ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

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ABSTRACT

BACKGROUND

Although previous studies have suggested the potential advantages of albumin administration in patients with severe sepsis, its efficacy has not been fully established.

METHODS

In this multicenter, open-label trial, we randomly assigned 1818 patients with severe sepsis, in 100 intensive care units (ICUs), to receive either 20% albumin and crystalloid solution or crystalloid solution alone. In the albumin group, the target serum albumin concentration was 30 g per liter or more until discharge from the ICU or 28 days after randomization. The primary outcome was death from any cause at 28 days. Secondary outcomes were death from any cause at 90 days, the number of patients with organ dysfunction and the degree of dysfunction, and length of stay in the ICU and the hospital.

RESULTS

During the first 7 days, patients in the albumin group, as compared with those in the crystalloid group, had a higher mean arterial pressure (P=0.03) and lower net fluid balance (P<0.001). The total daily amount of administered fluid did not differ significantly between the two groups (P=0.10). At 28 days, 285 of 895 patients (31.8%) in the albumin group and 288 of 900 (32.0%) in the crystalloid group had died (relative risk in the albumin group, 1.00; 95% confidence interval [CI], 0.87 to 1.14; P=0.94). At 90 days, 365 of 888 patients (41.1%) in the albumin group and 389 of 893 (43.6%) in the crystalloid group had died (relative risk, 0.94; 95% CI, 0.85 to 1.05; P=0.29). No significant differences in other secondary outcomes were observed between the two groups.

CONCLUSIONS

In patients with severe sepsis, albumin replacement in addition to crystalloids, as compared with crystalloids alone, did not improve the rate of survival at 28 and 90 days. (Funded by the Italian Medicines Agency; ALBIOS ClinicalTrials.gov number, NCT00707122.)

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OR DECADES, HUMAN ALBUMIN HAS BEEN administered to patients to provide adequate oncotic pressure and intravascular volume.[1] In 1998, however, a report from the Cochrane Injuries Group Albumin Reviewers indicated that the administration of albumin may be potentially harmful in critically ill patients, as compared with the administration of crystalloid solutions.[2] Subsequent meta-analyses reported contradictory findings.[3,4]

To clarify this issue, a large, double-blind, randomized trial (the Saline versus Albumin Fluid Evaluation [SAFE] study)[5] was conducted, in which 4% albumin solution was compared with normal saline as fluid replacement in critically ill patients, with results indicating that albumin administration was safe. A predefined subgroup analysis showed that patients with severe sepsis receiving albumin were at a lower, although not significantly lower, risk for death than those receiving normal saline. In addition, a subsequent study pointed out a potential benefit of maintaining serum albumin at a level of more than 30 g per liter in critically ill patients.[6]

There is a convincing rationale for the potential advantages of albumin administration during severe sepsis.[7] Albumin is the main protein responsible for plasma colloid osmotic pressure[8]; it acts as a carrier for several endogenous and ex-ogenous compounds,[9] with antioxidant and anti-inflammatory properties, and as a scavenger of reactive oxygen[10,11] and nitrogen[12] species and operates as a buffer molecule for acid–base equilibrium.[13] We therefore conducted a randomized, controlled trial to investigate the effects of the administration of albumin and crystalloids, as compared with crystalloids alone, targeting a serum albumin level of 30 g per liter or more in a population of patients with severe sepsis.

METHODS

STUDY OVERSIGHT AND DESIGN

We conducted the Albumin Italian Outcome Sepsis (ALBIOS) study — an investigator-initiated, multicenter, open-label, randomized, controlled trial — in 100 intensive care units (ICUs) in Italy. The members of the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study, were responsible for its execution and for the data analysis, made the decision to submit the manuscript for publication, and assume responsibility for the fidelity of the study to the protocol (available at NEJM.org).

