ORIGINAL ARTICLE

Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury

The SAFE Study Investigators*

ABSTRACT

BACKGROUND

The Saline versus Albumin Fluid Evaluation study suggested that patients with traumatic brain injury resuscitated with albumin had a higher mortality rate than those resuscitated with saline. We conducted a post hoc follow-up study of patients with traumatic brain injury who were enrolled in the study.

METHODS

For patients with traumatic brain injury (i.e., a history of trauma, evidence of head trauma on a computed tomographic [CT] scan, and a score of ≤13 on the Glasgow Coma Scale [GCS]), we recorded baseline characteristics from case-report forms, clinical records, and CT scans and determined vital status and functional neurologic outcomes 24 months after randomization.

RESULTS

We followed 460 patients, of whom 231 (50.2%) received albumin and 229 (49.8%) received saline. The subgroup of patients with GCS scores of 3 to 8 were classified as having severe brain injury (160 [69.3%] in the albumin group and 158 [69.0%] in the saline group). Demographic characteristics and indexes of severity of brain injury were similar at baseline. At 24 months, 71 of 214 patients in the albumin group (33.2%) had died, as compared with 42 of 206 in the saline group (20.4%) (relative risk, 1.63; 95% confidence interval [CI], 1.17 to 2.26; P=0.003). Among patients with severe brain injury, 61 of 146 patients in the albumin group (41.8%) died, as compared with 32 of 144 in the saline group (22.2%) (relative risk, 1.88; 95% CI, 1.31 to 2.70; P<0.001); among patients with GCS scores of 9 to 12, death occurred in 8 of 50 patients in the albumin group (16.0%) and 8 of 37 in the saline group (21.6%) (relative risk, 0.74; 95% CI, 0.31 to 1.79; P=0.50).

CONCLUSIONS

In this post hoc study of critically ill patients with traumatic brain injury, fluid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline. (Current Controlled Trials number, ISRCTN76588266.)

The Saline versus Albumin Fluid Evaluation (SAFE) study is 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. The writing committee of the SAFE–Traumatic Brain Injury study (John Myburgh, M.D., Ph.D., D. James Cooper, M.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Robyn Norton, Ph.D., M.P.H., Nicole Bishop, B.Sc., Sing Kai Lo, Ph.D., and Shirley Vallance, R.N.) takes responsibility for the content and integrity of this article. Address reprint requests to Dr. Myburgh at ANZICS Clinical Trials Group, Level 3, 10 Ievers Terrace, Carlton, VIC 3053, Australia, or at j.myburgh@unsw.edu.au.

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In patients with traumatic brain injury, resuscitation fluids are fundamental components of the restoration and maintenance of the systemic and cerebral circulations.[1,2] There is uncertainty about the best choice of fluids due to the lack of adequately powered randomized, controlled trials. Consequently, both crystalloid-based and colloid-based resuscitation strategies have been advocated.[3,4]

The Saline versus Albumin Fluid Evaluation (SAFE) study compared the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in intensive care units (ICUs).[5] Overall, the study showed no significant difference in the risk of death among patients who received albumin as compared to those who received saline. There was evidence of heterogeneity of treatment effects among patients who did and those who did not have a diagnosis of trauma; this evidence resulted from an increased number of deaths among patients with traumatic brain injury who received albumin.[5]

The clinical significance of these observations in patients with traumatic brain injury was uncertain for two main reasons. First, the SAFE study did not collect sufficiently detailed data to demonstrate that baseline factors known to influence outcome from traumatic brain injury were similar for patients assigned to albumin and for those assigned to saline. Second, the primary outcome of the SAFE study was the rate of death within 28 days after randomization, whereas current consensus recommendations cite mortality and functional neurologic outcomes between 6 and 24 months as appropriate outcome measures after traumatic brain injury.[6,7]

Because of the potential significance of the main results of the SAFE study, we undertook a post hoc follow-up study of patients from the SAFE study who had traumatic brain injury (the SAFE–TBI study). The aims of the study were to document baseline characteristics that are known to influence outcomes from traumatic brain injury in the albumin and saline groups and to compare death and functional neurologic outcomes in the two groups 24 months after randomization.

