

The SAFE Study: a landmark trial of the safety of albumin in intensive care

High-quality primary evidence from an Australian and New Zealand study provides a definitive answer

The 1998 report of a meta-analysis by the Cochrane Injuries Group Albumin Reviewers presented an important public health issue and questioned the practices of many doctors in Australian intensive care units (ICUs).¹ Using data from 24 studies involving 1419 patients, the meta-analysis reported that the administration of albumin-containing fluids to critically ill patients increased the absolute risk of death by 6%, suggesting one extra death for every 17 patients given albumin. The authors recommended that albumin should not be administered to critically ill patients outside the context of rigorously conducted, randomised trials. A subsequent meta-analysis did not resolve the issue of albumin's safety in the critically ill.^{2,3}

Due to its ready availability, albumin has been widely used in Australian ICUs. Even after the publication of the Cochrane review, half of all patients in surveyed ICUs in Australia received albumin during their ICU stay (R Bellomo, S Finfer, unpublished data). Extrapolating these results would mean that 50 000 patients received albumin in Australian ICUs each year and, if the Cochrane meta-analysis was correct, this would result in an

additional 3000 deaths annually. Thus, the issue of albumin's safety was of particular importance in Australia.

The recent publication of the SAFE (Saline versus Albumin Fluid Evaluation) study in the *New England Journal of Medicine*⁴ not only brings certainty to the issue of albumin's safety in a heterogeneous population of adult ICU patients, it also marks the coming of age of clinical research in Australian and New Zealand ICUs. The SAFE Study, a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australian Red Cross Blood Service, and The George Institute for International Health, was a double-blind, randomised controlled trial of albumin versus saline for fluid resuscitation involving 6997 patients. Conducted in 14 ICUs in Australia and two in New Zealand, it was funded by the National Health and Medical Research Council and the Health Research Council of New Zealand, and by direct grants from the Australian federal, state and territory governments, the two New Zealand hospitals and CSL Ltd. Internationally, the SAFE Study is the largest randomised controlled trial conducted in intensive care or transfusion medi-

Key findings of the SAFE Study⁴

6997 patients were randomised to receive either albumin (3497) or saline (3500).

The primary outcome (alive or dead at 28 days) was available for 6933 patients (99.1%).

No significant difference was seen between the albumin and saline groups in:

- 28-day all-cause mortality (20.9% v 21.1%; $P = 0.87$)
- days in the intensive care unit (6.5 [SD, 6.6] v 6.2 [SD, 6.2]; $P = 0.44$)
- days in hospital (15.3 [SD, 9.6] v 15.6 [SD, 9.6]; $P = 0.30$)
- days of mechanical ventilation (4.5 [SD, 6.1] v 4.3 [SD, 5.7]; $P = 0.74$)
- days of renal replacement therapy (0.5 [SD, 2.3] v 0.4 [SD, 2.0]; $P = 0.41$)

cine to date. An accompanying editorial acknowledged that the SAFE Study heralded a new era in critical care marked by the large, simple randomised trial.⁵

The design of the study reflected the SAFE collaborators' desire to conduct a definitive trial that would answer an important clinical question and provide results that would be widely applicable in ICUs around the world. As a result, the trial sought to include as many adult patients admitted to participating ICUs as possible by using broad, simple inclusion criteria and few exclusion criteria. The main inclusion criterion was that the treating clinician believed that fluid administration was indicated for the treatment of intravascular volume depletion. The primary outcome measure was all-cause mortality 28 days after randomisation. The only broad patient groups excluded were those admitted to the ICU after liver transplantation, burns or cardiac surgery. The study enrolled 6997 patients in 69 weeks, an average recruitment rate of 101 patients per week. The rapid recruitment rate was made possible by the commitment of the clinical staff in the participating ICUs, the provision for delayed consent, and web-based randomisation and fluid distribution. The blinded study design was possible as both study fluids were manufactured by CSL Ltd and packaged in specially designed blinding materials⁶ before distribution by the Australian Red Cross Blood Service, New Zealand Blood Service and participating centres' blood banks.