The trial was funded by the Italian Medicines Agency, which had no role in the conduct of the study, the reporting of the data, or the supply of

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Albumin Group (N = 903)	Crystalloid Group (N = 907)
Age — yr		
Median	70	69
Interquartile range	57–77	59–77
Female sex — no. (%)	360 (39.9)	357 (39.4)
Body-mass index†	27±6	27±6
Reason for ICU admission — no. (%)		
Medical	511 (56.6)	518 (57.1)
Elective surgery	69 (7.6)	58 (6.4)
Emergency surgery	323 (35.8)	331 (36.5)
Preexisting condition — no. (%)‡		
Liver disease	13 (1.4)	14 (1.5)
COPD	113 (12.5)	108 (11.9)
Chronic renal failure	44 (4.9)	32 (3.5)
Immunodeficiency	115 (12.7)	128 (14.1)
Congestive or ischemic heart disease	149 (16.5)	165 (18.2)
SAPS II score§		
Median	48	48
Interquartile range	37–59	37–60

Table 1. (Continued.)

Characteristic	Albumin Group (N = 903)	Crystalloid Group (N = 907)
Physiological variable¶		
Heart rate — beats/min	105±22	106±20
Mean arterial pressure — mm Hg	74±16	73±15
Central venous pressure — mm Hg	10.0±4.9	9.8±4.7
Urine output — ml/hr		
Median	50	50
Interquartile range	20–100	25–100
Lactate — mmol/liter		
Median	2.3	2.5
Interquartile range	1.4–4.2	1.6–4.3
Serum albumin — g/liter	24.1±6.3	24.2±6.2
Hemoglobin — g/dl	10.9±2.1	11.0±2.0
Central venous oxygen saturation — %		
Median	73	73
Interquartile range	65–79	68–80
SOFA score‖		
Median	8	8
Interquartile range	6–10	5–10
Organ dysfunction — no. (%)**		
1 organ	188 (20.8)	208 (22.9)
2 organs	361 (40.0)	303 (33.4)
3 organs	236 (26.1)	248 (27.3)
4 organs	89 (9.9)	115 (12.7)
5 organs	29 (3.2)	33 (3.6)
Shock — no. (%)††	565 (62.6)	570 (62.8)
Mechanical ventilation — no. (%)	709 (78.5)	737 (81.3)
Fluid administration in previous 24 hr — no. (%)		
Albumin	153 (16.9)	176 (19.4)
Synthetic colloids	452 (50.1)	479 (52.8)

*   Plus–minus values are means ±SD. There were no significant differences between the two groups except with respect to central venous oxygen saturation (P=0.02) and number of patients with organ dysfunction (P=0.04). COPD denotes chronic obstructive pulmonary disease, and ICU intensive care unit.

†   The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡   Among preexisting conditions, liver disease was defined as the presence of cirrhosis, portal hypertension, or previous episodes of liver insufficiency; immunodeficiency as the concurrent presence of immunosuppressive diseases or receipt of immunosuppressive therapies; and congestive or ischemic heart disease as New York Heart Association class II.

§   The Simplified Acute Physiology Score (SAPS II)[16] was used to assess the severity of systemic illness at baseline. Scores range from 0 to 163, with higher scores indicating more severe illness.

¶   Data on central venous pressure were available for 841 patients in the albumin group and 858 in the crystalloid group; data on lactate level, for 874 and 867, respectively; data on serum albumin level, for 821 and 813, respectively; data on hemoglobin level, for 893 and 894, respectively; and data on central venous oxygen saturation, for 798 and 802, respectively.

‖   The Sequential Organ Failure Assessment (SOFA) score[17] includes subscores ranging from 0 to 4 for each of five components (respiratory, coagulation, liver, cardiovascular, and renal components), with higher scores indicating more severe organ dysfunction. The scoring was modified by excluding the assessment of cerebral failure (the Glasgow Coma Scale), which was not performed in these patients, and by decreasing to 65 mm Hg the mean arterial pressure threshold for a cardiovascular subscore of 1, for consistency with the hemodynamic targets as defined according to the early goal-directed therapy.[15]

**   Organ dysfunctions were defined as a SOFA score of 2 or more on the respiratory component; 2 or more on the co-agulation component; 2 or more on the liver component; 1, 3, or 4 on the cardiovascular component; and 2 or more on the renal component.[5] A score of 2 on the cardiovascular component was not included because that score is assigned for the use of vasopressor drugs at low doses (a condition not considered to be strictly related to cardiovascular dysfunction).

