excess mechanism. A commentary printed immediately following the paper made the point that the large volumes of blood and fresh frozen plasma, given in equivalent quantities to both groups, would have amounted to over 300g albumin; the 25–75g supplement to the protocol group could not be expected to have any additional pharmacological effect.

Crystalloid versus colloid in fluid resuscitation [3]

In a systematic review of 17 trials with mortality data, including 814 patients, Choi *et al* [3] included various colloids and various crystalloids but no hypertonics. There were various hypovolaemic insults. Papers were included according to several methodological factors rather than simple allocation concealment as used in the previous two reviews. Although there was an imbalance of mortality favouring crystalloids, the authors correctly made a claim of no excess mortality, based on the statistical analysis. The different selection process used in this review meant that five papers were included that appeared in neither of the previous reviews. However, there were 16 papers included in the previous reviews that were not included in this review.

Critique of trial selection

The role of other factors in mortality

The confounding factors of imbalance of illness severity, different approaches to correction of physiological abnormalities and the interaction between other treatments that are not controlled are not declared in a systematic review. What the papers show is that some doctors can kill patients with colloids. The way a drug is used is as important a determinant of its effect as the properties of the drug itself. Of course, the skilled user will be taking these properties into account when judging how to use it.

The primary goal in the management of hypovolaemia is to stop volume loss (if possible) and restore the circulating volume. Many intensive care units use a fluid challenge regimen [20]. A small increment of blood volume is achieved (usually 200ml) and the effect of this is judged by measurement of central venous pressure and/or cardiac stroke volume. Other vital signs are usually taken into account as well. This is repeated until there is no further improvement with the blood volume increment. This way the right amount of fluid is individualised to the patient and fluid overload is rare. A fluid challenge requires the use of colloid since a 200-ml increment of blood volume is achieved with 200 ml colloid versus at least 800 ml isotonic saline. Unfortunately we do not know, in the individual, exactly how much of the saline will remain in the circulation for long enough to make the physiological measurements so no response may mean we have not given enough or transvascular leak is greater. With colloids, small molecules will leak but not at a rate that interferes with the interpretation of the measurements. Other treatment factors are almost certainly the reason for opposing results in some trials included in the reviews.

The use of mortality as the outcome measure

Most of the papers reviewed have been designed to assess their effects in terms of one or more physiological variables. They have been designed to assess mortality. A randomised controlled trial comparing one colloid with one crystalloid would require over 6500 patients to detect an excess colloid mortality of 4% on the basis of the data in the first systematic review. This assumes confounding factors are evenly distributed between groups, a type I error of 5% and a type II error of 2.5% with a control mortality of 20%. I have argued above that the choice of agent becomes less important if the way it is used is not well controlled (in the clinical rather than statistical sense). Unless we compare trials that have used the same endpoints in their design, the same physiological protocols for fluid administration, the same protocols for other circulatory treatment (inotropes, vasopressors, vasodilators), the same protocols for respiratory management and studied patients with the same severity of illness throughout their stay I cannot see how we can make a meaningful statement on comparative mortality. Since most of these

studies are not designed to assess mortality as an outcome these factors will not be controlled (in the statistical sense).

The problem of biochemical rather than haemodynamic endpoints

The albumin review demonstrated an excess mortality in all studies using albumin for the indication of hypoalbuminaemia. The problem is that correction of a biochemical endpoint as a primary goal in patients who do not otherwise need the fluid runs the risk of the effects of fluid excess. The easiest way of increasing colloid osmotic pressure is to give large doses of diuretics. The easiest way of reducing colloid osmotic pressure is to give large volumes of crystalloids. Both techniques will substantially alter blood volume. The currently accepted view is that maintenance of colloid osmotic pressure is of secondary importance to maintenance of circulating volume. It is true that use of well retained colloids may prevent further reductions in colloid osmotic pressure but very few intensive care units bother to measure colloid osmotic pressure. The primary goal in clinical reality is to restore circulating volume. Mortality from studies using fluid titrated to a biochemical endpoint is not related to clinical reality.

Inappropriate grouping of study treatments

I criticised the first review because a variety of colloids were considered as a single entity. I must make the same criticism of the albumin review that included a variety of albumin concentrations. It is important to understand that different concentrations of solution [21], the different molecular sizes and differences in electrical charge [22] and degrees of substitution and effects of substituting different carbon atoms in the hydroxyethyl starch molecules [23] all affect the physical and pharmacological properties of these colloids. Failing to separate the individual products is like looking at the effects of different antibiotics and grouping them according to chemical class rather than microbial sensitivity patterns. No one would consider that flucloxacillin is the same as benzylpenicillin, although both are undoubtedly penicillins.

Conclusions

Concluding anything from these systematic reviews is difficult. As is usual from such reviews, a question is posed as an input and a question is the output. Should we abandon the use of colloid solutions in intensive care? The evidence does not support such a conclusion; it simply demonstrates colloids may not be a major determinant of mortality. Since mortality was not the primary outcome measure in any of the studies assessed, even this conclusion has to be softened. Those of us who will continue to use colloid solutions must ask ourselves why. On our list of advantages we would never have cited a reduction in mortality. The reality is that our choice of fluid for resuscitation is one small part of a package of measures that we

adopt in our quest for the holy grail of reduced mortality. A switch to exclusive crystalloid use for the experienced colloid user would require a complete reassessment of goals of therapy, changes in attitude to the tolerance of oedema and its corresponding problems, changes in trigger points for escalation to other circulatory and respiratory support treatments and a re-education process that is bound to be associated with errors (and deaths?) during the phase of gaining experience in the methods.

Should we abandon the use of human albumin solutions? The reality is that many had, long before the publication of the systematic reviews, since there were cheaper alternatives available that are as and probably more effective.

Are we any the wiser? I have suggested the questions posed by the reviews, as well as the answers, were invalid. In that case we must agree that we are none the wiser. However, focussing on the problems of interpretation of the reviews leads us to understand a little more about the importance of the process of intensive care, ie the interplay between many different treatments and the role of those involved in delivering intensive care. Single treatments have so often failed the test of the randomised controlled trial in intensive care and this is not surprising in a field where the whole is considerably greater than the sum of its parts.

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