

Commentary

Conflicting clinical trial data: a lesson from albumin

Greg Martin

Assistant Professor of Medicine, Division of Pulmonary, Allergy and Critical Care, Emory University School of Medicine, Atlanta, Georgia, USA

Corresponding author: Greg Martin, greg.martin@emory.org

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See related research by Vincent *et al.* in this issue [<http://ccforum.com/content/9/6/R745>]

Abstract

Albumin is a frequently prescribed drug in hospitalized patients, and its effect on clinical outcomes has been scrutinized in recent years. Data from meta-analyses has suggested harm related to albumin therapy in critically ill patients, and new observational data are consistent with these results. However, appropriately powered randomized, controlled trials have shown albumin to be safe in broad groups of critically ill patients. This article will discuss the reasons for differences between observational and controlled trial data, and the implications for future albumin use and clinical research.

differences (either by proportional hazards regression or by subject pairs matched by propensity scores), albumin use remained associated with a higher risk of death.

Does this mean that albumin either causes or contributes to the death of critically ill patients? Because the data presented are observational in nature, it is impossible to draw that conclusion. Inherent to their nature, observational trials have one crucial deficiency: their design is not experimental. Each patient's treatment is chosen rather than randomly assigned, creating an unavoidable risk of selection bias and systematic differences in outcomes that are not due to the treatment itself. Although statistical adjustments can be made for identifiable differences between groups, it is impossible to be certain that all relevant characteristics have been considered and that adjustments are adequate. Thus, based on the SOAP data, it is only fair to conclude that albumin use is associated with an increased risk of dying in this population of ICU patients.

Introduction

The interpretation of clinical trial data is the cornerstone of both evidence-based medicine and medical practice [1,2]. The level of evidence that we apply to study results depends on the type of trial being reported. For example, randomized, controlled trials (RCTs) represent a higher level of evidence than observational trials. Thus, RCTs more appropriately guide the practice of medicine. Observational trials are statistically and financially efficient, however, and almost invariably precede results from an RCT. Can we base the care of critically ill patients on the results of observational data?

The 'SAFE' study

During the time that the SOAP study was being conducted, the Saline versus Albumin Fluid Evaluation (SAFE) trial was underway. This trial was designed in response to meta-analyses that suggested harm related to colloid use in ICU patients [4,5]. The SAFE trial randomized 7,000 critically ill patients requiring fluid resuscitation to receive isotonic saline or iso-oncotic albumin [6]. Among the pre-defined subgroups, traumatically injured patients with associated brain injuries had the greatest risk of death with albumin (relative risk, 1.62; 95% confidence interval, 1.12-2.34; $p=0.009$), while severe sepsis patients had the lowest risk of death (relative risk 0.87; 95% confidence interval, 0.74-1.02, $p=0.09$). However, there was no overall difference in organ dysfunction or 28-day survival according to the type of fluid administered.

The 'SOAP' study

The 'Sepsis Occurrence in Acutely Ill Patients' (SOAP) study represents an observational trial conducted in intensive care units (ICUs) from 24 European countries during a two-week period. In this issue of *Critical Care*, Vincent and colleagues [3] present SOAP study data related to albumin therapy in these patients. From this perspective, 11.2% of study subjects received albumin during their ICU stay, and those who received albumin were more frequently surgical patients and more likely to have cancer, liver cirrhosis, and sepsis. Patients who received albumin were more severely ill, confounding the findings of greater length of ICU stay and mortality. However, even after adjustment for these

Is SAFE better than SOAP?

How do we reconcile the differences between the multi-centered observational SOAP study and the randomized, controlled SAFE study? Fundamental differences in case-mix between European and Australian ICUs are unlikely to explain the full measure of difference. This is another example of contrasting results between an observational trial and a RCT. Investigators have tried to quantify the concordance between observational trials and RCTs, and have occasionally reported good agreement [7,8]. It is not uncommon, however, for RCTs to produce conflicting results when compared to observational trials [9,10]. As in other trials, conflicting results in this case are likely related to the inability to fully adjust observational data for differences between groups.