METHODS

STUDY DESIGN

A detailed description of the SAFE study design has been published previously.[8] In brief, the double-blind, randomized, controlled trial was conducted in multidisciplinary ICUs of 16 hospitals in Australia and New Zealand between November 2001 and June 2003. Eligible adult patients were randomly assigned to receive either 4% albumin (Albumex, CSL) or normal saline for all fluid resuscitation in the ICU until death, discharge, or 28 days after randomization. Randomization was stratified by a diagnosis of trauma (defined as an injury to the body caused by mechanical forces, excluding burns). Traumatic brain injury was defined as a diagnosis of trauma plus a score of 13 or less on the Glasgow Coma Scale (GCS)[9] at first hospital presentation and an abnormality on a computed tomographic (CT) scan of the head consistent with traumatic brain injury.

In the SAFE–TBI study, we identified all patients with traumatic brain injury from the SAFE study database. We included the patients presented in the main SAFE study report plus any additional patients with a diagnosis of head injury that was recorded on admission to the hospital as a component of the Acute Physiology and Chronic Health Evaluation (APACHE) II score.[10] We reviewed the clinical records and CT scans to confirm that all patients satisfied the SAFE–TBI study criteria. The study protocol was approved by the ethics committees of all participating institutions. Written informed consent was obtained from the patient, whenever possible, or from a legal surrogate.

We collected data from case-report forms, clinical records, and CT scans from the SAFE study to determine baseline demographic characteristics, severity of injury, and brain-specific variables associated with neurologic outcomes. Finally, we determined prospectively the vital status and functional neurologic outcomes 24 months after randomization. In June 2005, data collection concluded, 2 years after the final patient was recruited into the SAFE study. All data collectors and trained assessors were unaware of the treatment assignment.

BASELINE ASSESSMENT

We obtained baseline information on age, sex, and the severity of the illness and the injury. The APACHE II score[10] was calculated from worst values in the 24 hours before randomization, and the Abbreviated Injury Scale (1990 revision with 1998 update)[11] was calculated by trained assessors.

The indexes specific to brain injuries that we used were the last recorded GCS score before randomization (while the patient was not sedat-

ed), a separate recording of the motor component of the GCS, and an assessment of the severity of brain injury from the last CT scan performed before randomization. The presence or absence of traumatic subarachnoid hemorrhage and CT scores, calculated according to the Marshall classification,[12] were recorded independently by two of the investigators, who were unaware of the treatment assignments.

We recorded the incidence and frequency of systemic hypotension (defined as a documented episode of systolic blood pressure of <90 mm Hg or a mean arterial pressure of <65 mm Hg) occurring within 24 hours after injury but before randomization,[13] the presence or absence of a monitoring device for intracranial pressure, and episodes of intracranial hypertension occurring before and after randomization. For the purposes of this study, intracranial hypertension was defined as intracranial pressure greater than 30 mm Hg for two consecutive readings at least 30 minutes apart. The study management committee selected this upper threshold of intracranial pressure as an index of severity above which intracranial hypertension would be a probable pathologic mechanism for death.

FOLLOW-UP ASSESSMENT AND OUTCOME MEASURES

The primary outcome measures were the mortality rate and functional neurologic outcome 24 months after randomization. Deaths occurring in the hospital more than 28 days after randomization were determined from hospital records. Patients surviving beyond hospital discharge were located, and deaths occurring between the time of discharge from the hospital and 24 months after randomization were recorded. Patients who were alive 24 months after randomization were interviewed by a single, trained assessor. The assessor used a standardized structured telephone questionnaire[14] to determine the score on the eight-grade Extended Glasgow Outcome Scale,[15,16] on which 8 indicates minimal or no disability and 1 indicates death. Neurologic outcomes were then defined as favorable (grades 5 to 8) or unfavorable (grades 1 to 4).

For patients who died within 28 days after randomization, the primary cause of death was determined using a classification designed by three of the investigators during the conduct of the SAFE study. Allocations of primary and secondary causes of death were determined from case-report forms, hospital records, and death certificates. The primary cause of death was determined independently by two of the investigators, who were unaware of the treatment assignments. When there was disagreement, a third investigator, who also was unaware of the treatment assignments, allocated a primary cause of death and the majority view was accepted.