††   Shock at the time of randomization was defined as a score of 3 or 4 on the cardiovascular component of the SOFA.[5]

study fluids. Albumin administered during the study was provided by each participating institution as part of the clinical treatment of critically ill patients. The study protocol and the informed-consent process were approved by the ethics committee at each participating institution. Written informed consent or deferred consent was obtained from each patient.

Randomization was performed centrally, with the use of a computer-generated and blinded assignment sequence. Randomization was stratified according to the participating ICU and the interval between the time that the patient met the clinical criteria for severe sepsis and randomization. The conduct of the trial was overseen by the data and safety monitoring board, which performed an interim analysis after the enrollment of 700 patients.

PATIENTS

Patients 18 years of age or older who met the clinical criteria for severe sepsis[14] within the previous 24 hours at any time during their stay in the ICU were enrolled in the study after being screened for eligibility criteria. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

STUDY TREATMENTS

Patients were randomly assigned to receive either 20% albumin and crystalloid solution (albumin group) or crystalloid solution alone (crystalloid group) from randomization until day 28 or discharge from the ICU, whichever came first. During the early phase of volume resuscitation, fluids were administered in both groups according to early goal-directed therapy.[15]

After randomization, patients in the albumin group received 300 ml of 20% albumin solution. From day 1 until day 28 or ICU discharge (whichever came first), 20% albumin was administered on a daily basis, to maintain a serum albumin level of 30 g per liter or more. In both groups, crystalloids were administered whenever it was clinically indicated by the attending physician. The administration of synthetic colloids was not allowed. All other treatments were at the discretion of the attending physician.

OUTCOMES

The primary outcome measure was death from any cause at 28 days after randomization. The principal secondary outcome measure was death from any cause at 90 days after randomization. Additional secondary outcomes were the number of patients with organ dysfunction and the degree of dysfunction and the length of stay in the ICU and the hospital. The severity of systemic illness was assessed with the use of the Simplified Acute Physiology Score, with scores ranging from 0 to 163 and higher scores indicating more severe illness.[16] Organ function was assessed daily with the use of the Sequential Organ Failure Assessment (SOFA) score,[17] which ranges from 0 to 4 for each of five components (respiratory, coagulation, liver, cardiovascular, and renal components), with higher scores indicating more severe organ dysfunction (Table S1 in the Supplementary Appendix). New organ failures were defined as a change in a component score during the study from a baseline score of 0, 1, or 2 to a score of 3 or 4.[5,18,19] Tertiary outcomes, which were assessed in post hoc analyses, included the use of renal-replacement therapy, the incidence of acute kidney injury, the duration of mechanical ventilation, and the time to suspension of the administration of vasopressor or inotropic agents.

STATISTICAL ANALYSIS

We originally determined that a sample of 1350 patients would provide the study with 80% power to detect an absolute between-group difference of 7.5 percentage points in mortality at 28 days, on the basis of an estimated baseline mortality of 45%, with a two-sided P value of less than 0.05 indicating statistical significance. The study protocol specified the possibility of increasing the sample to 1800 patients on the basis of a recommendation by the data and safety monitoring board during an interim analysis.

All the analyses were conducted on an intention-to-treat basis. Binary outcomes were compared with the use of the chi-square test, and continuous outcomes with the use of the Wilcoxon rank-sum test. Comparisons of fluid volumes and physiological data over time were performed with the use of a two-factor analysis of variance for repeated measurements. We calculated survival estimates according to the Kaplan–Meier method and compared them using a log-rank test. We performed an adjusted analysis using robust Poisson regression for binary outcomes. In a post hoc analysis, the primary and principal

**Figure 1. Serum Albumin Levels through Day 28 and Net Fluid Balance through Day 7.**

Panel A shows the serum albumin concentration through day 28 in patients receiving albumin and crystalloids or crystalloids alone. Day 0 was defined as the time of randomization. Data are medians, with I bars indicating interquartile ranges. The P value is for the between-group comparison performed with the use of a two-factor analysis of variance for repeated measurements to test time (29 days for serum albumin, including day 0) and group effects. Panel B shows the net fluid balance through day 7 for patients receiving albumin and crystalloids or crystalloids alone. The daily net fluid balance was calculated as the difference between the total amount of administered fluid (including 20% albumin; crystalloids; other blood products, such as packed red cells, fresh-frozen plasma, or platelets; and other fluids) and the total amount of excreted fluid each day (including urinary output and other fluid losses, such as fluids potentially removed with continuous renal-replacement therapy, fluids lost as feces, aspirated gastric content, drainage fluids, and insensible perspiration). For day 1, the net fluid balance was computed from the time of randomization to day 1, which averaged 16 hours in the two study groups. The horizontal line in the boxes indicates the median, the top and bottom of the box the interquartile range, and I bars the 5th and 95th percentile range. The P value is for the between-group comparison performed with the use of the two-factor analysis of variance for repeated measurements to test time (7 days) and group effects.

