Point of view

Albumin and resuscitation: a sense of Déjà Vu

"First get your facts; then you can distort them at your leisure" Mark Twain

Human albumin is a single polypeptide chain of 585 amino acid residues with a calculated molecular weight of 66,248.[1] It functions as a plasma carrier for free fatty acids, bilirubin, tryptophan, trace metals (e.g. Cu^{2+}, Ag^{2+}, Hg^{2+}), thyroxine, cortisol, and drugs (e.g. aspirin, frusemide, phenothiazines, benzodiazepines, warfarin), maintains intravascular oncotic pressure, and may have other important functions (e.g. free radical scavenger,[1,2] anticoagulant, and maintenance of capillary permeability[3]). It is difficult to conceive that it could be a lethal agent.

Replacement of plasma with albumin during plasmapheresis (for a variety of conditions) has been associated with 4 deaths during 1,945 procedures in one study,[4] and eight deaths during 15,658 procedures in another.[5] The most frequent complications reported were hypocalcaemia (2.2 mmol of calcium gluconate for each liter of 4% albumin solution infused corrected this) and anaphylactoid reactions (with albumin replacement being associated with fewer adverse reactions when compared with fresh frozen plasma, dextran 40, modified fluid gelatin, or hydroxyethyl starch).[4-6]

Nonetheless, the Cochrane Injuries Group Albumin Reviewers recent meta-analysis regarding studies that compared groups treated with and without intravenous albumin, concluded that "for every 17 critically ill patients treated with albumin there is one additional death".[7] They searched the medical literature and included only those prospective and randomised trials where administration of human albumin was compared with saline in the management of hypovolaemic, burns, and hypoalbuminaemic patients, and where mortality had been documented in all groups.

To combine such a diverse group of patients under the rubric of 'critical illness' and attempt to draw conclusions that are valid for all critically ill patients, highlights the problems that arise when statistical analysis is performed by a group, none of whom have expertise in adult intensive care.

For example, trials were included that were greater than 20 years old when resuscitation fluids were used in amounts that are considered to be excessive by today's standards. Volume for volume, it is not difficult to believe that excessive use of saline solutions with albumin will be more hazardous than excessive use of saline without albumin.

Nevertheless, considering data from the three groups is informative. Criticisms concerning the burns patients group have been published.[8] Concerning intravenous albumin in the management of hypoalbuminaemia in critically ill patients (i.e. the hypoalbuminaemic group): in the presence of a normal intravascular volume, hypoalbuminaemia is caused largely by redistribution of albumin from the intravascular to the interstitial compartment. Serum albumin levels decrease with acute illness[9-11] (it is a 'negative' acute phase reactant[12]); it is a marker of underlying disease rather than a cause for it.[1] Most studies have demonstrated no benefit in administering albumin to simply correct a low serum albumin level,[13,14] and most Intensivists understand this. It is conceivable that administering albumin to this group (i.e. a group that does not require albumin) is associated with an increase in mortality.

Concerning the treatment of clinically significant hypovolaemia due to blood loss (i.e. the hypovolaemic group); the resuscitation fluids of isotonic saline or 4% or 5% albumin in isotonic saline to replace the plasma loss have been studied extensively. Albumin in isotonic saline maintains a greater intravascular distribution of the exogenously administered fluid compared with isotonic saline, and most studies have confirmed this by documenting a saline volume of 2 to 4 times that of albumin in isotonic saline, to achieve a comparable haemodynamic effect.[15-20]

However, the importance in maintaining normal oncotic pressure (i.e. normal plasma albumin) to minimise interstitial oedema formation and protect the lung from pulmonary oedema has not been established.[15,18] There are currently no prospective randomised controlled trials in this group of patients that have shown a reduction in mortality when using isotonic saline with 4% or 5% albumin compared with isotonic saline alone.

The Cochrane Injuries Group Albumin Reviewers meta-analysis 'hypovolaemic group' consisted of 13 studies. All patients received blood products and therefore received human albumin. However, some patients received more albumin (albumin group) than others (saline group). The albumin group had 38 deaths in 256 patients and the saline group had 26 deaths in 278 patients, the absolute risk increase was 5.5% with a 95% confidence interval (CI) of - 0.05% to + 11.03% (i.e. of questionable significance).

However, a closer look at this group reveals two subgroups. Six of the 13 studies compared treatment with albumin in isotonic saline with isotonic saline, during or following haemorrhage due to trauma or

surgical blood loss.[15,18,20-23] The remaining 7 studies compared intravenous albumin with saline in patients who had been hypoalbuminaemic rather than hypovolaemic or who were haemodynamically stable and required maintenance fluids only.[24-30] Replacement of lost intravascular volume in the latter group had been either completed or was not required. These 7 studies were inappropriately included in the 'hypovolaemic' group. Moreover, while in-hospital mortality was documented in all studies it was not a primary end point. Mortality during the resuscitation period (i.e. study-period mortality) would have been of greater value, as it would have more likely reflected the beneficial or harmful effects of the resuscitation fluids.

In reviewing the 'study-period' mortality in the six 'hypovolaemic' studies, the albumin group had 3 deaths in 106 patients and the saline group had 9 deaths in 136 patients. The absolute risk reduction with albumin was 3.79%. From these data one could have concluded that 'for every 27 critically ill patients treated *without* albumin there is one additional death' (although the 95% CI ranged from - 1.45 to + 9.02, i.e. of questionable significance).

A more recent meta-analysis of randomised clinical trials of adult patients requiring fluid resuscitation comparing isotonic crystalloids with colloids did not confirm the Cochrane Injuries Group Albumin Reviewers findings; they concluded that "methodological limitations preclude any evidence-based clinical recommendations".[31] The call for a large randomised controlled trial is acknowledged.

One puzzling aspect of the Cochrane Injuries Group Albumin Reviewers was their disregard for the standard publication embargo or 'Ingelfinger rule' (i.e. work is first published before or at the time a media release occurs),[32] by releasing their findings 6 weeks before the BMJ publication, impairing the standard process of peer review.[33] This was compounded by the intriguing response to criticism by the UK Cochrane Centre director, saying that he would "attempt to sue anyone who had given me an infusion of albumin; and would not give my informed consent to take part in a randomised trial";[34] hardly the statement of an unbiased and scientific mind.

Nevertheless, one useful aspect of this whole episode is that it has set the stage for what hopefully will be a definitive trial, answering once and for all the question 'is there any difference in mortality when 0.9% saline (crystalloid) is used for resuscitation of the hypovolaemic patient when 4% or 5% albumin (colloid) is added'.

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