What did the study find? The primary outcome was available for 99.1% of the 6997 patients randomised; of these, 726 assigned albumin (20.9%) and 729 assigned saline (21.1%) had died by Day 28. The relative risk of death for patients assigned albumin compared with patients assigned saline was 0.99 (95% CI, 0.91–1.09; $P = 0.87$). There were no differences in secondary outcomes, with patients assigned albumin and saline having similar incidences of new organ failure, similar durations of mechanical ventilation and renal replacement therapies, and similar ICU and hospital lengths of stay. Key findings of the study are shown in the Box.

The study identified six predefined subgroups: patients with and without trauma, with and without severe sepsis, and with and without acute respiratory distress syndrome (ARDS). As a previous meta-analysis had suggested that trauma patients resuscitated with colloid solutions had higher mortality than those resuscitated with crystalloid solutions,⁷ trauma was a stratification variable in the study. Patients with severe sepsis and ARDS were identified at baseline to determine whether the increased capillary permeability to albumin seen in those conditions^{8,9} resulted in a treatment effect

that differed from that seen in the study patients without those conditions. Within the predefined subgroups there was limited evidence of a treatment effect favouring saline in patients with trauma, and favouring albumin in patients with severe sepsis. The possibly detrimental effect of albumin in patients with trauma was limited to patients with evidence of traumatic brain injury, namely those patients admitted to the ICU as a result of trauma who had a documented unседated Glasgow Coma Scale score less than 14 and evidence of brain injury on cerebral computed tomography. The investigators cautioned readers that such subgroup differences frequently occur by chance, and the accompanying editorial advised cautious interpretation of the subgroup findings.⁵

Thus, the study demonstrated that, in this heterogeneous population of adult ICU patients, albumin can be considered safe, without demonstrating any clear efficacy advantage over saline. The SAFE Study achieved its goal of providing a definitive answer to an important clinical question. The result is widely applicable in those ICUs around the world where purified albumin is available. In addition, the study has demonstrated that investigators in Australian and New Zealand ICUs are capable of conducting large-scale collaborative trials on modest budgets and in a realistic timeframe. The SAFE Study has been described as a landmark study that heralds a new era in critical care.⁵ We hope that it will be only the first of many such studies.

Simon R Finfer

Chair, Australian and New Zealand Intensive Care Society
Clinical Trials Group Executive, Melbourne, VIC

Neil W Boyce

Transfusion Medicine Specialist, Australian Red Cross Blood Service
Melbourne, VIC

Robyn N Norton

Principal Director, The George Institute for International Health
University of Sydney, Sydney, NSW
ctg@anzics.com.au

Competing interests: All three authors played prominent roles in the design, conduct and publication of the SAFE Study.

- 1 Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998; 317: 235-240.
- 2 Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; 135: 149-164.
- 3 Summaries for patients. Whether albumin therapy improves or worsens survival of critically ill patients is not known. *Ann Intern Med* 2001; 135: S-25.
- 4 The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350: 2247-2256.
- 5 Cook D. Is albumin safe? [editorial] *N Engl J Med* 2004; 350: 2294-2296.
- 6 ANZICS Clinical Trials Group and Institute for International Health SAFE Study Investigators. The Saline vs. Albumin Fluid Evaluation (SAFE) Study (ISRCTN76588266): design and conduct of a multi-centre, blinded randomised controlled trial of intravenous fluid resuscitation in critically ill patients. Available at: bmj.com/cgi/content/full/326/7389/559/DC1 (accessed Jun 2004).
- 7 Choi PT, Yip G, Quinonez LG, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med* 1999; 27: 200-210.
- 8 Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. *Br J Anaesth* 2000; 85: 599-610.
- 9 Lewis CA, Martin GS. Understanding and managing fluid balance in patients with acute lung injury. *Curr Opin Crit Care* 2004; 10: 13-17. □