RESULTS

STUDY POPULATION

From August 2008 through February 2012, a total of 1818 patients with severe sepsis were randomly assigned to receive 20% albumin and crystalloid solution (910 patients) or crystalloid solution alone (908) for fluid replacement. Per protocol, patient enrollment was stratified according to the interval between the time the patient met the clinical criteria for severe sepsis and randomization: 6 hours or less (579 patients [31.8%]) versus more than 6 hours (1239 [68.2%]). A total of 8 patients were excluded from the analysis
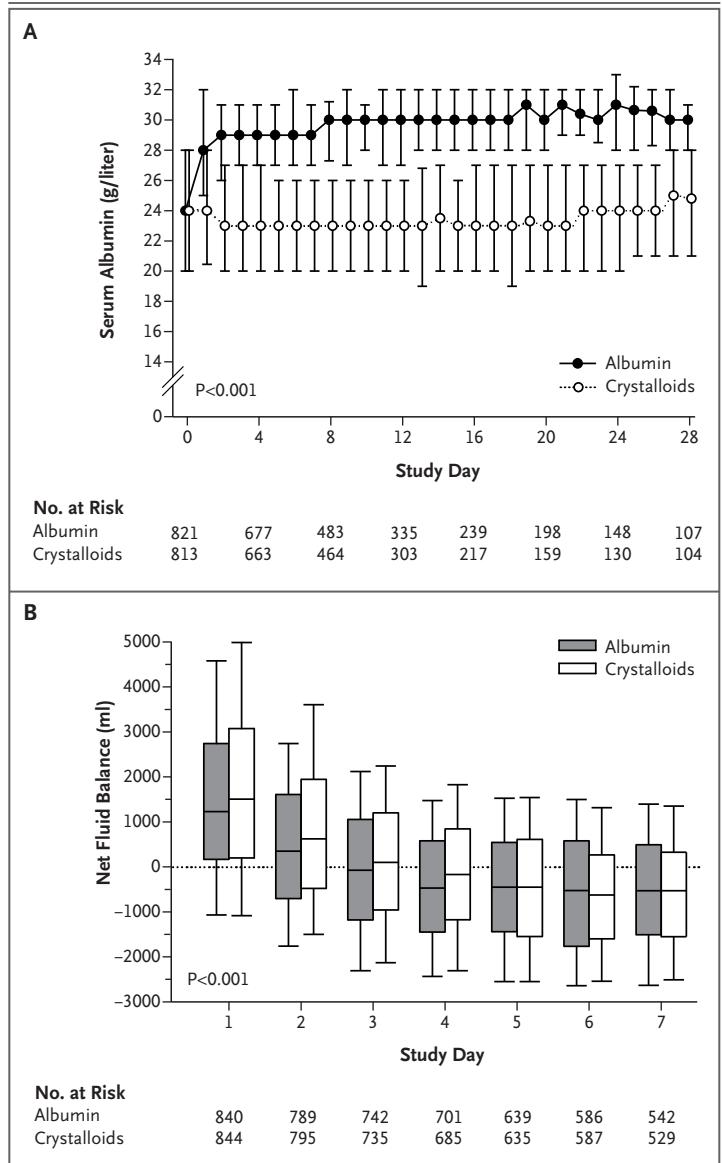
(2 patients in the albumin group owing to withdrawal of consent, and 5 in the albumin group and 1 in the crystalloid group owing to a randomization error) (Fig. S1 in the Supplementary Appendix).