The George Institute for International Health and the Australian and New Zealand Intensive Care Society Clinical Trials Group performed the data and site management and data analysis independent of funding agencies. The manuscript was prepared by the writing committee and revised by the study investigators, who approved the final manuscript.

STATISTICAL ANALYSIS

The data were exported from the study database and analyzed with the use of Stata software, version 8.2, and SPSS software, version 12. All analyses were performed on an intention-to-treat basis. Where data were missing, we report the number of available observations and make no assumptions about the missing data.

Univariate analyses of proportions were compared with the use of the chi-square test or Fisher's exact test, and continuous variables were compared with the use of unpaired t-tests or analysis of variance. The results of comparisons of event rates in the two groups are presented as relative risks with 95% confidence intervals. Baseline covariates known to be associated with increased mortality from traumatic brain injury (age older than 60 years,[17] GCS score of ≤8,[18] systolic pressure of <90 mm Hg,[19] and traumatic subarachnoid hemorrhage[20]) were fitted to a multivariate logistic-regression model, and the odds ratio at 24 months was adjusted accordingly.

Survival times were compared in the two groups with the use of the log-rank test and are presented as a Kaplan–Meier curve unadjusted for baseline covariates. Analyses were conducted in all patients and in subgroups according to the Brain Trauma Foundation classification of severity of traumatic brain injury: patients with a last recorded GCS score of 3 to 8 before randomization, while not sedated, were classified as having

severe traumatic brain injury, and those with a GCS score of 9 to 12 were classified as having moderate traumatic brain injury.[18]

RESULTS

STUDY PATIENTS

We identified 515 patients with traumatic brain injury. Of these, 492 were reported in the SAFE study.[5] An additional 23 patients were identified by their APACHE II diagnosis of head injury that was recorded on admission to the hospital. A total of 55 patients were then excluded: 14 did not have a diagnosis of trauma on admission, 20 had a last prerandomization GCS score of greater than 13 without sedation, 19 had a last prerandomization CT scan scored as normal, and 2 withdrew consent for follow-up. Of the remaining 460 patients, 231 (50.2%) were assigned to receive albumin and 229 (49.8%) to receive saline (Fig. 1).

Baseline demographic characteristics, injury-severity scores, hemodynamic variables, and variables specific to brain injury were similar in the two groups (Table 1). We classified 160 patients in the albumin group (69.3%) and 158 in the saline group (69.0%) as having severe traumatic brain injury (GCS score, 3 to 8). CT scores were obtained for 213 (92.2%) and 207 (90.4%) patients in the albumin and saline groups, respectively. The CT-scan scores and the proportion of patients with traumatic subarachnoid hemorrhage on CT were similar in the two groups, as was the incidence of prerandomization hypotension.

Overall, monitoring of intracranial pressure was performed in 137 of 203 patients in the albumin group (67.5%) and 147 of 213 patients in the saline group (69.0%). Monitoring of intracranial pressure was performed in 104 of 137 patients with severe traumatic brain injury in the albumin group (75.9%) and in 114 of 147 patients with

