Clinical Role of Albumin in the Critically Ill

The seemingly secure therapeutic role of albumin in patients requiring intravascular volume resuscitation has been challenged. Simon Finfer, MD, MBBS, MRCP, reviewed the evidence for and against the therapeutic use of human albumin in the critically ill patient. An active Australian researcher, Dr. Finfer is an associate professor with the University of Sydney, Monash University in Melbourne and the George Institute for International Health. He also is a senior staff specialist in intensive care at Royal North Shore Hospital of Sydney in St. Leonards, Sydney, Australia.

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- Overall, with the exception of patients with TBI, albumin is at least as safe as saline.
- The safety of other colloids is not well established.
- Another trial in patients with TBI is unlikely.
- Whether albumin is beneficial in hypoalbuminemia and severe sepsis requires further study.

The review had a profound effect, especially in the United Kingdom, where there was an approximate 40% reduction in the use of albumin. Australian doctors often use albumin, which is supplied free to hospitals. In many places albumin is expensive, but in Australia it often is the cheapest fluid available. “This makes the question of harm associated with albumin very serious,” explained Dr. Finfer. “Because Australians and New Zealanders are strong-willed and independently minded people, our reaction was not to stop giving albumin. The researchers found no difference in the overall mortality across the whole range of baseline serum albumin, another test of heterogeneity, researchers concluded that the treatment effect is the same in patients with a baseline serum albumin concentration of <30 g/L and as a marker of illness severity. Approximately 40% of the patients enrolled in the study had a baseline serum albumin concentration of ≤25 g/L. They were slightly older and had a different distribution of intensive care unit (ICU) admission diagnoses. Postoperative patients were more likely to be hypoalbuminemic than medical patients.

Interestingly, the Acute Physiologic and Chronic Health Evaluation (APACHE) II scores were almost exactly the same between the two groups, which seems intuitively strange if albumin is a marker of severity of illness and a risk of death, as is the APACHE II score. This may be explained by the difference in the diagnostic groups. The APACHE II score generates a risk of death not only from the numerical score, but also from the admission diagnosis. That difference in postoperative patients and diagnostic mix may explain this apparent anomaly.

In patients with a baseline serum albumin concentration of ≤25 g/L, the point estimate for the relative risk of death favors albumin, but the confidence intervals cross unity. When examined using a test of heterogeneity, researchers concluded that the treatment effect is the same in patients with a baseline serum albumin above or below the predetermined cut point of 25 g/L.

The reviewers concluded that, while there was no evidence that albumin reduced mortality, it was possible that albumin might be beneficial for some subgroups and that albumin may increase mortality in patients with hypoalbuminemia and burns.

Albumin Treatment for Hypoalbuminemia

Two papers published in 2006 addressed this issue. The first paper was a preplanned analysis from the SAFE Study Investigators (BMJ, 2006;333:1044), and the second was a pilot study by Dubois et al. (Crit Care Med. 2006;34:2536). The latter study considered the use of albumin to treat hypoalbuminemia and to achieve a particular serum albumin concentration. In that study, 105 patients with a serum albumin concentration of ≤30 g/L were assigned to two groups. One group received 300 mL of 20% albumin on the first day and then 200 mL/day thereafter if the serum albumin concentration was <31 g/L. In patients with a serum albumin concentration of ≤30 g/L and ≥31 g/L, the control group did not receive any albumin or any other equivalent volume resuscitation. The review found no difference in the overall mortality in patients with hypoalbuminemia and burns.

The Cochrane Injuries Group’s review was updated and republished in 2004 and included the SAFE study data in the hypovolemia group (The Albumin Reviewers, Cochrane Database of Systematic Reviews, 2004;4). The reviewers concluded that, while there was no evidence that albumin reduced mortality, it was possible that albumin might be beneficial for some subgroups and that albumin may increase mortality in patients with hypoalbuminemia and burns.

The Cochrane Injuries Group’s review was the impetus for the Saline Versus Albumin Fluid Evaluation (SAFE) study, which compared the effects of resuscitation with albumin versus saline on mortality in approximately 7,000 adult patients. Dr. Finfer and his co-investigators compared the effects of 4% human albumin or saline on 28-day all-cause mortality in patients in intensive care requiring intravascular volume resuscitation (The SAFE Study Investigators. N Engl J Med. 2004;350:2247).

The study was designed as a safety study to determine whether administering albumin caused harm. Predefined subgroups were limited to those who, at baseline, had a diagnosis of acute respiratory distress syndrome or severe sepsis, or who had suffered trauma with or without brain injury.