These results reinforce the rationale for RCTs carrying the greatest weight when applying evidence to medical decision making. Studies suggesting concordance between observational trials and RCTs have limitations that preclude firm conclusions [7,8]. The biomedical literature is replete with well-conducted RCTs that conflict with prior observational data. Similarly, the fact that meta-analyses inaccurately predict the results of RCTs up to 35% of the time reinforces the gold standard of the RCT in medical decision making [11]. This hierarchy is supported by regulatory agencies, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), who rely upon RCTs as the primary evidence for drug licensing. Despite the limitations of observational trials, they serve an important purpose in biomedical research. They are essential in conditions where randomization is difficult or unethical, and they are useful in monitoring for drug toxicity, studying risk factors for disease and prognosis, determining if evidence is being applied and effectiveness achieved, and guiding the design of future controlled trials.

What are the implications of the SOAP and SAFE trials for albumin use and future albumin research? First, it is important to recognize that modern studies of albumin in general ICU patients do not suggest harm [6]. Albumin is predominantly a niche product, however, and efficacy almost certainly varies according to the patient type and clinical diagnosis. Furthermore, the clinical benefit of albumin may not relate to its oncotic properties, but rather to its anti-oxidant and anti-inflammatory biochemical effects [12,13]. Therefore, additional focused RCTs of albumin are warranted, particularly in conditions where it has shown promise (e.g. septic shock), in order to better understand its application to critically ill patients.

Conclusion

Observational trials will forever remain as essential tools in medicine, primarily for their efficiency and where randomization is unethical. Results from observational trials, however, may not accurately predict the magnitude or direction of subsequent RCTs. For that reason, we must rely

upon RCTs for clinical decision making whenever possible, incorporating observational data only when superior contemporary evidence is not available. The available evidence shows that albumin therapy is safe in broadly defined groups of critically ill patients, but may be either beneficial or harmful in specific subgroups or individual patients. The final chapter for albumin use in critically ill patients is far from being written.

Competing interests

The author(s) declare that they have no competing interests.

References

1. Evidence-Based Medicine Working Group: **Evidence-based medicine. A new approach to teaching the practice of medicine.** *J Am Med Assoc* 1992, **268**:2420-2425.
2. Preventive Services Task Force: *Guide to Clinical Preventive Services: Report of the US Preventive Services Task Force.* 2nd edition. Baltimore: Williams and Wilkins; 1996.
3. Vincent JL, Sakr Y, Reinhart K, Sprung CL, Gerlach H, Ranieri VM, the 'Sepsis Occurrence in Acutely Ill Patients' investigators: **Is albumin administration in the acutely ill associated with increased mortality?** *Crit Care* **9**:R745-R754.
4. Cochrane Injuries Group Albumin Reviewers: **Human albumin administration in critically ill patients: systematic review of randomised controlled trials.** *Br Med J* 1998, **317**:235-240.
5. Schierhout G, Roberts I: **Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials.** *Br Med J* 1998, **316**: 961-964.
6. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R: **A comparison of albumin and saline for fluid resuscitation in the intensive care unit.** *N Engl J Med* 2004, **350**:2247-2256.
7. Concato J, Shah N, Horwitz RJ: **Randomized, controlled trials, observational studies, and the hierarchy of research designs.** *N Engl J Med* 2000, **342**:1887-1892.
8. Benson K, Hartz AJ: **A comparison of observational studies and randomized, controlled trials.** *N Engl J Med* 2000, **342**: 1878-1886.
9. Sacks H, Chalmers TC, Smith H Jr: **Randomized versus historical controls for clinical trials.** *Am J Med* 1982, **72**:233-240.
10. Chalmers TC, Celano P, Sacks HS, Smith H Jr: **Bias in treatment assignment in controlled clinical trials.** *N Engl J Med* 1983, **309**:1358-1361.
11. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F: **Discrepancies between meta-analyses and subsequent large randomized, controlled trials.** *N Engl J Med* 1997, **337**: 536-542.
12. American Thoracic Society: **Evidence-based colloid use in the critically ill: American Thoracic Society Consensus Statement.** *Am J Respir Crit Care Med* 2004, **170**: 1247-1259.
13. Quinlan GJ, Martin GS, Evans TW: **Albumin: biochemical properties and therapeutic potential.** *Hepatology* 2005, **41**:1211-1219.