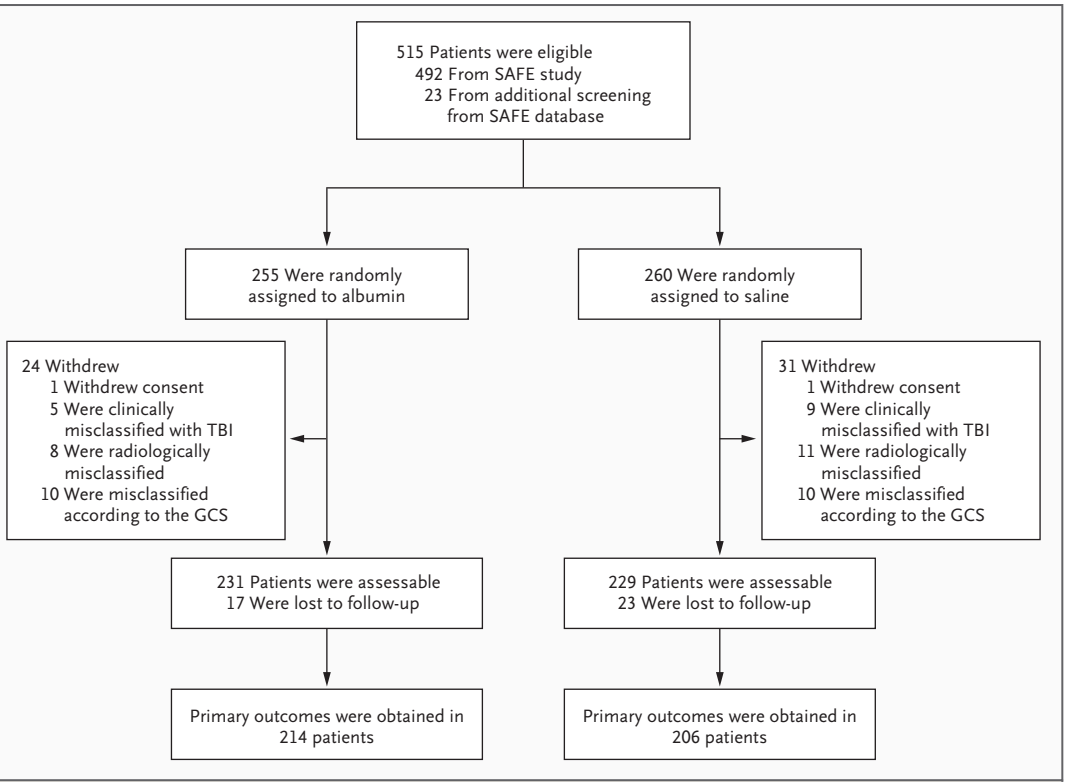

Figure 1. Enrollment of Patients and Assessment of Primary Outcomes.

SAFE denotes the Saline versus Albumin Fluid Evaluation study, TBI traumatic brain injury, and GCS Glasgow Coma Scale. Additional screening from the SAFE database was performed according to Acute Physiology and Chronic Health Evaluation II[10] diagnostic codes.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Albumin Group (N=231)	Saline Group (N=229)	P Value
Age — yr			0.62
Median	37	35	
Interquartile range	23–55	23–50	
Age >55 yr — no. (%)	51 (22.1)	40 (17.5)	0.22
Male sex — no. (%)	179 (77.5)	169 (73.8)	0.36
Injury severity†			
APACHE II score	20.4±6.1	19.70±6.4	0.21
Abbreviated Injury Scale score	28.6±9.9	28.2±10.5	0.68
Mean arterial pressure — mm Hg	82.5±13.7	84.0±13.7	0.23
Heart rate — beats/min	85.9±21.5	86.8±20.4	0.65
Central venous pressure — mm Hg	7.3±3.5	7.5±3.8	0.74
Serum albumin — g/liter	31.2±7.7	32.0±6.9	0.25
GCS score‡			0.54
Median	7	7	
Interquartile range	4–9	5–9	
3 to 8 — no. (%)	160 (69.3)	158 (69.0)	0.54
9 to 12 — no. (%)	53 (22.9)	44 (19.2)	0.54
13 — no. (%)	18 (7.8)	27 (11.8)	0.54
Score for motor responses on GCS			0.51
Median	4	4	
Interquartile range	2–5	2–5	
Scores on CT scanning§			
Diffuse Injury II — no./total no. (%)	114/213 (53.5)	110/207 (53.1)	0.93
Diffuse Injury III — no./total no. (%)	28/213 (13.1)	30/219 (13.7)	0.70
Diffuse Injury IV — no./total no. (%)	9/213 (4.2)	6/222 (2.7)	0.46
Nonevacuated mass lesion — no. (%)	54 (25.4)	53 (24.3)	0.96
Evacuated mass lesion — no. (%)	8 (3.8)	8 (3.6)	0.96
Traumatic subarachnoid hemorrhage — no. (%)	110 (51.6)	97 (46.9)	0.33
Prerandomization hypotension — no./total no. (%)	61/201 (30.4)	70/212 (33.0)	0.37
Intracranial pressure on insertion — mm Hg	15.0±12.9	12.4±7.2	0.06
Prerandomization intracranial hypertension — no./total no. (%)	11/108 (10.2)	11/114 (9.6)	0.89

