CRITICAL CARE

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Is albumin use SAFE in patients with traumatic brain injury?

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Expanded Abstract

Citation

Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai LS, Vallance S: Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007, 357:874-884 [1].

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. The SAFE investigators conducted a post hoc follow-up study of patients with traumatic brain injury who were enrolled in the study.

Methods

Objective: 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.
Design: A *post hoc* follow-up study of patients with traumatic brain injury who were enrolled in the SAFE study.
Setting: Intensive care units of 16 academic tertiary hospitals in Australia and New Zealand.
Subjects: 460 patients 18 years or older 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]).
Intervention: 231 (50.2%) received four percent albumin and 229 (49.8%) received saline.
Outcomes: The primary outcome measures were the mortality rate and functional neurologic outcome 24 months after randomization. Multivariate logistic-regression was used to adjustment for baseline covariates known to be associated with increased mortality from traumatic brain injury (age older than 60 years, GCS score of 8, systolic pressure of <90 mm Hg, and traumatic subarachnoid hemorrhage). Analyses were conducted in all patients and in subgroups according to severity of traumatic brain injury.

Results

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 severity of brain injury were similar at baseline. At 2 years, 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.)

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Commentary

Traumatic brain injury (TBI) is devastating with catastrophic consequences. Early recognition of injury and prompt delivery of focused care of the traumatic brain injured patient is essential to patient outcome. Resuscitative fluids are one of the cornerstones in the management of the critically ill. For years, there has been debate regarding the optimal choice of fluids in the traumatic brain injured population. Central to this debate has been the relative merits of albumin versus saline. In 1998, a meta-analysis by the Cochrane Injuries Group concluded that the administration of albumin containing fluids to the critically ill increased absolute risk of death by 6% [2]. Following this finding, uncertainty about the best choice of fluids persisted due to a lack of adequately powered randomized, controlled trials. Subsequently, a large, multicenter trial, the Saline versus Albumin Fluid Evaluation (SAFE) trial, found no difference in 28-day mortality for critically ill patients resuscitated with albumin versus saline [3]. Subgroup analysis of SAFE participants suggested an increased number of deaths among patients with TBI who received albumin. The clinical significance of these findings were unclear due to lack of baseline data about factors known to be associated with increased mortality from traumatic brain injury and concern about the use of short-term outcomes when outcomes between 6 and 24 months are recommended after TBI.

To determine the potential significance of this finding, the SAFE study investigators undertook this *post-hoc* analysis (SAFE-TBI) [1], which included obtaining relevant baseline characteristics from case report forms, clinical records, and CT scans, and a determination of vital status and functional neurologic outcomes 24 months after randomization. The authors compared mortality and functional neurologic outcomes in patients with TBI in the saline and albumin groups at two years after randomization and used multivariate logistic-regression to adjustment for baseline covariates known to be associated with increased mortality from traumatic brain injury. Analyses were conducted in all patients and in subgroups according to severity of traumatic brain injury. The authors found that resuscitation with albumin was associated with higher mortality rates. Furthermore, there were significantly fewer favorable neurologic outcomes at 24 months in the albumin group. However, this difference appeared to be due to the greater mortality rates in the albumin group, since functional outcomes in survivors were similar between groups. When stratified by TBI severity, the increase in unfavorable outcomes seen with albumin were only significant in those with severe TBI (GCS score of 3-8).

SAFE-TBI is a well done *post-hoc* analysis. The two groups were well balanced in terms of baseline characteristics, the follow-up at two years was excellent (90%), the results were very consistent, the differences in mortality were quite large, and the conclusion drawn was consistent with the findings. The study has a few weaknesses that deserve mention. Because it is a post-hoc subgroup analysis, it can only suggest associations and cannot prove a cause-effect relationship between albumin and mortality due to the potential for chance subgroup findings. Though patients were randomized and investigators blinded to which fluid patients were receiving, it remains possible that there were differences in the clinical management of their TBI, something which the authors were unable to capture.

Based on the results of SAFE-TBI and other studies, the Cochrane group concluded that there is no evidence from randomized controlled trials in critically ill or trauma patients that resuscitation with colloids compared to crystalloids reduces the risk of death [4]. Notwithstanding, recent studies of experimental TBI in mouse models have renewed interest in the use of colloids [5,6]. Baker and colleagues demonstrated enhanced electrophysiological recovery with albumin versus saline resuscitation [5]. Exo and colleagues found that colloids exhibited favorable effects on acute resuscitation parameters versus hypertonic saline or lactated ringers and that colloid use did not increase hippocampal neuronal death [6]. To explore the efficacy of albumin as a neuroprotective agent for TBI in humans, a randomized controlled trial, Albumin for Intracerebral Hemorrhage Intervention (ACHIEVE), is currently underway [7].

Recommendation

The findings of SAFE-TBI are another important addition to the unfavorable existing literature concerning the superiority of colloid over crystalloid. Based on the current evidence and the fact that albumin is far more expensive than crystalloids, it seems reasonable to avoid the use of albumin when resuscitating patients with severe TBI. Adequately powered randomized controlled trials will be needed to definitely answer the question of which resuscitation fluid to use in TBI.

Competing interests
The authors declare no competing interests.

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