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Albumin Infusions Do Not Improve Outcomes in Hospitalized Patients with Decompensated Cirrhosis: The ATTIRE Trial

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LIVER

This article reviews China L, Freemantle N, Forrest E et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. NEJM 2021; 384: 808-817.

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STRUCTURED ABSTRACT

Question: Does administering repeated daily infusions of 20% albumin solution, targeting a serum albumin level of ≥3.0 g/dL, reduce the incidence of infection, renal dysfunction, and death among hospitalized patients with decompensated cirrhosis compared with standard care?

Design: Multicenter, open-label, parallel-group randomized controlled trial (RCT).

Setting: Thirty-five hospitals across England, Scotland and Wales between January 2016 and June 2019.

Patients: Included patients were: (a) age ≥18 years; (b) hospitalized with acute complications of decompensated cirrhosis; (c) had a serum albumin level <3.0 g/dL within 72 hours of hospital admission; and (d) had an anticipated hospital stay of 5 days or longer. Investigators used their clinical judgement to avoid recruiting patients with (a) expected short-term hospitalization and (b) good short-term survival. Exclusion criteria included patients with advanced hepatocellular carcinoma (with life expectancy < 8 weeks) and patients who received palliative care.

Interventions/Exposure: Twenty percent human albumin solution (infused at 100 ml/hr) beginning on day 1 of recruitment into study, with goal to maintain albumin level ≥3.5 g/dL vs standard care. Albumin infusions were continued for a maximum of 14 days post randomization, until discharge, or when patient was deemed fit for discharge, whichever came first. Notably, albumin was *not* withheld in patients in the standard of care group with spontaneous bacterial peritonitis, hepatorenal syndrome, or those who underwent large-volume paracentesis due to ethical concerns (given the established benefit of albumin in these scenarios, as recommended by society guidelines). Patients were evaluated until day 15, at discharge, or when patient was deemed fit for discharge.

Outcome: The primary endpoint was a composite endpoint that included: (a) infection of any cause, which was adjudicated by physician and did not require positive cultures; (b) renal dysfunction defined as serum creatinine >50% higher than level at randomization; or, (c) death between trial day 3 and trial day 15 or date of discharge if occurring before trial day 15. Outcomes were assessed beginning on trial day 3 as a pre-trial feasibility study demonstrated serum albumin levels ≥3.0 g/dL were reached in most patients within 3 days.

Secondary endpoints included: (a) death at 28 days, 3 months, and 6 months; (b) the composite primary endpoint components; (c) total amount of albumin administered; (d) length of hospital stay; (e) days in the intensive care unit (ICU); (f) incidence of other organ dysfunctions; (g) incidence of liver transplantation within 6 months of trial enrollment; (h) model for end-stage liver disease (MELD) score at end of trial; (i) use of terlipressin for kidney dysfunction, hypotension or variceal bleeding; and finally, (j) serious adverse events. Quality of life and cost-effectiveness analyses are also planned.

Data Analysis: Intention-to-treat analysis, time-to event analysis and mixed effects logistic regression model.

Funding: Health Innovation Challenge Fund, a partnership between the Wellcome Trust and the Department of Health and Social Care.

Results: Eight hundred twenty-nine patients were randomized and 777 unique patients ultimately had data that could be evaluated. The albumin and standard care groups were matched at baseline. Mean age was 53.8 (SD 10.6 years), 70.2% were men, and most (89.7%) had alcohol-related liver disease (ALD). The most common reason for hospitalization was new or worsening ascites (67%), followed by hepatic encephalopathy (19%) and variceal hemorrhage (15%). Overall, patients were recruited to the study 1 day post-hospitalization on average, and median length of stay was 8 days (interquartile range [IQR] 6 -15 days) in the albumin group and 9 days (IQR 6 – 15 days) in the standard care group. Mean serum albumin level at time of enrollment was 2.3 (SD .37 g/dL); median 200 g (IQR 140–

280 g) of 20% albumin was administered in the albumin group compared to 20 g (IQR 0-120) in the standard care group; 49.4% of patients in the standard care group received no albumin.

Overall, incidence of the primary composite endpoint was similar in the albumin and standard of care groups: 29.7% vs 30.2%; adjusted odds ratio (OR) = 0.98; 95% confidence interval (CI) 0.78 -1.33. Time-to-event analysis showed no significant difference in infection, kidney dysfunction, or death between the 2 groups: Hazard Ratio (HR) = 1.04; 95% CI: 0.81–1.35. Further, there was no difference in primary endpoint events in the albumin vs standard care group in any of the prespecified subgroup analyses based on MELD, baseline serum albumin level, use of antibiotics, and number of organ dysfunctions, among others. There were no significant differences in secondary outcomes, including death or time to death.

Compared to the standard care group, more adverse events occurred in the albumin group. Specifically, serious adverse events due to pulmonary edema or fluid overload were numerically higher in the albumin group: 6% vs 2%.

COMMENTARY

Why Is This Important?

