Crystalloid versus Albumin for Volume Resuscitation in Septic Shock: A Large-Scale, Real-World Analysis

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Background

Septic shock is a life-threatening condition marked by severe circulatory failure. Although crystalloids are the primary resuscitation fluid, the benefit of adjunctive albumin remains uncertain. We evaluated the 28-day outcomes in adults with septic shock receiving early albumin (within 24 hours) versus standard care alone, hypothesizing no significant difference in mortality or secondary organ dysfunction.

Methods

A retrospective analysis using TriNetX evaluated adult patients (≥18 years) presenting with septic shock and treated with norepinephrine, from March 2016 to March 2026, comparing early injectable albumin plus crystalloids versus crystalloids alone. After propensity score matching for 47 baseline covariates (including demographics, hemodynamics, comorbidities, and labs), 28-day outcomes were assessed, including mortality (primary outcome), and secondary outcomes: acute kidney injury (AKI)/hemodialysis dependence, mechanical ventilation dependence, tachyarrhythmia, hepatic injury/failure, and MACE outcomes including acute myocardial infarction (AMI), stroke, and heart failure (HF).

Results

Post-matching, the analysis included 25,894 patients in each cohort. Contrary to our hypotheses, 28-day mortality was significantly higher in the albumin cohort compared to the crystalloid cohort (28.4% vs. 23.9%; risk difference 0.044, $p<0.001$; aHR 1.177). Additionally, the need for

invasive mechanical ventilation was significantly higher in the albumin cohort compared to the crystalloid cohort (11.1% vs. 5.8%, $p<0.001$), along with dependence on hemodialysis (6.6% vs. 3.2%, $p<0.001$), the incidence of tachyarrhythmia (4.9% vs. 4.3%, $p=0.023$) and AKI (8.3% vs. 5.3%, $p<0.001$). Regarding MACE outcomes, the incidence of AMI was significantly lower in the albumin group compared to the crystalloid group (1.2% vs. 1.6%, $p=0.003$), along with a similar incidence of stroke (0.9% vs 1.0%, $p=0.679$), but a greater occurrence of HF in the albumin cohort (3.3% vs 2.8%, $p=0.004$).

Conclusion

Although propensity matching balanced measured baseline covariates, early adjunctive albumin was associated with higher 28-day mortality, AKI/hemodialysis dependence, and mechanical ventilation compared to crystalloids alone. Because albumin is often administered as a rescue therapy for refractory shock in real-world settings, unmeasured confounding by indication likely persists despite rigorous matching. While these retrospective findings suggest caution, they primarily highlight the need for prospective trials to identify specific clinical phenotypes that may safely benefit from albumin resuscitation.