

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

Editorial by Vincent

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BMJ 2006;333:1044-6

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 hospital stay, 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.¹ 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.^{2,3} 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.⁴ 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.^{2,3} 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 χ^2 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



This is the abridged version of an article that was posted on bmj.com on 13 October 2006: <http://bmj.com/cgi/doi/10.1136/bmj.38985.398704.7C>

>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 severe 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 score⁵) 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,⁶ 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 1.16 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 (table¹), the odds ratios for death of 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

Multivariate analysis of association of baseline characteristics (including baseline serum albumin concentration) and assigned group (albumin or saline) with risk of death

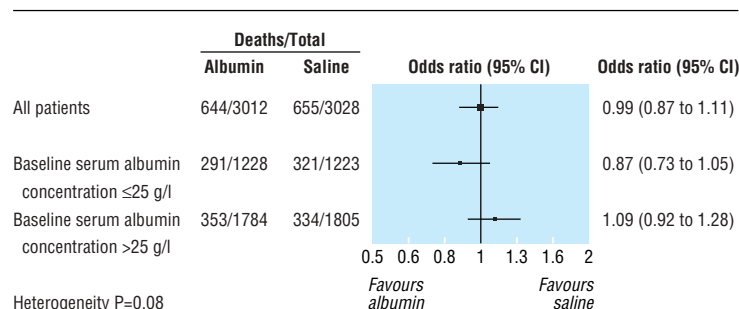
Baseline characteristic	P value	Odds ratio* (95% CI)
Albumin as binary variable:		
Age	<0.0001	1.030 (1.025 to 1.035)
Source of admission to intensive care unit	<0.0001	
Acute physiology and chronic health evaluation II score	<0.0001	1.072 (1.061 to 1.083)
Sequential organ failure assessment score:		
Liver component	<0.0001	—
Cardiovascular component	<0.0001	—
Mechanical ventilation	0.001	1.326 (1.120 to 1.570)
Heart rate	<0.0001	1.007 (1.003 to 1.010)
Baseline serum albumin concentration as binary variable	0.0009	0.772 (0.663 to 0.899)
Albumin v saline group	0.999	1.000 (0.869 to 1.151)
Albumin as continuous variable:		
Age	<0.0001	1.030 (1.025 to 1.034)
Source of admission to intensive care unit	<0.0001	
Acute physiology and chronic health evaluation II score	<0.0001	1.072 (1.061 to 1.083)
Sequential organ failure assessment score:		
Liver component	<0.0001	—
Cardiovascular component	<0.0001	—
Mechanical ventilation	0.0008	1.334 (1.126 to 1.580)
Heart rate	0.001	1.006 (1.003 to 1.010)
Baseline serum albumin concentration as continuous variable	<0.0001	0.979 (0.969 to 0.989)
Albumin v saline group	0.944	0.995 (0.864 to 1.145)

*For age, per one year increase in age; for acute physiology and chronic health evaluation II score, per one point increase in score; for heart rate, per one beat per minute increase in rate.

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



Unadjusted odds ratio (95% confidence interval) of death in all patients and in subgroups with baseline serum albumin concentration of 25 g/l or less and more than 25 g/l. (Heterogeneity of treatment effect in subgroups with baseline serum albumin concentration ≤25 g/l v >25 g/l, $P = 0.08$)

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

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

we found only limited evidence that outcomes were different and this only after correction for baseline risk factors. When we considered the effect of baseline serum albumin concentration as a continuous variable across albumin concentrations, baseline concentration had no impact on outcome even after correction for baseline risk factors, suggesting that albumin and saline produce similar outcomes across the range of albumin concentrations observed in our study.

A recent meta-analysis (3782 acutely ill adults, children, and neonatal patients) assessed the effect of resuscitation with albumin or other fluids on outcomes other than mortality. The authors concluded that albumin significantly reduced overall morbidity.⁷ This contrasts with the findings of the saline versus albumin fluid evaluation study in which there were no significant differences in morbidity in patients resuscitated with either fluid.³ In the current analysis we found no interaction between baseline serum albumin concentration and resuscitation fluid for length of stay in the intensive care unit, duration of renal replacement therapy, or duration of mechanical ventilation. We found borderline evidence that patients with a baseline serum albumin concentration more than 25 g/l resuscitated with albumin had a shorter hospital stay. In the absence of any other significant heterogeneity, we interpret this as a chance finding.

The strengths of our study are the size and methodological strengths of the saline versus albumin fluid evaluation study, which contributed 82.8% of the data for the latest Cochrane meta-analysis.^{4,8} The weaknesses are those inherent in subgroup analyses and that the original study was not primarily designed to determine the effect of treating hypoalbuminaemia with albumin—patients received the amount of fluid the clinician thought necessary to restore or maintain intravascular volume, not to achieve or maintain a particular serum albumin concentration. Patients assigned to albumin maintained higher albumin concentrations but this was not associated with clear benefit. Although recognising the limitations of our analysis, the 2004 Cochrane review reported only 637 patients and 86 deaths from 10 trials (six in adults) of patients treated for hypoalbuminaemia.⁴ Of the 6997 adults in the saline versus albumin fluid evaluation study, 2451 had a recorded baseline serum albumin concentration of 25 g/l or less of whom 612 died.

In conclusion, resuscitation with albumin and saline in the intensive care unit produces similar patient outcomes irrespective of patients' baseline serum albumin concentrations. Although albumin does not increase the risk of mortality, the evidence is

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.

Funding: Auckland District Health Board, New Zealand; Australian Commonwealth Department of Health and Aged Care; CSL, Melbourne, Victoria; Middlemore Hospital, New Zealand; Australian National Health and Medical Research Council; Health Department of Western Australia; Health Research Council of New Zealand; New South Wales Health Department; Northern Territory Health Services; Queensland Health Services Department; Royal Hobart Hospital, Tasmania; South Australian Department of Human Services; and Victorian Department of Human Services.

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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(Accepted 12 September 2006)

doi 10.1136/bmj.38985.398704.7C

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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Langlois CV, ed. *De recuperatione terre sancte: traité de politique général par Pierre Dubois*. Paris: Picard, 1891: 51-2, 70-1. Cited by Rowland B. *Medieval women's guide to health*. Kent, OH: Kent State University Press, 1981:1