Balanced Multielectrolyte Solution vs. Normal Saline – the PLUS Study

Key Article

Finfer S, et al. Balanced multielectrolyte solution versus saline in critically ill adults. N Engl J Med. 2022; published online Jan 18, 2022.

Background

- 0.9% NS is the most commonly administered IVF to patients in the ICU
- As we've discussed here on the podcast many times, there are many concerns about 0.9% NS and the risk of kidney injury and increased mortality in some disease states (i.e., sepsis).
- As a result, there has been an increase in the use of balanced salt solutions.
- Whether the use of balanced solutions improves outcomes in ICU patients remains controversial.
- The SMART trial compared balanced salt solutions with saline in a single center in the US and showed better outcomes with salt solutions.
- However, a smaller trial conducted at 4 sites in New Zealand demonstrated no benefit.

Objective

- The Plasma-Lyte 148 versus Saline (PLUS) Study was conducted to determine if 90-day mortality would be lower in critically ill adults who received a balanced multielectrolyte solution (BMES) compared with saline.

Methods

- The PLUS Study was an investigator-initiated, double-blind, parallel-group, randomized, controlled trial conducted at 53 ICUs in Australia and New Zealand.
- Patients
    - Included
        - 18 years of age or older
        - Admitted to the ICU
        - Fluid resuscitation deemed necessary by the treating physician
        - Expected to be in the ICU on 3 consecutive days
    - Excluded
        - Had specific fluid requirements
        - Had received disqualifying fluid resuscitation (> 500 ml of fluid prescribed and administered in the ICU)
        - Imminent risk for death
        - Preexisting life expectancy of less than 90 days
        - TBI or at risk for cerebral edema
- Interventions
    - Patients received assigned trial fluid for all fluid resuscitation and compatible crystalloid therapy for up to 90 days after randomization.
    - Treating clinician decided the amount and rate of fluid administration.

    - Once the patient was outside of the ICU, the type of fluid administered was not dictated
    - All other treatments were at the discretion of the treating clinicians
- Primary Outcome
    - Death from any cause within 90 days of randomization
- Secondary Outcomes
    - Peak serum creatinine during the first 7 days
    - Maximum increase in creatinine during the ICU stay
    - Receipt of RRT
    - Receipt and duration of vasopressor medications
    - Duration of mechanical ventilation
    - ICU and hospital LOS
    - Death from any cause during the ICU stay

Results

- A total of 5037 patients underwent randomization
    - BMES Group: 2515
    - Saline Group: 2522
- Data on primary outcome available for:
    - BMES Group: 2433
    - Saline Group: 2413
- Baseline characteristics similar
    - 45% were admitted to the ICU from the OR or PACU
    - 79% were intubated
    - 42% had sepsis
    - Within 24 hours of randomization, both groups received similar amounts of IVFs
- Fluids administered
    - 96% of patients got IVFs
    - Median duration of treatment with assigned fluid was 6 days
    - Median volume of fluid was 3.9 liters in the BMES Group and 3.7 liters in the Saline Group
- Primary Outcome – 90-day all-cause mortality
    - BMES Group:21.8%
    - Saline Group: 22%
    - Results were similar after adjusting for baseline risk factors and secondary analyses
    - No heterogeneity in the effect of IVFs based on subgroups
- Secondary Outcomes
    - No differences in
        - Max serum creatinine level during the first 7 days
        - Max increase in serum creatinine during the ICU LOS
        - Days alive and free of mechanical ventilation
        - Days alive and free of pressors
        - Days alive and free of RRT
- No difference in adverse events between the groups

Limitations

- Initially estimated that 8800 patients would be needed to show an absolute difference of 2.9% in 90-day all-cause mortality from an estimated baseline mortality of 23%. In August 2020, the

trial-management committee and the sponsor decided to stop enrollment. They then estimated a sample size of 5000 patients to detect an absolute difference of 3.8%.

- Use of Plasma-Lyte 148
- Did not control for all fluid patients received outside of the ICU
- Did not examine effects of BMES in patients with TBI

Take Home Points

- The PLUS study found no evidence that the use of Plasma-Lyte 148 reduced 90-day all-cause mortality in critically ill ICU patients compared with those who received saline.
- An updated meta-analysis that includes this study's data suggests that there is a high probability that the use of balanced solutions reduces mortality among critically ill adults.
- Consider individual patient characteristics, cost/availability of fluids, and drug compatibility when selecting IVFs.