Patients with decompensated cirrhosis are at high risk of developing infections that can result in renal failure and death. Intravenous albumin has been used for over 70 years in patients with cirrhosis and continues to be widely prescribed for volume expansion in this population of patients with peripheral arterial vasodilation. Societal guidelines recommend albumin infusion in patients with spontaneous bacterial peritonitis, hepatorenal syndrome, and after large-volume paracentesis.[1]

Albumin, the most abundant protein in serum, not only generates oncotic pressure but has several other functions, including antioxidant, ligand binding and endothelial stabilizing effects.[2,3] Preclinical studies suggest albumin also appears to have an anti-inflammatory role which could result in decreased systemic inflammation and fewer infections, resulting in reduced rates of renal dysfunction and improved survival. However, no large-scale RCTs to date have confirmed this hypothesis. Rather, results of clinical trials of albumin use in cirrhosis are conflicting[4, 5], with recent meta-analyses finding no difference between albumin vs other plasma expanders in preventing death after large-volume paracentesis, and no interventions reducing all-cause mortality in patients with hepatorenal syndrome.[5, 6]

This RCT, the Albumin to Prevent Infection in Chronic Liver Failure (ATTIRE) trial, aimed to clarify the role and potential benefit of targeted albumin infusions (vs standard care) to reduce rates of infection, renal dysfunction and death, among a population of hospitalized patients at high risk of developing infections and subsequent

mortality. Trials, such as this one, involving hospitalized patients with cirrhosis are challenging and the investigators should be commended for their efforts to tackle this important question about a common clinical scenario.

Key Study Findings

There was no benefit to using albumin to reach and maintain a target serum albumin level ≥3.0 g/dL in hospitalized patients with cirrhosis to minimize infection, renal dysfunction or death compared to standard of care with targeted albumin infusion: 29.7% vs 30.2%; adjusted OR= 0.98, 95% CI 0.71 – 1.33, nor any benefit for any secondary endpoints or across prespecified subgroups.

No significant between-group differences were observed in a time-to-event analysis (HR 1.04, 95% CI 0.81 – 1.35). Compared to standard care, the albumin group received 3x-10x the amount of albumin and had more serious adverse events due to pulmonary edema or fluid overload: 6% vs 2%.

Caution

This trial included sicker hospitalized patients compared to prior trials published in 2018[4, 5] and was not blinded due to concerns about harm to patients receiving excess volumes of "non-albumin" fluid, and routine albumin measurements would have unblinded the trial. Investigators assessed the primary endpoint at time of hospital discharge, rather than predefined time point post-randomization, which may lead to misinterpretation of data and difficulty comparing results with other trials. Excess administration of albumin can be harmful and lead to serious adverse events, particularly cardiopulmonary complications (i.e., pulmonary edema) as observed in this study. The incidence and severity of cardiopulmonary complications become of particular concern in clinical scenarios where albumin therapy is used in combination with terlipressin (recently FDA approved in the US). Finally, as 89.7% of patients had cirrhosis due to alcohol use, with a large proportion having acute alcoholic hepatitis, results may not be generalizable to patients with other etiologies of cirrhosis.

My Practice

I follow the American Association for the Study of Liver Diseases (AASLD) 2021 Practice Guidance on the Diagnosis, Evaluation and Management of Ascites, Spontaneous Bacterial Peritonitis, and Hepatorenal Syndrome.[1] I administer IV albumin to hospitalized patients with refractory ascites, those with hepatorenal syndrome, spontaneous bacterial peritonitis, and at time of large volume paracentesis (LVP), as supported by these guidelines. These guidelines acknowledge the results of the ATTIRE trial and do not recommend use of targeted albumin in hospitalized patients with decompensated cirrhosis outside of the aforementioned scenarios.

For patients with spontaneous bacterial peritonitis (SBP), albumin is not just a

volume expander but prevents progression of acute kidney injury and improves survival, with the sickest patients (bilirubin >5 mg/dL or Cr >1.0 mg/dL) deriving most benefit.[7,8] I do administer the dose of albumin (1.5 g/kg body weight on day 1 and 1 g/kg body weight on day 3) that was used in the trial conducted by Sort and colleagues, though it should be acknowledged that this dosage was arbitrarily selected.[7] For patients undergoing LVP, I administer the recommended 6-8 g per liter of ascites removed. In my practice, my colleagues and I also administer 50 g albumin to patients undergoing paracentesis <4 liters. The optimal doses of albumin for patients with SBP as well as at time of LVP has yet to be determined and more prospective studies are needed in this area.

Data regarding the long-term use of albumin in outpatients with cirrhosis and diuretic-responsive ascites remain controversial and its routine use in clinical practice is not currently supported by the guidelines.[1] A study by Angeli and colleagues demonstrated 20-40 g/week albumin was an effective treatment for muscle cramps in patients with cirrhosis[9], and while this is mentioned in the AASLD guideline as a therapy to consider, this is not something I have personally adopted in my clinical practice.

For Future Research

To improve generalizability and allow for cross-study comparison, future randomized trials in hospitalized patients with advanced cirrhosis should ideally define outcomes based on prespecified timepoints rather than ending data collection at time of hospital discharge.

Conflict of Interest

Dr. Rich has served as consultant for AstraZeneca.

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