After follow-up, data regarding death at 90 days were available for 888 of 903 patients (98.3%) in the albumin group and for 893 of 907 (98.5%) in the crystalloid group. Baseline characteristics were similar between the two study groups, except for a slight imbalance in the number of patients with organ dysfunction and values of central venous oxygen saturation (Table 1). The primary site of

infection, the type of identified microorganism, and the proportion of patients receiving antibiotics were similar in the two groups (Table S2 in the Supplementary Appendix).

FLUID THERAPY AND TREATMENT EFFECTS

During the first 7 days, the albumin group, as compared with the crystalloid group, received a significantly larger volume of 20% albumin solution (P<0.001) and less crystalloid solution (P<0.001). In the albumin group, the administra-tion of 20% albumin solution accounted for a median daily average of 4.3% (interquartile range, 2.9 to 5.8) of the total administered fluids. The total daily amount of administered fluids in the first 7 days did not differ significantly between the albumin group and the crystalloid group (3738 ml [interquartile range, 3174 to 4437] and 3825 ml [interquartile range, 3205 to 4533], respectively; P=0.10) (Table S3 in the Supplementary Appendix).

The serum albumin level was significantly

Table 2. Outcomes.

Outcome	Albumin Group	Crystalloid Group	Relative Risk (95% CI)	P Value
Primary outcome: death at 28 days — no./total no. (%)	285/895 (31.8)	288/900 (32.0)	1.00 (0.87–1.14)	0.94
Secondary outcomes				
Death at 90 days — no./total no. (%)	365/888 (41.1)	389/893 (43.6)	0.94 (0.85–1.05)	0.29
New organ failures — no./total no. (%)*				0.99
None	372/836 (44.5)	383/841 (45.5)		
1 organ	283/836 (33.9)	287/841 (34.1)		
2 organs	130/836 (15.6)	123/841 (14.6)		
3 organs	40/836 (4.8)	36/841 (4.3)		
4 organs	10/836 (1.2)	11/841 (1.3)		
5 organs	1/836 (0.1)	1/841 (0.1)		
SOFA score†			—	0.23
Median	6.00	5.62		
Interquartile range	4.00–8.50	3.92–8.28		
SOFA subscore†				
Cardiovascular			—	0.03
Median	1.20	1.42		
Interquartile range	0.46–2.31	0.60–2.50		
Respiratory			—	0.63
Median	2.00	2.00		
Interquartile range	1.56–2.48	1.57–2.50		
Renal			—	0.15
Median	0.83	0.75		
Interquartile range	0.14–2.14	0.07–2.00		
Coagulation			—	0.04
Median	0.64	0.50		
Interquartile range	0.00–1.62	0.00–1.59		
Liver			—	0.02
Median	0.28	0.20		
Interquartile range	0.00–1.00	0.00–0.92		
Length of stay — days				
In ICU			—	0.42
Median	9	9		
Interquartile range	4–18	4–17		
In hospital‡			—	0.65
Median	20	20		
Interquartile range	10–36	9–38		

Table 2. (Continued.)

Outcome	Albumin Group	Crystalloid Group	Relative Risk (95% CI)	P Value
Tertiary outcomes§				
Renal-replacement therapy — no./total no. (%)¶	222/903 (24.6)	194/907 (21.4)		0.11
Acute kidney injury — no./total no. (%)‖	183/834 (21.9)	190/837 (22.7)		0.71
Duration of mechanical ventilation — days**			—	0.50
Median	6	6		
Interquartile range	2–14	2–13		
Time to suspension of vasopressor or inotropic agents — days††			—	0.007
Median	3	4		
Interquartile range	1–6	2–7		

*   New organ failures were defined by a change in a specific component of the SOFA[17] from a score of 0, 1, or 2 at baseline to a score of 3 or 4 during the study period.[5,17,18]
†   The values are the median and interquartile range of the SOFA score, representing the average of the daily SOFA scores for each individual patient during his or her study period (including the SOFA score at baseline). No imputation was performed for missing data.
‡   The length of stay in the hospital included the length of stay in the ICU.
§   Tertiary outcomes were analyzed in post hoc analyses.
¶   Included are patients with any form of renal-replacement therapy prescribed by the attending physician during the study period, including patients with chronic renal failure at baseline.
‖   Acute kidney injury was defined according to the risk, injury, failure, loss, and end-stage kidney injury (RIFLE) criteria[20] for acute kidney injury on the basis of daily incremental increases in serum creatinine levels from baseline during the study period.
** The duration of ventilatory support includes only the time during the study period, which was not necessarily the total duration of ventilatory support.
†† The time to the suspension of vasopressor or inotropic agents was assessed as the number of days of administration of vasopressor or inotropic agents in patients for whom such treatment was ongoing at baseline. Data were available for 582 patients in the albumin group and 576 in the crystalloid group.