* Plus–minus values are means ±SD. Because of rounding, not all percentages total 100. APACHE denotes Acute Physiology and Chronic Health Evaluation, GCS Glasgow Coma Scale, and CT computed tomography.
† Higher scores on the injury-severity scales indicate more severe illness. APACHE II scores range from 0 to 72, and Abbreviated Injury Scale scores from 0 to 75.
‡ Scores range from 15 (normal) to 3 (deep coma).
§ Diffuse Injury II includes all diffuse injuries with the presence of basal cisterns and a midline shift of less than 5 mm and no high- or mixed-density lesions greater than 25 ml, Diffuse Injury III includes all diffuse injuries with compressed or absent basal cisterns and a midline shift of less than 5 mm and no high- or mixed-density lesions greater than 25 ml, and Diffuse Injury IV includes all diffuse injuries with a midline shift of more than 5 mm and no high- or mixed-density lesions greater than 25 ml.

severe traumatic brain injury in the saline group (77.6%). Initial mean (±SD) intracranial pressure was 15.0±12.9 mm Hg in the albumin group and 12.4±7.2 in the saline group. The incidence of prerandomization intracranial hypertension was similar in the two groups.

FLUIDS ADMINISTERED AND TREATMENT EFFECTS

During the first 48 hours in the ICU, patients in the albumin group received significantly less study fluid than did patients in the saline group (Table 2). There was no significant difference in the volumes of study fluid administered after the first 2 days. Apart from an increased requirement for red-cell transfusion on the second day in the albumin group, the volumes of nonstudy fluid administered during the first 4 days were similar in the two groups.

There was no significant difference in mean systemic arterial pressure or heart rate between the groups on any of the first 4 days. Mean central venous pressure was significantly higher in the albumin group than in the saline group during the first 24 hours. The serum albumin concentration was significantly higher in the albumin group than in the saline group on each of the first 4 days. There was no significant difference in the incidence of post-randomization intracranial hypertension between the two groups.

OUTCOMES

The primary outcomes were obtained in 214 patients in the albumin group (92.6%) and 206 patients in the saline group (90.0%). At 24 months, 71 of 214 patients in the albumin group (33.2%) had died, as compared with 42 of 206 patients in the saline group (20.4%) (relative risk, 1.63; 95% confidence interval [CI], 1.17 to 2.26; P=0.003). The majority of deaths had occurred by 28 days in both groups: 61 of 71 deaths in the albumin group (85.9%) as compared with 36 of 42 deaths in the saline group (85.7%) (Table 3). The proportion of patients who were brain-dead was not recorded.

Traumatic brain injury was identified as the primary cause of death at 28 days in 46 of 61 deaths in the albumin group (75.4%) and 30 of 36 deaths in the saline group (83.3%). In the albumin group, 50 of 61 deaths (82.0%) occurred in the ICU, as did 25 of 36 deaths in the saline group (69.4%).

In patients with severe traumatic brain injury (GCS score, 3 to 8), 61 of 146 patients in the albumin group (41.8%) had died at 24 months as compared with 32 of 144 in the saline group (22.2%) (relative risk, 1.88; 95% CI, 1.31 to 2.70; P<0.001). In the remaining patients (moderate traumatic brain injury; GCS score, 9 to 12), 8 of 50 patients in the albumin group (16.0%) had died at 24 months as compared with 8 of 37 in the saline group (21.6%) (relative risk, 0.74; 95% CI, 0.31 to 1.79; P=0.50).

Adjustment for baseline covariates did not change the study findings. Comparing the albumin group with the saline group, the adjusted odds ratio of death at 24 months was 1.70 (95% CI, 1.03 to 2.83; P=0.04). Among patients with severe traumatic brain injury, the adjusted odds ratio of death was 2.38 (95% CI, 1.33 to 4.26; P=0.003); among patients with moderate traumatic brain injury, the adjusted odds ratio was 0.38 (95% CI, 0.10 to 1.49; P=0.17).

