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Journal club critique

The routine use of albumin for fluid resuscitation of critically ill patients is not warranted

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Expanded Abstract

Citation

Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. NEJM 2004, 350:2247-2256.[1]

Hypothesis

When 4% albumin is compared with 0.9% sodium chloride (normal saline) for intravascular-fluid resuscitation in patients in the intensive care unit (ICU), there is no difference in the 28-day rate of death from any cause.

Methods

Design: Multicenter, double blind, randomized controlled trial

Setting: Closed, multidisciplinary ICUs of 16 academic tertiary hospitals in Australia and New Zealand between November 2001 and June 2003

Patients: 6997 ICU patients ≥ 18 years of age who were judged by their treating physician to require fluid resuscitation to maintain or increase intravascular volume, with this decision supported by the fulfillment of at least one objective criterion. Patients admitted to the ICU after cardiac surgery, after liver transplantation, or for the treatment of burns were excluded.

Intervention: Patients were randomly assigned to receive either 4% albumin or normal saline, with randomization stratified according to institution and whether there was a diagnosis of trauma on admission to the ICU. Study fluids were supplied in identical 500-ml bottles, and blinding was ensured through the use of specially designed masking cartons and specially designed and manufactured administration sets. The effectiveness of the blinding was confirmed in a formal study before the trial was initiated. The treating clinicians determined the amount and rate of fluid administration. In addition to the study fluid, patients received maintenance fluids, specific replacement fluids, enteral or parenteral nutrition, and blood products at the discretion of the treating clinicians. The monitoring of central venous pressure, pulmonary-artery catheterization, and all other aspects of patient care were performed at the discretion of the treating clinicians.

Outcomes: The primary endpoint was 28-day all-cause mortality. Secondary endpoints were the proportion of patients with new organ failure and the duration of mechanical ventilation, renal replacement therapy, and ICU and hospital stay. Differences in the primary endpoint were also examined in six predefined subgroups according to the baseline presence or absence of trauma, severe sepsis, and acute respiratory distress syndrome (ARDS). The study had 90% power to detect a 3% absolute difference between groups for the primary endpoint.

Results

Of the 6997 patients who underwent randomization, 3497 were assigned to receive albumin and 3500 to receive saline. Both groups had similar baseline characteristics. Of those who completed 28-day follow up, there were 726 deaths (20.9%) in the albumin group, as compared with 729 deaths (21.1%) in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09; P=0.87). There were no differences in secondary endpoints between groups.

A post-hoc subgroup analysis of trauma patients showed a trend towards increased mortality in the albumin group, which appeared to be due to a greater number of deaths in trauma patients with associated brain injury. Among patients who had trauma without brain injury, there was no

difference in mortality between the groups. In patients with severe sepsis there was a trend towards decreased mortality in the albumin group. There were no differences between groups in mortality for patients with ARDS.

Conclusion

In patients in the ICU, use of either 4% albumin or normal saline for fluid resuscitation resulted in similar outcomes at 28 days.

Commentary

Albumin has been used for over 50 years for fluid resuscitation in the ICU, despite the lack of any adequately powered randomized clinical trials with mortality as a primary endpoint. Furthermore, two recent large meta-analyses revealed conflicting results;[2,3] one concluded that albumin was associated with increased mortality whereas the other failed to detect this effect.

The Saline versus Albumin Fluid Evaluation (SAFE) Study addressed one of the most pressing questions faced by intensivists. The data showed that there is no advantage to resuscitation with albumin as compared to normal saline. This study has several strengths worth mentioning. First, the investigators went to great lengths to ensure blinding. Albumin is yellow and tends to foam during administration, making it very easy to distinguish from saline. Specially designed masking cartons and administration sets were used to prevent unblinding and the effectiveness of these measures was ensured by a formal study prior to the trial. Second, this study enrolled a very large number of patients in a relatively small period of time, which was facilitated by the use of delayed consent provision. Such an approach would not have been possible had this trial been conducted in the United States. Third, compliance was outstanding and contamination was negligible, an exceptional achievement considering the size and scope of the trial.

A few limitations deserve consideration. First, the study hypothesis suggests that this was an equivalence trial. However, the study was powered to detect a 3% difference in 28-day morality. The absence of a detectable difference *suggests* equivalence, but proof of equivalence would require a different sample size. Second, during the first four days, patients in the albumin group received 71.0 mL more packed red cells than those assigned to receive normal saline. Given the recent concern that blood transfusion may be associated with worse outcomes, it is possible the additional, albeit small, volume of packed red blood cells received biased the results in favor of normal saline. Third, despite extensive measures taken to ensure blinding, clinicians were able to obtain serum albumin levels. It is conceivable that a rising serum albumin concentration would be indicative of randomization to the albumin group. However, the differences in mean daily serum albumin levels between groups were quite small and it seems unlikely that clinicians would have be successful in using this measure to guess treatment assignment.

Recommendation

Based on the results of this study, we conclude that the routine use of albumin for fluid resuscitation of critically ill patients is not warranted. Albumin solutions for resuscitation may still be warranted in certain highly selected patient populations, such as liver transplant patients and those with burns. Whether albumin or normal saline confers benefit in other selected patient populations, such as those with traumatic brain injury or sepsis, requires further study.

Competing interests

The authors declare that they have no competing interests.

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