The researchers found no difference in the overall mortality at 28 days with a relative risk of 0.99. “We concluded that, overall, the routine use of either 4% albumin or normal saline for intravascular volume expansion produces similar outcomes in a heterogenous population of adult intensive care patients,” stated Dr. Finfer.

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albumin concentration increased in those patients assigned to receive albumin, but the study was not designed to maintain a certain serum albumin concentration. Whether giving albumin to achieve a certain serum albumin concentration is beneficial is currently unknown. That is another reason to be conservative about how we interpret these data.”

**Albumin and Other Populations**

One of the SAFE study subgroups that sparked a great deal of interest was the trauma subgroup. In the analysis of the overall trial, the point estimate for the risk of death for the trauma subgroup favored saline. It was expected that the subgroup of patients with traumatic brain injury would benefit more from albumin than from saline. Surprisingly, it was the one subgroup where the reverse appeared to be the case.

“The comparison of the treatment effect in those with trauma versus those without trauma suggested that this is something that we should take reasonably seriously,” Dr. Finfer commented. “When we looked at patients with trauma, with and without a brain injury, the mortality rate was exactly the same in the trauma patients without brain injury; it was 6.2% in both groups. The excess deaths occurred in the patients with brain injury, and that result was a great surprise to the investigators.”

Traumatic brain injury recovery is a long process. Consequently, it was decided to do a follow-up study examining functional neurologic recovery at 2 years. A retrospective chart review was done to gather additional data on severity of injury at baseline and the incidence of secondary insults. Computed tomography (CT) brain scans also were reviewed. Data collection was performed by persons who remained blinded to treatment allocation. The results of the study will be available later this year.

The SAFE study researchers also looked at the subgroup of patients with severe sepsis. “We found an apparent treatment effect going the other way,” Dr. Finfer explained. “The point estimate for the group with severe sepsis favored albumin, and those without severe sepsis thus went the other way.” The test of common relative risk revealed a P value of .06, which suggested that this is a hypothesis worth exploring further.

“There is obviously theoretical evidence about how albumin may have beneficial effects in patients with severe sepsis,” continued Dr. Finfer. “The Cochrane Injuries Group compared albumin to crystalloid. The problem may be that intensive care units have switched to another colloid - a synthetic colloid - and the data supporting the safety, let alone the efficacy, of all other colloids are really very weak.”

**Supporting Evidence From Malaria Trials**

More than 1 million children die of falciparum malaria in sub-Saharan Africa each year. Most of them died with cerebral edema. Consequently, the standard treatment for children with severe falciparum malaria is fluid restriction.

Kathryn Maitland, PhD, MBBS, and a group of researchers have been working in Kilifi and other centers in Africa, and have conducted a randomized control trial of volume expansion with albumin or saline in children with severe malaria (Maitland et al. Clin Infect Dis. 2005;40(3):39). In this pilot study, 130 children were assigned to an albumin, saline or control group. The primary outcome measure was a reduction in base deficit, but researchers also reported death and neurologic deficit. There was no difference in the resolution of base deficit, but there was a significant reduction in mortality in those patients assigned to the albumin group. The mortality rate was significantly lower among patients who received albumin (3.0%) than among those who received saline (18%), which is a highly significant relative risk reduction (5.5). These phase 2 data are encouraging, and a phase 3 trial is planned.

**Future Study**

Dr. Finfer presented the data on the SAFE study to the Food and Drug Administration’s (FDA) Blood Products Advisory Committee, who voted that the safety concerns raised by the Cochrane Injuries Group had been resolved, with the caveat that further information was needed to determine the safety of albumin in patients with traumatic brain injury and septic shock. Dr. Finfer noted that this is a slightly inaccurate interpretation, as the safety in patients with severe sepsis or septic shock was not questioned by the SAFE study.

“Overall, with the exception of patients with traumatic brain injury, albumin is at least as safe as saline,” Dr. Finfer concluded. “In patients with traumatic brain injury, I think it would be wise to avoid the use of albumin during the acute resuscitation phase. The safety of other colloids is really not well established.”

Dr. Finfer also said that the benefit of albumin to patients with hypalbuminemia or severe sepsis requires further study: “They will both need to be large studies and they should look at a robust outcome, namely mortality,” he suggested.

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**Continuing Education Self-Assessment**

**Clinical Role of Albumin in the Critically Ill**

1. Which of the following is true about albumin?
   a. It is recommended to maintain or increase intravascular volume in critically ill patients.
   b. It is as safe as saline in the treatment of patients with traumatic brain injury.
   c. Both a and b are true.

2. Patients with trauma and brain injury assigned to receive albumin have higher mortality rates than those given saline.
   a. True
   b. False