We observed significantly fewer favorable neurologic outcomes at 24 months in the albumin group (96 of 203 [47.3%]) than in the saline group (120 of 198 [60.6%]) (relative risk, 0.78; 95% CI, 0.65 to 0.94; P=0.007). Similarly, there were fewer favorable neurologic outcomes in the patients with severe traumatic brain injury in the albumin group (51 of 139 [36.7%]) than in the saline group (77 of 140 [55.0%]) (relative risk, 0.67; 95% CI, 0.51 to 0.87; P=0.002).

The smaller number of favorable outcomes observed in the albumin group was due to a greater mortality rate, since the functional outcomes in the patients who survived were similar in the two groups (relative risk, 0.95; 95% CI, 0.83 to 1.08; P=0.41). The probability of survival was significantly different in the albumin and the saline groups (P=0.007) (Fig. 2).

DISCUSSION

We conducted a post hoc follow-up study of patients with traumatic brain injury recruited into the SAFE study.[5] The demographic characteristics and severity of brain injury at baseline were similar in the patients assigned to saline and in those assigned to albumin for fluid resuscitation. We determined mortality and functional outcomes at 24 months and found that the rate of death was significantly higher among patients assigned to albumin than among those assigned to saline. The difference was due to a higher mortality rate within 28 days after randomization in the subgroup of patients with severe traumatic brain injury (GCS score, 3 to 8) who were treated with albumin.

Our study was a large, double-blind comparison of fluid therapy in patients with traumatic brain injury; it has a number of methodologic strengths. Patients with traumatic brain injury were identified a priori in the SAFE study. We maintained

Table 2. Fluids Administered and Physiological Effects of Treatment.*

Variable	Albumin Group		Saline Group		P Value†
	No. of Patients	Value	No. of Patients	Value	
Study fluid — ml					
Day 1	231	1267.0±972.3	229	1766.6±1555.5	<0.001
Day 2	223	686.8±834.5	223	911.9±1277.5	0.03
Day 3	207	329.7±531.2	196	435.2±697.97	0.09
Day 4	186	197.6±366.6	178	201.7±428.6	0.92
Nonstudy fluid — ml					
Day 1	231	1694.8±1444.7	229	1881.9±1410.1	0.16
Day 2	223	3258.6±1507.2	223	3287.9±1462.7	0.84
Day 3	207	3070.5±1358.5	195	3259.5±1355.7	0.16
Day 4	186	3026.9±1369.3	178	3191.4±1134.3	0.21
Packed red cells — ml					
Day 1	230	93.0±275.2	229	73.4±239.3	0.42
Day 2	223	141.9±343.1	223	72.2±243.9	0.01
Day 3	207	63.6±233.6	197	76.9±229.6	0.56
Day 4	186	51.6±184.3	178	58.9±174.2	0.69
Net fluid positive balance — ml					
Day 1	230	1275.4±1446.5	225	1990.9±1839.6	<0.001
Day 2	223	885.7±1694.7	223	1317.8±1882.5	0.01
Day 3	207	551.1±1366.2	195	643.2±1640.8	0.54
Day 4	186	141.7±1265.8	178	−3.6±1264.0	0.27
Mean arterial pressure — mm Hg					
Day 1	228	88.6±11.0	229	88.7±12.5	0.93
Day 2	223	91.9±11.9	223	90.3±10.7	0.13
Day 3	207	92.4±12.3	196	91.2±11.3	0.33
Day 4	185	92.9±12.4	179	93.1±11.4	0.83
Heart rate — beats/min					
Day 1	227	82.1±20.6	229	82.3±19.2	0.90
Day 2	223	81.3±19.9	223	81.9±18.4	0.72
Day 3	207	83.3±20.4	197	83.4±17.9	0.96
Day 4	185	87.3±21.2	179	84.8±18.5	0.23
Central venous pressure — mm Hg					
Day 1	149	9.9±3.9	161	8.9±3.6	0.01
Day 2	166	10.3±3.7	174	9.4±3.4	0.03
Day 3	149	9.7±3.6	157	9.7±3.9	0.98
Day 4	138	10.1±3.8	144	9.7±3.9	0.45
Serum albumin — g/liter					
Day 1	121	31.3±6.7	132	28.2±5.3	0.001
Day 2	204	33.4±6.3	211	26.9±5.3	<0.001
Day 3	180	32.4±6.3	179	25.7±5.0	<0.001
Day 4	161	31.8±6.2	164	24.9±4.9	<0.001
Post-randomization intracranial hypertension — no. (%)	128	38 (29.7)	133	45 (33.8)	0.47

* Plus–minus values are means ±SD. Because of rounding, not all percentages total 100.
† P values are for the comparison between the means for each variable at each time point.

