Vitamin C, Hydrocortisone, Thiamine vs. Hydrocortisone in Patients with Septic Shock

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Key Article

Fujii, Tomoko, et al. "Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial." *JAMA* (2020).

Background

- Sepsis remains a common and life-threatening condition that is associated with a high percentage of deaths in the hospital
- Steroids, thiamine and vitamin C each have physiologic rationale as potential therapies to improve patient-centered outcomes in septic shock
- In 2017, Paul Marik published a single-center retrospective before-and-after study of 94 patients showing a significant mortality benefit to patients that received high-dose thiamine, vitamin C, and hydrocortisone compared to those who did not receive this
- Many providers adopted this approach, termed “metabolic resuscitation” or the “Marik cocktail” based on this study, for care of patients with septic shock
- To date, no randomized trial has evaluated the impact of these 3 therapies together compared to hydrocortisone alone in patients with septic shock

Objective

- Compare resolution of shock and days alive in patients with septic shock randomized to therapy with high-dose thiamine, vitamin C, and hydrocortisone compared to those who received only hydrocortisone

Study

- Multi-center, open-label, parallel-group randomized control trial from 5/18-7/19
- 10 ICUs across Australia, New Zealand and Brazil
- Inclusion criteria: admission to ICU with primary diagnosis of septic shock (Sepsis-3) definition [suspected or documented infection, 2 point increase in SOFA score, lactate > 2 mmol/L] and at least 2 hours of vasopressor dependence
- Patients had to be enrolled *within 24 hours of meeting septic shock criteria*

- Exclusion criteria: age < 18, pre-existing DNR order, imminent death, additional indication for hydrocortisone, diagnosis of septic shock > 24 hours, disease with strong indication for any study drugs
- Intervention
    - Intervention group: vitamin C 1.5 g q6 hrs, hydrocortisone 50 mg q6 hrs, thiamine 200 mg q12 hrs
    - Control group: hydrocortisone 50 mg q 6 hrs
        - Treating ICU attending physician could administer thiamine at their discretion, but not vitamin C
- Outcomes
    - Primary: time alive and free of vasopressors at day 7 after randomization
        - Cessation of vasopressors defined as discontinuation of all vasoactive medications for at least 4 hours AND MAP > 65 mm Hg or BP goal set by treating clinician
    - Secondary:
        - 28-day, 90-day, ICU and hospital mortality
        - 28-day cumulative mechanical ventilation-free days
        - 28-day renal replacement-free days
        - Delta SOFA score at day 3
        - 28-day ICU free-days
        - Hospital length of stay

Results

- 211 patients were included in the analysis (786 patients screened, 216 were randomized of which 5 later withdrew)
- Primary outcome: NO DIFFERENCE in time alive and free of vasopressors at 7 days (p = 0.83)
    - Intervention group: median of 122.1 hours
    - Control group: median of 124.6 hours
- Secondary Outcomes
    - No difference in all-cause 28 day, 90 day or hospital mortality
    - No difference in 28-day cumulative vasopressor-free days, mechanical ventilator-free days, or renal-replacement free days
    - Delta SOFA was greater in the intervention group at 3 days (median -2 vs. -1, p = 0.02)
    - Adverse events
        - Intervention group: 2 total (1 with fluid overload, 1 with hyperglycemia), 1 in control group with GI bleed

Limitations Identified by Authors

- Trial was open label and lacked blinded outcome assessment
- Individual effects of vitamin C and thiamine were not assessed separately
- Thiamine levels were not measured in the trial

- Target MAP was not standardized and not collected
- Time to antibiotics not collected (however all patients had received antibiotics at time of randomization)
- Trial not powered to detect mortality differences (or other patient-centered outcomes)
- Adverse events were reported only when treating clinicians adjudicated, and no systematic investigation for adverse effects was completed

Take Home Points from Gabe

- **Appropriate skepticism of retrospective single center studies**
- **Expect more studies on this to be published in the near future (at least 37 trials are ongoing or have plans to enroll patients!)**
- **There is a role for vitamin C and thiamine in patients with absolute deficiencies (e.g. beri-beri and scurvy) but likely not for all patients with septic shock and benefit should be assessed on a patient-centered level**
- **Unintended consequences exist from blind adoption of this therapeutic regimen (i.e. false hope for patients / families, potential delay in known life-saving therapies (antibiotics), diverting research funds, etc.)**