higher in the albumin group than in the crystalloid group from day 1 to day 28 (P<0.001) (Fig. 1A). During the first 7 days, patients in the albumin group had a significantly lower heart rate than those in the crystalloid group (P=0.002), as well as a significantly higher mean arterial pressure (P=0.03) (Table S4 and Fig. S2 in the Supplementary Appendix). Daily net fluid balances were lower in the albumin group than in the crystalloid group (P<0.001) (Fig. 1B). The median cumulative net fluid balance was also significantly lower in the albumin group than in the crystalloid group (347 ml [interquartile range, −3266 to 4042] vs. 1220 ml [interquartile range, −2767 to 5034], P=0.004) (Table S5 in the Supplementary Appendix).
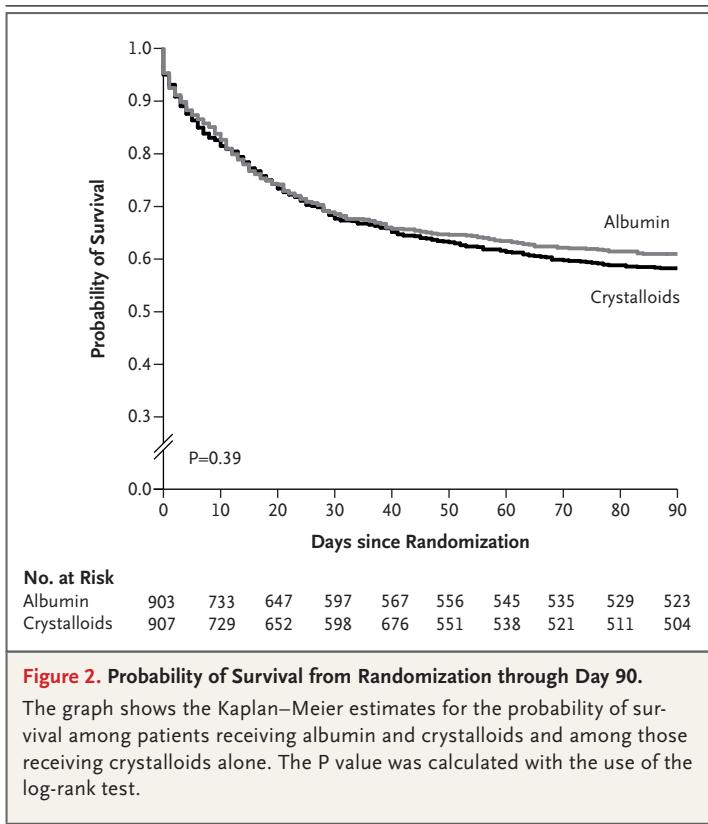
OUTCOMES

At 28 days after randomization, 285 of 895 patients (31.8%) in the albumin group and 288 of 900 (32.0%) in the crystalloid group had died (relative risk in the albumin group, 1.00; 95% confidence interval [CI], 0.87 to 1.14; P=0.94) (Table 2). At 90 days of follow-up, 365 of 888 patients (41.1%) in the albumin group and 389 of

893 (43.6%) in the crystalloid group had died (relative risk, 0.94; 95% CI, 0.85 to 1.05; P=0.29). No significant difference in the probability of survival was observed between the albumin group and the crystalloid group during the 90 days after randomization (P=0.39) (Fig. 2).

No significant difference was observed between the two study groups with respect to either the number of newly developed organ failures or the median SOFA score (Table 2). Analysis of the SOFA score for each organ system revealed that, as compared with the crystalloid group, the albumin group had a lower cardiovascular score (P=0.03), a higher coagulation score (P=0.04), and a higher liver score (P=0.02). No significant differences were observed in other secondary and tertiary outcomes, with the exception of the time to suspension of the administration of vasopressor or inotropic agents, which was shorter in the albumin group than in the crystalloid group (P=0.007) (Table 2).