Table 3. Primary and Secondary Outcomes.*

Outcome	Albumin Group	Saline Group	Relative Risk (95% CI)	P Value
All patients				
Deaths — no./total no. (%)				
Within 28 days	61/231 (26.4)	36/229 (15.7)	1.68 (1.16–2.43)	0.005
Within 6 mo	68/221 (30.8)	40/217 (18.4)	1.67 (1.18–2.35)	0.003
Within 12 mo	69/220 (31.4)	40/216 (18.5)	1.69 (1.20–2.38)	0.002
Within 24 mo	71/214 (33.2)	42/206 (20.4)	1.63 (1.17–2.26)	0.003
Favorable score on the GOSe at 24 mo	96/203 (47.3)	120/198 (60.6)	0.78 (0.65–0.94)	0.007
Survivors at 24 mo	96/132 (72.7)	120/156 (76.9)	0.95 (0.83–1.08)	0.41
Patients with a GCS score of 3–8				
Deaths — no./total no. (%)				
Within 28 days	55/160 (34.4)	30/158 (18.9)	1.83 (1.23–2.71)	0.002
Within 6 mo	60/154 (38.9)	32/149 (21.5)	1.81 (1.26–2.61)	0.001
Within 12 mo	61/153 (39.9)	32/149 (21.5)	1.86 (1.29–2.67)	0.001
Within 24 mo	61/146 (41.8)	32/144 (22.2)	1.88 (1.31–2.70)	<0.001
Favorable score on the GOSe at 24 mo	51/139 (36.7)	77/140 (55.0)	0.67 (0.51–0.87)	0.002
Survivors at 24 mo	51/78 (65.4)	77/108 (71.3)	0.92 (0.75–1.12)	0.39
Patients with a GCS score of 9–12				
Deaths — no./total no. (%)				
Within 28 days	6/53 (11.3)	5/44 (11.4)	0.99 (0.33–3.05)	0.99
Within 6 mo	6/49 (12.2)	6/41 (14.6)	0.84 (0.29–2.40)	0.74
Within 12 mo	6/49 (12.2)	6/40 (15)	0.82 (0.29–2.34)	0.71
Within 24 mo	8/50 (16.0)	8/37 (21.6)	0.74 (0.31–1.79)	0.50
Favorable score on the GOSe at 24 mo	36/49 (73.5)	24/36 (66.7)	1.10 (0.83–1.47)	0.51
Survivors at 24 mo	36/44 (81.8)	24/33 (72.7)	1.13 (0.88–1.43)	0.34

* GCS denotes Glasgow Coma Scale, and GOSe denotes Extended Glasgow Outcome Scale, on which 8 indicates minimal or no disability and 1 indicates death. Scores of 5 to 8 on the GOSe are considered favorable.

blinding of treatment assignment throughout the study period and achieved 2-year follow-up completion rates in excess of 90%. This compares favorably with other studies that have assessed the degree of disability after traumatic brain injury, in which the average loss to follow-up is 19%.[21] We were able to adjust our analysis using clinically relevant baseline covariates. The mortality rates among patients assigned to albumin in this study are consistent with mortality rates from similar international epidemiologic studies.[22-24] The study was designed post hoc, and some data were collected retrospectively. It remains possible that our results represent a chance subgroup finding.

Before our study, another randomized, controlled trial examined the effect of the choice of resuscitation fluid on the outcome of traumatic brain injury.[25] In that double-blind trial, a single dose of hypertonic saline was compared with isotonic saline for prehospital resuscitation of patients with traumatic brain injury. The trial did not identify a difference in long-term neurologic outcomes.

