

Jeffry Nahmias MD MHPE

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

Tomoko Fujii, MD, PhD; Nora Luethi, MD; Paul J. Young, MBChB, PhD; Daniel R. Frei, BSc, MBChB et al. *JAMA*. 2020 Jan 17. doi: 10.1001/jama.2019.22176.

<https://pubmed.ncbi.nlm.nih.gov/31950979-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/>

Context

The evidence supporting the use of Vitamin C and thiamine for earlier shock resolution in septic shock, with or without concurrent steroid use, is conflicting. The anti-inflammatory and antioxidant effects of Vitamin C have led researchers to explore its utility as an adjunctive therapy in sepsis, and thiamine deficiency has been reported in up to 20% of critically ill patients with sepsis. A previous randomized pilot study by Fowler et al. of 24 patients with severe sepsis demonstrated prompt reductions in SOFA scores and reduced pro-inflammatory biomarkers for patients receiving intravenous Vitamin C compared to patients receiving a placebo. Used in combination with hydrocortisone, these two agents (Vitamin C and thiamine) showed a reduction in propensity-adjusted mortality in a single center, before-after study evaluating patients with sepsis ($p=0.02$). Thus, the investigators of this trial sought to prospectively examine the effects of Vitamin C, thiamine and hydrocortisone against hydrocortisone monotherapy for patients with septic shock.

Methods

The study design was a multicenter, open-label, randomized controlled trial of 211 patients from 10 ICUs in Australia, New Zealand, and Brazil. Investigators enrolled patients from May 2018 to June 2019 and only included patients who met Sepsis-3 definition for septic shock. Patients were randomized to intravenous (IV) hydrocortisone (50mg every 6 hours) versus the same hydrocortisone dose plus IV Vitamin C (1.5g every 6 hours) and IV thiamine (200mg every 12 hours) until septic shock resolved or up to 10 days. The primary outcome was time of being alive and free of vasopressor administration up to day 7. Secondary outcomes included 28-day and 90-day mortality, vasopressor free days, and renal replacement therapy free days, as well as change in SOFA score at day 3. Primary outcome data were analyzed using a Wilcoxon rank sum test and presented using the Hodges-Lehmann estimator of the median of all paired differences.

Findings

From 786 patients screened, 216 were randomized (5 patients withdrew: 2 in intervention and 3 in control group)

- Median time from eligibility to first dose of vitamin C was 12.1 hours compared with 8.9 hours for the hydrocortisone control group.
- No serious adverse events or suspected unexpected serious adverse reactions were reported

Primary outcome (107 patients in intervention group vs. 104 patients in control group)

- No difference in time alive and free of vasopressors up to day 7 (median 122.1 hours in intervention group vs 124.6 hours in control group)
- The median of all paired differences was -0.6 hours (95% CI, -8.3 to 7.2 hours; $p=.83$)

Secondary outcomes

- No difference in 28-day, all-cause mortality (22.6% intervention group vs 20.4% control group, $p=.69$)
- No difference in 90-day mortality (28.6% intervention vs 24.5% control)
- No difference in 28-day cumulative vasopressor-free days, ventilation-free days and renal replacement therapy free days.
- Change in SOFA score at day 3 was significantly greater in the intervention group (median -2 vs -1 , $p=.02$)

Commentary

This study is strengthened by its multicenter/multinational design and its relatively large sample size. However, the median time from eligibility to receiving Vitamin C was somewhat lengthy at 12 hours. In addition, limitations include the lack of blinding and the fact that Vitamin C and thiamine were not studied individually. Furthermore, the authors note this study was not powered to detect any difference in secondary outcomes. That said they correctly point out that they found no benefit in multiple secondary outcomes and despite showing a significant difference in SOFA score at day 3, the mortality during any observation period points toward unfavorable effects in the intervention group.

Implications for practice

While previous retrospective and/or smaller studies demonstrated a benefit to the use of Vitamin C, this study importantly provides a larger randomized trial on this topic. While the use of IV Vitamin C and thiamine was not associated with significant adverse reactions, the addition of IV Vitamin C and thiamine to hydrocortisone did not improve the duration of time alive and vasopressor administration over 7 days or the 90-day mortality rate. Since evidence is still evolving on the role of hydrocortisone in septic shock, the dose and type of steroids given may also be a confounder that needs to be tested in future studies. In the meantime, the use of Vitamin C and thiamine is not currently supported as a routine treatment for septic shock.