Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study

Saline versus Albumin Fluid Evaluation Study Investigators

Abstract

Objective To determine whether outcomes of resuscitation with albumin or saline in the intensive care unit depend on patients’ baseline serum albumin concentration.

Design Analysis of data from a double blind, randomised controlled trial.

Setting Intensive care units of 16 hospitals in Australia and New Zealand.

Participants 6045 participants in the saline versus albumin fluid evaluation (SAFE) study.

Interventions Fluid resuscitation with 4% albumin or saline in patients with a baseline serum albumin concentration of 25 g/l or less or more than 25 g/l.

Main outcome measures Primary outcome was all cause mortality at 28 days. Secondary outcomes were length of stay in the intensive care unit, length of stay in hospital, duration of renal replacement therapy, and duration of mechanical ventilation.

Main results The odds ratios for death for albumin compared with saline for patients with a baseline serum albumin concentration of 25 g/l or less and more than 25 g/l were 0.87 and 1.09, respectively (ratio of odds ratios 0.80, 95% confidence interval 0.63 to 1.02; P = 0.08 for heterogeneity). No significant interaction was found between baseline serum albumin concentration as a continuous variable and the effect of albumin and saline on mortality. No consistent interaction was found between baseline serum albumin concentration and treatment effects on length of stay in the intensive care unit, length of stay in hospital, duration of renal replacement therapy, or duration of mechanical ventilation.

Conclusion The outcomes of resuscitation with albumin and saline are similar irrespective of patients’ baseline serum albumin concentration.

Trial registration ISRCTN76588266.

Introduction

A Cochrane meta-analysis suggested that albumin for the treatment of hypovolaemia, hypoalbuminaemia, and burns in critically ill patients increased the risk of mortality. Subsequently the saline versus albumin fluid evaluation (SAFE) study reported no important difference in the overall risk of death for adults given albumin or saline for fluid resuscitation in intensive care units. An updated Cochrane meta-analysis incorporating data from that study found no evidence that albumin reduces the risk of mortality in critically ill patients but a suggestion that it may increase the risk of death in patients with hypoalbuminaemia and burns. We determined whether outcomes of resuscitation with albumin or saline in the intensive care unit are influenced by baseline serum albumin concentration and whether either fluid can be recommended on the basis of patients’ baseline serum albumin concentration.

Methods

Details of the saline versus albumin fluid evaluation study are published elsewhere. The randomised controlled trial was carried out in the intensive care units of 16 hospitals in Australia and New Zealand between November 2001 and June 2003. Adults were randomly assigned to 4% albumin (Albumex; CSL, Melbourne, Australia) or normal saline for fluid resuscitation until death, discharge, or 28 days after randomisation (see bmj.com for exclusion criteria).

The primary outcome was all cause mortality within 28 days of randomisation. Secondary outcomes were length of stay in the intensive care unit and hospital and duration of mechanical ventilation and renal replacement therapy.

Statistical analysis

We used χ² tests for categorical variables and t tests or analysis of variance for continuous variables to assess the association of baseline variables, including baseline albumin concentration, with mortality at 28 days. Baseline covariates were then fitted to logistic regression models to determine those independently associated with mortality.

We examined baseline albumin concentration as a binary variable using a predetermined cut-off (≤ 25 g/l or > 25 g/l), and as a continuous variable. We assessed the effect of treatment and baseline albumin concentration on 28 day mortality using logistic regression; we used the interaction between baseline albumin concentration and treatment to examine whether the risk of death for those assigned to either treatment was consistent between different baseline albumin concentrations. We carried out the logistic regression without adjustment for other baseline risk factors, then adjusted for those covariates significant at the P < 0.10 level. We also examined the heterogeneity of treatment effect on secondary outcomes.

Results

Data on baseline albumin concentration were available for 6045 patients, 3014 assigned to albumin. The distribution of baseline characteristics within each stratum of baseline albumin concentration (≤ 25 g/l or...
> 25 g/l was similar between treatment groups (see bmj.com).

Overall 2451 (40.5%) patients had a baseline albumin concentration of 25 g/l or less (1228 patients (50.1%) in the albumin group and 1223 patients (49.9%) in the saline group). Those with a baseline albumin concentration of 25 g/l or less were older and were more likely to be admitted to the intensive care unit after surgery, more likely to have sepsis or acute respiratory distress syndrome, and less likely to have traumatic brain injury. Severity of illness (acute physiology and chronic health evaluation score II score) was similar for patients in either stratum for baseline albumin concentration (see bmj.com).