Crystalloid-based fluid strategies are favored in trauma-resuscitation protocols,[26] although the evidence supporting these strategies in cases of brain injury is limited. Most of these protocols are based on a pragmatic approach to resuscitation, on the assumption that prompt restoration of the volume of circulating blood and the prevention of hypotension may improve the outcome in patients with brain injury.[19,27] The use of hypertonic crystalloid solutions has also been proposed for increasing plasma osmolality and decreasing cerebral edema.[28,29]

Colloid-based fluid-resuscitation strategies, in-

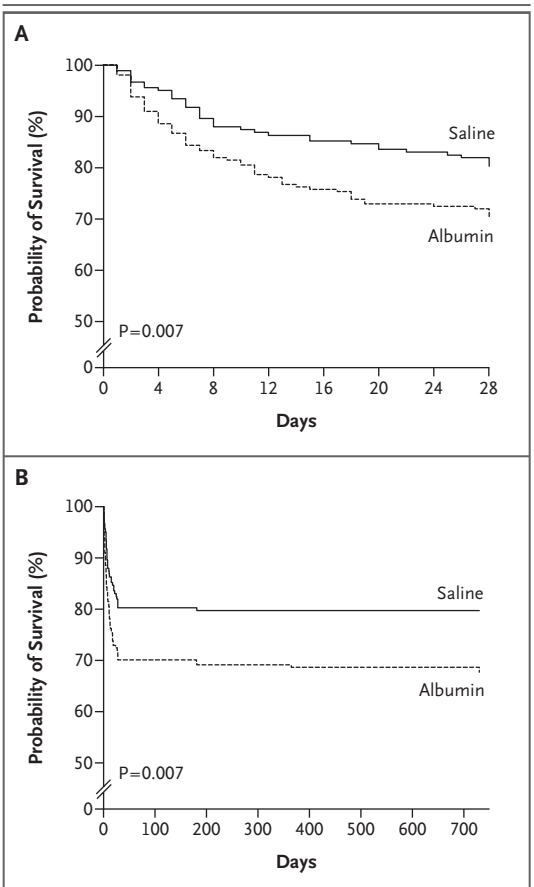

Figure 2. Kaplan–Meier Estimates of the Probability of Survival.

The figure shows the probability of survival at 28 days (Panel A) and at 24 months (Panel B) among patients with traumatic brain injury who were assigned to receive albumin and those who were assigned to receive saline. P=0.007 for each by the log-rank test.

cluding the use of albumin, have similarly been based on physiological principles, with the aim of maintaining or augmenting plasma oncotic pressure to minimize extravasation of intravascular fluid into the brain interstitium.[30] Studies in animals, however, have shown equivocal effects of albumin in modulating intracranial fluid shifts in models of both traumatic brain injury and stroke.[31,32] A single-center longitudinal case series reported reduced mortality after the institution of a treatment strategy that included the administration of albumin.[33] More recently, the same authors have reported an increase in the number of patients who have had unfavorable neurologic outcomes after using this strategy.[34]

Our study provides post hoc data to guide the choice of resuscitation fluid in patients with traumatic brain injury, but the biologic mechanisms for the observed differences in mortality are unclear. Because there was no difference in hemodynamic-resuscitation end points or in the cause and time of death between the two groups, one mechanism may be exacerbation of vasogenic or cytotoxic cerebral edema induced by the administration of albumin.[35,36] Initial intracranial pressure tended to be higher in the albumin group, although this difference was not substantial. The magnitude of the increase in intracranial pressure may also have been masked by therapeutic interventions, some of which may have had adverse effects. Furthermore, we defined post-randomization intracranial hypertension as an intracranial pressure that exceeded 30 mm Hg for two consecutive readings at least 30 minutes apart, and it remains possible that differences in lesser degrees of intracranial hypertension may have occurred and could explain the difference in outcome we observed. Further detailed analyses of biologic mechanisms associated with intracranial hypertension are required.

In conclusion, in our study comparing albumin with saline for intravascular fluid resuscitation in the ICU, higher mortality rates were observed among patients with severe traumatic brain injury who received 4% albumin than among those who received saline. These findings suggest that saline is preferable to albumin during the acute resuscitation of patients with severe traumatic brain injury.

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APPENDIX

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