



Article Appraisal

Article: Hydrocortisone, Vitamin C and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study

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Resident Reviewer Name(s) and Residency Affiliation: Dr. Mark Sanderson, FRCPC; Dr. Trevor Skutezky, RCPS-EM, PGY-2

Faculty Methodology/Bio-statistics Resource Person: Dr. John Tallon

Background and Study Objective(s):

Sepsis and septic shock are common presentations to the ED, with a mortality rate of around 50%. The intent of this study was to explore the effects of a cocktail of vitamin C, hydrocortisone, and thiamine, which the authors theorize may act synergistically, on the mortality of patients that present with sepsis or septic shock. Prior studies have suggested that IV vitamin C may provide some benefit in the metabolic resuscitation of patients with sepsis and septic shock.

Study Design:

This study was a retrospective before-after study based on electronic health record database. The study included non-pregnant, adult (age \geq 18) patients with no limitations to their goals of care; a diagnosis of severe sepsis or septic shock per the 1992 American college of Chest Physicians/Society of Critical Care Medicine Consensus definitions; and procalcitonin levels greater than or equal to 2ng/mL admitted to the Sentara Norfolk Regional Hospital ICU in Virginia, USA. In the first 7 months of the study, between June 2015 and December 2015 patients were treated with standard ICU sepsis management. Following a change in practice at Sentara Norfolk, patients in the following seven months were treated with standard ICU management in addition to a cocktail consisting of IV vitamin C, hydrocortisone, and thiamine within the first 24 hours. 94 patients were enrolled, 47 in each group. Propensity score matching was used to account for confounding variables.

The following outcomes were analyzed:

Primary - Hospital survival

Secondary - Duration of vasopressor therapy, Requirement for renal replacement therapy (RRT), ICU LOS, Change in serum procalcitonin, SOFA score of 72 hours

Results:

	Comparison	Treatment
Mortality*	40.4%	8.5%
Duration of pressor	54.9 hours \pm 28.4	18.3 hours \pm 9.8
RRT	37%	10%
72 hour SOFA change	0.9 \pm 2.7	4.8 \pm 2.4
ICU LOS	4 days (median; range 4-10)	4 days (median; range 3-5)
72 hour PCT clearance	33.9% (-62.4-64.3)	86.4 (80.1-90.8)

*Primary study outcome

The above findings were all determined to be statistically significant with a p value < 0.05. The primary study outcome, survival to hospital discharge was markedly improved in the treatment group, with an absolute difference of 31.9% and an NNT of \sim 3. Likewise, all secondary outcomes showed marked improvement in the treatment group. A further logistic regression identified three independent risk factors for in hospital mortality in the study group: Treatment with the vitamin C protocol, the APACHE IV score, and need for mechanical ventilation.

Validity of Results:

This study demonstrates a large treatment effect in the Vitamin C, hydrocortisone and thiamine group, which sets the stage for a future RCT. However, there are several key limitations to this study. Specifically, the before-after design does not provide causation and uncontrolled before-after studies have been previously noted to demonstrate large treatment effects that were subsequently dismissed by RCTs. Furthermore, key variables that could significantly impact the results are not standardized between groups. The most striking omission is time to antibiotics.

Generalizability of Results:

While the patient population of the Sentarra Norfolk General Hospital appear to be similar to those encountered in large BC hospitals practice variations limit external validity. The nature of this study, specifically it's single centre design, limits external validity strongly. Local practice variations may have been present that were not captured by the study parameters.

Furthermore the before and after nature of the study makes it difficult to interpret the results and how this practice could be implemented elsewhere. Lastly procalcitonin levels, although well researched, are not routinely used in all BC ICUs, and it's significance to our practice is difficult to ascertain.

The Bottom Line:

Despite a large treatment effect and significant p values the proposed cocktail is not yet ready for standard of care in all sepsis and septic shock patients. However, given the minimal cost and strong safety profile of vitamin c and thiamine, it is reasonable to administer these medications in the sickest septic shock patients who are already receiving hydrocortisone.