Vasopressors and The Older Critically Ill Patient – The 65 Trial

Key Article

- *Lamontagne F, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension. JAMA. 2020. Published online 2/12/20.*

Article Background

- Vasopressors often administered in the ICU to avoid hypotension and associated patient outcomes (AKI, MI, and death)
- However, vasopressors can also reduce blood flow due to vasoconstriction and can adversely affect cardiac, metabolic, and immune function
- Blood pressure used to guide administration of vasopressors
- SSC Guidelines recommend MAP target of 65 mm Hg, with a higher target for older patients and those with chronic HTN. 2016 SSC Update acknowledged lack of evidence for targeting higher MAP values
- 2 relatively recent trials (SEPSISPAM, OVATION) suggest association of increased pressor exposure to target higher MAP with death in patients older than 65 years
- Does greater exposure to vasopressors lead to harm in older patients?

Objective

- Determine whether reducing exposure to vasopressors through permissive hypotension (MAP 60-65 mm Hg) reduces 90-day mortality in ICU patients 65 years and older with vasodilatory hypotension.

Study

- Multicenter, pragmatic, randomized trial
- 65 ICUs in the UK
- Inclusion criteria
  - Adults aged 65 years and older
  - Admitted to a participating ICU
  - Within 6 hours of a vasopressor infusion started for vasodilatory hypotension; received adequate fluid resuscitation, and expected to be on pressors for at least 6+ hours.
- Exclusion criteria
  - Contraindications to permissive hypotension
  - Imminent risk of death
  - Vasopressors used for non-vasodilatory shock reasons

    - Treatment for brain or spinal cord injury
- Intervention
    - Permissive Hypotension Group
        - Vasopressors administered to target MAP 60-65 mm Hg
        - Had trial-specific prompts on infusion pumps and in medical notes for higher MAP alarms
    - Usual Care Group
        - Received vasopressors at the discretion of treating clinicians
    - Choice of vasopressor and other interventions were left to the treating clinician (NE, epinephrine, vasopressin, phenylephrine, dopamine, terlipressin, and metaraminol could all be used)
    - Adherence: defined as appropriate reduction or discontinuation of vasopressor when the MAP was higher than the upper limit of 65 mm Hg
    - Deviation: defined by failure to reduce or discontinue vasopressors when the MAP remained > 65 mm Hg for 3 or more consecutive hours
- Outcomes
    - Primary: 90-day all-cause mortality
    - Secondary:
        - Mortality at ICU discharge
        - Mortality at DC from acute care hospital
        - Duration of survival to longest available follow up
        - Duration of respiratory or renal support during ICU LOS
        - Days alive and free of respiratory and renal support within first 28-days
        - Duration of ICU LOS
        - Cognitive decline in survivors at 90 days and 1 year
        - Health-related quality of life in survivors at 90-days and 1 year

Results

- 2600 patients enrolled
    - 2598 unique patients – 1291 Permissive Hypotension, 1307 Usual Care
    - **Overall – 2463 included in analysis of primary outcome** (1221 Permissive Hypotension, 1242 Usual Care)
    - Groups well matched with exception of proportion of patient's dependent on assistance for ADLs (34.4% in Permissive Hypotension Group, 30.9% in Usual Care Group)
    - MAP immediately prior to randomization:
        - Permissive Hypotension: 69.9 mm Hg
        - Usual Care: 71.1 mm Hg
    - Clinical Management
        - Permissive Hypotension Group
            - Lower exposure to vasopressors (median 33 hours vs. 38 hours)
            - Lower median total dose (17.7 mg vs. 26.4 mg)
            - Mean and peak MAP values lower (66.7 vs. 72.6; 83 vs. 92)

        - Adherence: 11.3% occurrence in Permissive Hypotension Group
        - No differences in fluid balance, urine output, or use of inotropes
- Primary outcome: 90-day all-cause mortality
    - Permissive Hypotension: 41%
    - Usual Care: 43.8%
    - Absolute difference -2.85%; 95% CI, -6.75 to 1.05; p-0.15)
    - OR 0.82 (95% CI, 0.68 to 0.98)
- Secondary Outcomes
    - No difference in ICU mortality and mortality at acute care hospital DC
    - No difference in mean duration of ICU LOS, hospital LOS, days alive and free from respiratory and renal support to day 28
    - No difference in cognitive decline and health-related scores at 90 days and 1 year
- Adverse events
    - Permissive Hypotension: 6.2%
    - Usual Care: 5.8%
    - No difference
- Subgroup Analysis
    - More pronounced reduction in mortality in Permissive Hypotension Group patients who were chronically hypertensive
        - Chronic hypertension subgroup 90-day mortality
        - Permissive Hypotension: 38.2%
        - Usual Care: 44.3%
        - Adjusted OR 0.67

Limitations Identified by Authors

- Interventions were not blinded
- 90-day mortality in the Usual Care Group was higher than anticipated
- Non-consent and withdrawals were slightly higher than anticipated in the sample-size calculation
- Attributable mortality not adjudicated

Take Home Points

- **Permissive hypotension compared to usual care did not result in a statistically significant reduction in 90-day mortality among ICU patients > 65 years of age receiving pressors for vasodilatory hypotension.**
- **No adverse events in a lower MAP target for older patients**
- **Suggestion of possible benefit with lower MAP target in patients with chronic hypertension**