Baseline albumin concentration as a binary and continuous variable was independently associated with mortality. Other baseline factors independently associated with mortality were age, reason for admission to the intensive care unit, acute physiology and chronic health evaluation II score, liver and cardiovascular components of the sequential organ failure assessment score; mechanical ventilation at baseline, and heart rate (P < 0.10).

After adjusting for baseline risk factors, a baseline albumin concentration of 25 g/l or less was independently associated with risk of death (odds ratio 1.30, 95% confidence interval 1.01 to 1.51). The findings were similar (table) when baseline albumin concentration was treated as a continuous variable (odds per 1 g/l decrease in albumin concentration 1.02, 95% confidence interval 1.01 to 1.03).

Patients assigned to albumin had a higher mean albumin concentration during the seven days after randomisation (see bmj.com). This difference was apparent for patients with a baseline albumin concentration of 25 g/l or less or more than 25 g/l (P < 0.0001 for both). On average, patients assigned to albumin received a lower daily volume of resuscitation fluid than patients assigned to saline (see bmj.com).

**Patient outcomes**

Among patients with a baseline albumin concentration of 25 g/l or less, deaths occurred in 291 (23.7%) assigned to albumin and 321 (26.2%) assigned to saline (odds ratio 0.87, 95% confidence interval 0.73 to 1.05). In patients with a baseline albumin concentration of more than 25 g/l, deaths occurred in 353 (19.8%) assigned to albumin and 334 (18.5%) assigned to saline (odds ratio 1.09, 95% confidence interval 0.92 to 1.28; figure and bmj.com).

The ratio of the odds ratios for patients with a serum albumin concentration of 25 g/l or less and more than 25 g/l was 0.80 (95% confidence interval 0.63 to 1.02). After adjustment for baseline risk factors for death (table), the odds ratios for death for patients with a serum albumin concentration of 25 g/l or less and more than 25 g/l were 0.84 and 1.15 (ratio of odds ratios 0.73, 95% confidence interval 0.55 to 0.97). P values for heterogeneity of treatment effects between those with a baseline albumin concentration of 25 g/l or less and more than 25 g/l with and without adjustment for baseline risk factors were 0.08 and 0.04 (figure and bmj.com). When baseline albumin concentration was treated as a continuous variable, no significant interaction was found between concentration and treatment for 28 day mortality (unadjusted P = 0.73, adjusted P = 0.94). No significant interaction was found between baseline albumin concentration and treatment group for length of stay in the intensive care unit, duration of mechanical ventilation, and renal replacement therapy (P values 0.50, 0.85, and 0.33), but an interaction of borderline significance was found for length of hospital stay (P = 0.05 without correction for multiple hypothesis testing; see bmj.com).

**Discussion**

Our study does not provide evidence that the effect of resuscitation with albumin compared with saline in the intensive care unit is different in patients with different baseline serum albumin concentrations. Nor does it provide evidence to support the suggestion that albumin increases the risk of mortality in patients with hypoalbuminaemia. When the odds ratios for death were compared in patients with a baseline serum albumin concentration of 25 g/l or less or more than 25 g/l...
Research

What is already known on this topic

Administering albumin may increase the risk of death in critically ill patients with hypoalbuminaemia.

What this study adds

Irrespective of patients’ baseline serum albumin concentration, fluid resuscitation with albumin or saline produced similar outcomes across the range of albumin concentrations observed in our study. Although albumin does not increase the risk of mortality in patients with hypoalbuminaemia, data do not support its routine use to maintain or increase intravascular volume in critically ill adults.

Insufficient to support the routine use of albumin to maintain or increase intravascular volume in adults with hypoalbuminaemia in intensive care units.

Contributors: See bmj.com.

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Competing interests: The saline versus albumin fluid evaluation study was part funded by CSL. CSL has acted as a sponsor for scientific meetings of the Australian and New Zealand Intensive Care Society and its clinical trials group. CSL has paid travel expenses for Simon Finfer and Rinaldo Bellomo to present the results of the SAFE study at scientific and industry sponsored meetings. Andrew Davies and Diane Stephens own shares in CSL.

Ethical approval: This study was approved by the ethics committees of the University of Sydney and of each of the participating institutions.

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Endpiece

Western influence in the Holy Land

In 1306 lawyer Pierre Dubois, an enterprising political pamphleteer, put forward a scheme for recovering Western influence in the Holy Land. Let intelligent, good-looking women be trained as doctors, be married to Eastern potentates, and use their talents and positions to gain power. As a preparation, the women should be educated from the age of four or five in Latin, Greek, Hebrew, Arabic, medicine and surgery.

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