Albumin Administration in the Management of Critically Ill Patients: Is It Safe?

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0196-0644/$-see front matter

doi:10.1016/j.annemergmed.2008.07.047

[Ann Emerg Med. 2009;54:114-116.]

SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals*' Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician(s) knowledgeable in the subject area.

The source for this systematic review abstract is: Alderson P, Bunn F, Li Wan Po A, et al; Albumin Reviewers. Human albumin solution for resuscitation and volume expansion in critically ill patients. *Cochrane Database Syst Rev.* 2004;(4):CD001208. doi:10.1002/14651858.CD001208.pub2. The *Annals*' EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review, as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To quantify the effect on mortality of human albumin and plasma protein fraction administration on the management of critically ill patients.

DATA SOURCES

The authors searched MEDLINE, EMBASE, and BIDS Index to Scientific and Technical Proceedings; reference lists of trials and review articles were reviewed, and authors of identified trials were contacted (search last updated August 2004).

STUDY SELECTION

Randomized controlled trials comparing albumin/plasma protein fraction with no albumin/plasma protein fraction, or with a crystalloid solution, in critically ill patients with hypovolemia, burns, or hypoalbuminemia.

DATA EXTRACTION AND ANALYSIS

Two reviewers extracted data and assessed quality independently. The analysis was stratified according to patient type. Relative risks (RRs) and 95% confidence intervals (CIs) for mortality were calculated for each trial on an intention-to-treat basis. Heterogeneity between trials was tested using an I^2 test. Where possible, summary RRs and 95% CIs were calculated using a fixed-effects model. If the source of heterogeneity could obviously be related to patient type or allocation concealment, then the analysis was stratified on this dimension.

MAIN RESULTS

Thirty-two trials met the inclusion criteria and reported death as an outcome. There were 1,632 deaths among 8,452 trial participants. For hypovolemia, albumin use did not reduce mortality (RR=1.01; 95% CI 0.92 to 1.10). This estimate was heavily influenced by the results of the Saline versus Albumin Fluid Evaluation (SAFE) trial, which contributed 91% of the information (based on weighted meta-analysis). For burns, albumin use increased mortality (RR=2.40; 95% CI 1.11 to 5.19); for hypoalbuminemia, albumin's increase in mortality was not statistically significant (RR=1.38; 95% CI 0.94 to 2.03). There was no substantial heterogeneity between the trials in the various categories (I^2=0%). The pooled RR of death with albumin administration was 1.04 (95% CI 0.95 to 1.13).

CONCLUSIONS

There is no evidence that albumin reduces mortality compared with cheaper alternatives such as saline solution for patients with hypovolemia. There is also no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminemia. However, selected populations of critically ill patients in which albumin may be beneficial remains to be determined. In view of the absence of evidence of a mortality benefit from albumin and its increased cost compared to alternatives, such as saline solution, it would seem reasonable

that albumin should be used only within the context of well-concealed and adequately powered randomized controlled trials.

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COMMENTARY: CLINICAL IMPLICATION

The administration of resuscitation fluids to the critically ill patient for volume resuscitation is a cornerstone of management. Two main classes of fluid expand the plasma volume: colloid and crystalloid solutions. The most commonly used crystalloid fluids are normal saline solution and Ringer's lactate. Colloid fluids include hydroxyethyl starch solutions, albumin (5% and 25%), gelatins, and dextrans, with hydroxyethyl starch fluids being the dominant colloid used for resuscitation in North America and Europe.[1,2] Until recently, there has been insufficient evidence of benefits and harms to guide the use of fluids in resuscitation.[3,4]

Clinicians who favor the use of colloid fluids argue that hypo-oncotic crystalloids leak from the plasma to excessively expand the interstitial fluid volume and create peripheral edema.[5] In contrast to crystalloid solutions, colloid solutions are macromolecules that under normal physiologic conditions do not pass through the endothelial layer and into the interstitial space.[6] Thus, colloids have the potential advantage of requiring much less volume to expand the intravascular space. Critically ill patients are often in a physiologically compromised state, however, resulting in endothelial injury and microcirculatory dysfunction. In these circumstances, colloid solutions may freely pass from intravascular to interstitial spaces.[6] Albumin may act as an antioxidant and influence vascular permeability, but none of these purported benefits have translated into improved outcomes.[7] In fact, a systematic review in 1998 suggested a 6% excess risk of death for critically ill patients resuscitated with albumin.[8] This led to a reduction in albumin use in the United Kingdom and likely elsewhere.[9]

This updated Cochrane Review included 32 trials involving 8,452 participants. The review concludes that albumin is not associated with a reduced risk of death overall or in the specific setting of hypovolemia. In the subgroups of patients who were burned or hypoalbuminemic, albumin was associated with a significant increase and a trend toward an increased risk of death, respectively. These findings should be considered hypothesis generating, requiring confirmation through large randomized controlled trials. The authors conclude that because albumin is not associated with a mortality benefit, and because it is more expensive than crystalloids, it should be used only in the context of adequately powered randomized controlled trials. They also acknowledge that the results of the systematic review were heavily influenced by a single randomized controlled trial of 6,997 heterogeneous critically ill patients resuscitated with 4% albumin versus normal saline solution. This trial failed to identify a difference between the resuscitation strategies (RR=0.99; 95% CI 0.91 to 1.09). One a priori subgroup analysis of patients with severe sepsis[3] suggested a trend toward reduced mortality (RR=0.87; 95% CI 0.74 to 1.02). Conversely, a post hoc subgroup analysis of patients with traumatic brain injury[10] revealed an increased risk of death associated with albumin use (RR=1.63; 95% CI 1.17 to 2.26). These findings illustrate that fluid selection may have disparate effects in different critically ill patients. Editorialists agree that future randomized controlled trials examining albumin's effects are required in specific critically ill populations.[11,12]

TAKE-HOME MESSAGE

Early fluid resuscitation is the cornerstone of management for the patient who requires volume resuscitation. Resuscitation with albumin fluid for critically ill patients who are hypovolemic and in need of volume resuscitation is not associated with increased survival. Until further evidence emerges on the role of albumin in specific critically ill patient populations, emergency physicians should use crystalloids for resuscitation and restrict the use of albumin.

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EBEM TEACHING POINT

Role of Industry Funding

The pharmaceutical industry funds more than 70% of drug trials.[13] There is strong suspicion that this industry funding may bias the trial results reported and the interpretation of these results. In our examination of the funding source for the 32 trials included in this review, only 1 trial was provided with industry and nonindustry funding; a further 18 trials received nonindustry funding. The remaining 12 trials did not reveal a funding source, and hence it is unclear whether industry sponsored these studies.

Several systematic reviews of randomized controlled trials have examined the role of industry funding and authors' conclusions; most have found that industry sponsorship is associated with proindustry results and conclusions.[14,15] The reasons for these positive associations are not clear. Although industry-funded trials appear to be of equal or higher methodological quality than nonindustry-funded trials,[14] research results and conclusions may be influenced by ghost management and authorship,[16] publication bias, or other design biases that are not identified or explained by an examination of trial quality or disclosure of the funding source.[14]

Additional research is required to understand why industry-sponsored trials appear more likely to be associated with publications supporting their treatment interventions. Readers

of reviews should be cognizant of the potential bias introduced by industry funding, and the medical literature should be interpreted with the funding source in mind.

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