In subgroup analyses, no significant difference was observed in the prespecified subgroups that were stratified according to the interval between the time the patient met the clinical crite-

Figure 2. Probability of Survival from Randomization through Day 90.

The graph shows the Kaplan–Meier estimates for the probability of survival among patients receiving albumin and crystalloids and among those receiving crystalloids alone. The P value was calculated with the use of the log-rank test.

ria for severe sepsis and randomization (Fig. S3 in the Supplementary Appendix). Conversely, a significant difference was observed in a post hoc subgroup analysis that included 1121 patients with septic shock, as compared with 660 without septic shock, at the time of enrollment (relative risk with septic shock, 0.87; 95% CI, 0.77 to 0.99; relative risk without septic shock, 1.13; 95% CI, 0.92 to 1.39; P=0.03 for heterogeneity) (Fig. S3 in the Supplementary Appendix). Adjustment for baseline covariates did not significantly modify these results (Table S6 in the Supplementary Appendix).

DISCUSSION

The main results of this large-scale trial provide evidence regarding both the efficacy and the safety of the use of human albumin during severe sepsis — an interventional strategy that has long been debated.[21,22] The addition of albumin to crystalloids during the first 28 days of treatment to maintain a serum albumin level of 30 g per liter or more is safe but does not provide a survival advantage over crystalloids alone, over a follow-up period of 90 days. Similar findings were observed in the subgroup stratified according to the interval between the time the patient met the clinical criteria for severe sepsis and treatment application.

The findings in our trial may appear to contradict those of the predefined subgroup analysis from the SAFE study,[5] which suggested a survival advantage with an albumin-based strategy during severe sepsis. The plausibility of this hypothesis was supported by the significant hemodynamic advantages observed[23] and by further investigations showing that the correction of hypoalbuminemia reduced the severity of organ dysfunction.[4,6] Similar beneficial effects were also suggested by a large meta-analysis, which concluded that the use of albumin-containing solutions could be associated with lower mortality than that seen with other fluid regimens.[24]

Our results confirm that administration of albumin produces small but significant hemodynamic advantages. A significantly greater proportion of patients in the albumin group than in the crystalloid group reached the targeted mean arterial pressure within 6 hours after randomization (Table S7 in the Supplementary Appendix). During the first 7 days, the mean arterial pressure was higher, whereas the heart rate and net fluid balance were lower, in the albumin group than in the crystalloid group. Moreover, the average cardiovascular SOFA subscore over the course of the study period was lower in the albumin group, and the time to the suspension of inotropic or vasopressor agents was shorter, indicating a decreased use of vasopressors. These effects were obtained with similar amounts of administered fluids in the two study groups. These findings confirm a physiological advantage of albumin administration during severe sepsis, including a larger fluid distribution within the intravascular compartment and, in addition, possible effects of albumin as a scavenger of nitric oxide,[12] mediating peripheral vasodilatation during sepsis.[25,26]

The secondary outcomes also provide a detailed profile of the safety of albumin administration during severe sepsis. The incidence of new organ failures during the study was similar in the two groups. We observed slightly higher average SOFA subscores for liver and coagulation in the albumin group, indicating a higher serum bilirubin and a lower platelet

count, respectively, than were observed in the crystalloid group. Nonetheless, the absolute excess in the serum bilirubin concentration in the albumin group was marginal (median, 1.0 mg per deciliter [interquartile range, 0.6 to 1.7] vs. 0.9 mg per deciliter [interquartile range, 0.5 to 1.5], P<0.001) and was probably related to the methods used to prepare albumin solutions, which may be inefficient in clearing bilirubin content from plasma.[21,27] The slight reduction in platelet counts in the albumin group may be a further marker of a larger expansion of the intravascular compartment in this group than in the crystalloid group, with a consequent dilution of the hemoglobin content (Table S4 in the Supplementary Appendix).

