CRISTAL Trial

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Prior Trials

SAFE Trial, 2004 *NEJM*. 4% Albumin vs NS. 28-day mortality (doi: 10.1056/NEJMoa040232) Cochrane Review, 2013. Colloids vs crystalloids. Mortality (doi: 10.1002/14651858.CD000567.pub6) ALBIOS Trial, 2014 *NEJM*. 20% Albumin vs usual care. 28-day mortality (doi: 10.1056/NEJMoa1305727)

PICO Format Question

- P: ICU pt w/ hypovolemic shock
- I: colloid IVF resus
- C: crystalloid IV fluid resus
- O: 28-day all-cause mortality

Multicenter, open-label, randomized comparative trial N=2,857 ICU patients with hypovolemic shock Colloids (n=1,414) Crystalloids (n=1,443) Setting: 57 ICUs in France, Belgium, Canada, Algeria, and Tunisia Enrollment: 2003-2012 (stopped after interim analysis) Follow-up: 90 days Analysis: Intention-to-treat Primary outcome: All-cause mortality at 28 days

Inclusion Criteria

Hypovolemic patients requiring fluid resuscitation who had not received fluid during the current hospital course. Acute hypovolemia defined by: MAP ¡60mmHg Orthostatic hypotension (decrease in systolic ¿20mmHg from supine to semirecumbent) Delta pulse pressure ¿13% Evidence of low filling pressures and low cardiac index (assessed invasively or noninvasively) Signs of tissue hypoperfusion or hypoxia, including 2: Glasgow Coma Scale score ¡12 Mottled skin UOP ¡25mL/hr Capillary refilling time ¿3 sec Arterial lactate ¿2mmol/L BUN ¿56mg/dL Fractional excretion of sodium ¡1%

Exclusion Criteria

Previous fluid therapy in ICU Anesthesia-related hypotension Advanced chronic liver failure Chronic renal failure Acute anaphylaxis Inherited coagulation disorder DNR order Pregnant Burned ¿20% of BSA Allergy to any study drug Refused consent Dehydrated Brain death/organ donor

Interventions

Patients were randomized to a group with stratification by center and admission diagnoses Colloids: Volume resuscitation with either hypooncotic solutions (eg, gelatins, 4-5% albumin) or hyperoncotic solutions (eg, dextrans, hydroxyethylstarches, 20-25% albumin) Crystalloids: Volume resuscitation with isotonic saline, hypertonic saline, or buffered solutions (eg, LR) Investigators chose which type of the predesignated fluid and how much to administer except: Total dose of hydroxyethyl starch was maximum of 30 mL/kg Must follow local regulatory agency recommendations Both groups received maintenance fluid with isotonic crystalloids Both groups received albumin for hypoalbuminemia (¡2 g/L) per the discretion of the treating physician Discontinuation of treatment on transfer out of ICU

Primary Outcome

All-cause mortality at 28 days 25.4% vs 27.0% (RR 0.96; 95% CI 0.88-1.04; P=0.26)

Secondary Outcomes

All-cause mortality at 90 days 30.7% vs. 34.2% (RR 0.92; 95% CI 0.86-0.99; P=0.03; NNT=29) Alive and not on RRT First 7 days: 4.8 vs. 4.6 days (MD 0.2; 95% CI -0.4 to 0.8; P=0.99) First 28 days: 13.9 vs. 13.1 days (MD 0.8; 95% CI -1.6 to 3.3; P=0.90) Alive and not on mechanical ventilation First 7 days: 2.1 vs. 1.8 days (MD 0.30; 95% CI 0.09 to 0.48; P=0.01) First 28 days: 14.6 vs. 13.5 days (MD 1.10; 95% CI 0.14-2.06; P=0.01) Alive and not on vasopressors First 7 days: 5.0 vs. 4.7 days (MD 0.30; 95% CI -0.03 to 0.50; P=0.04) First 28 days: 16.2 vs. 15.2 days (MD 1.04; 95 % CI -0.04 to 2.10; P=0.03) All-cause mortality in ICU 25.1% vs. 28.1% (RR 0.92; 95% CI 0.85-1.00; P=0.06) All-cause mortality in hospital 30.1% vs. 32.6% (RR 0.94; 95% CI 0.87-1.02; P=0.07) ICU stay in first 28 days 8.3 vs. 8.1 days (MD 0.2; 95% CI -0.5 to 0.9; P=0.69) Hospital stay in first 28 days 11.9 vs. 11.6 days (MD 0.3; 95% CI -0.5 to 1.1; P=0.37) Any RRT 11.0% vs. 12.5% (RR 0.93; 95% CI 0.83-1.03; P=0.19) Median volume administered by day 7 in ICU 2L vs. 3L (P¡0.001) Duration of resuscitation therapy 2 vs. 2 days (P=0.93)

Subgroup Analysis

Primary outcome: Sepsis: 27.8% vs. 29.0% (HR 0.95; 95% CI 0.78-1.10) Trauma: 15.3% vs. 13.0% (HR 0.93; 95% CI 0.80-1.10) Hypovolemic shock not from sepsis or trauma: 23.6% vs. 26.6% (HR 0.87; 95% CI 0.69-1.10) Interaction of homogeneity across the three strata P=0.07

Open label design Long recruitment period, which didn't achieve enrollment goals due to early trial discontinuation Not powered to detect the primary endpoint Researchers estimated they would need 1,505 patients per group (total of 3,010 patients) to detect an absolute difference of 5% in 28-day mortality with colloids The trial hints that there may be a benefit of administering colloids to improve 90-day all-cause mortality Clinicians were not blinded to fluid assignment because the researchers could not realistically stock enough blinded solutions in the ICUs Recruitment and study period exceeded 9 years Comparison of two classes of fluids and allowed clinicians to use whatever member of the class was available, not two specific fluid formulations Initiation of renal replacement therapy may have been biased by physician knowledge of allocation (i.e. increased use or RRT in patients receiving colloids) No adverse events reported