Post hoc univariate and multivariate analyses of data from the 1121 patients with septic shock showed significantly lower mortality at 90 days in the albumin group than in the crystalloid group. Conversely, in the subgroup of patients with severe sepsis without shock, mortality appeared to be higher among those who were treated with albumin than among those treated with crystalloids alone, although the difference was far from significant. This analysis was not prespecified, and therefore it may be characterized by well-known biases. Nonetheless, a state of shock associated with severe sepsis represents a well-defined clinical entity. Moreover, if the oncotic, anti-inflammatory, and nitric oxide–scavenging properties of albumin are of clinical importance, these may be maximally exploited in the conditions that are the most severe, such as cardiovascular dysfunction.

Our trial has certain limitations. First, we included the use of albumin solutions with a greater concentration than those used in the SAFE study (20% vs. 4%). Consequently, the volume of albumin solution that was administered was markedly lower than that administered in the SAFE study, since our goal was to correct hypoalbuminemia and not to directly replace intravascular volume. Second, the observed mortality at 28 days was lower than originally expected, thereby increasing the likelihood that the study was underpowered. Finally, only approximately one third of the patients were enrolled during the early phase of severe sepsis.

In conclusion, the use of albumin in addition to crystalloids to correct hypoalbuminemia, as compared with the use of crystalloids alone, in patients with severe sepsis during their stay in the ICU did not provide a survival benefit at 28 or 90 days, despite improvements in hemodynamic variables. The clinical benefit of albumin that was seen in the post hoc analysis of the subgroup of patients with septic shock warrants further confirmation.

REFERENCES

1. Erstad BL, Gales BJ, Rappaport WD. The use of albumin in clinical practice. Arch Intern Med 1991;151:901-11.
2. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ 1998;317:235-40.
3. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. Ann Intern Med 2001;135:149-64.
4. Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 2003; 237:319-34.

5. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247-56.

6. Dubois MJ, Orellana-Jimenez C, Melot C, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. Crit Care Med 2006;34:2536-40.

7. Quinlan GJ, Martin GS, Evans TW. Albumin: biochemical properties and therapeutic potential. Hepatology 2005;41:1211-9.

8. Weil MH, Henning RJ, Puri VK. Colloid oncotic pressure: clinical significance. Crit Care Med 1979;7:113-6.

9. Sudlow G, Birkett DJ, Wade DN. The characterization of two specific drug binding sites on human serum albumin. Mol Pharmacol 1975;11:824-32.

10. King TP. On the sulfhydryl group of human plasma albumin. J Biol Chem 1961;236:PC5.

11. Quinlan GJ, Margarson MP, Mumby S, Evans TW, Gutteridge JM. Administration of albumin to patients with sepsis syndrome: a possible beneficial role in plasma thiol repletion. Clin Sci (Lond) 1998;95:459-65.

12. Stamler JS, Jaraki O, Osborne J, et al. Nitric oxide circulates in mammalian plasma primarily as an S-nitroso adduct of serum albumin. Proc Natl Acad Sci U S A 1992;89:7674-7.

13. Reeves RB. Temperature-induced changes in blood acid-base status: Donnan rCl and red cell volume. J Appl Physiol 1976;40:762-7.

14. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644-55.

15. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.

16. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957-63. [Erratum, JAMA 1994;271:1321.]

17. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22:707-10.

18. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med 1998;26:1793-800.

19. Moreno R, Vincent JL, Matos R, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care: results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. Intensive Care Med 1999;25:686-96.

20. Kellum JA, Bellomo R, Ronco C. The concept of acute kidney injury and the RIFLE criteria. Contrib Nephrol 2007;156:10-6.

21. Vincent JL. Relevance of albumin in modern critical care medicine. Best Pract Res Clin Anaesthesiol 2009;23:183-91.

22. Vincent JL, Gottin L. Type of fluid in severe sepsis and septic shock. Minerva Anestesiol 2011;77:1190-6.

23. The SAFE Study Investigators. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med 2011;37:86-96.

24. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. Crit Care Med 2011;39:386-91.

25. Hollenberg SM, Piotrowski MJ, Parrillo JE. Nitric oxide synthase inhibition reverses arteriolar hyporesponsiveness to endothelin-1 in septic rats. Am J Physiol 1997;272:R969-R974.

26. Titheradge MA. Nitric oxide in septic shock. Biochim Biophys Acta 1999;1411:437-55.

27. McCann KB, Vucica Y, Famulari S, Bertolini J. Effect of processing methods on colouration of human serum albumin preparations. Biologicals 2009;37:32-6.

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