Literature Review of the Combination Hydrocortisone, Ascorbic Acid, and Thiamine (HAT) Therapy in Reducing Mortality in Critically Ill Patients with Sepsis or Septic Shock

by Charina A. Ruiz, PharmD

Question

Does hydrocortisone, ascorbic acid, and thiamine (HAT) therapy reduce mortality in critically ill patients with sepsis or septic shock compared to placebo or standard of care?

Sepsis is a life-threatening illness characterized by a dysregulated host response to infection contributing to one-third to one-half of all hospital deaths as well as more than 5 million deaths annually worldwide.[1] The current management of sepsis and septic shock include administration of intravenous fluids, vasoactive medications, and broad-spectrum antibiotics. High dose ascorbic acid has been recently explored as adjunctive therapy in sepsis due to its anti-inflammatory and antioxidant properties. Effects of ascorbic acid include reduction of endothelial permeability, improvement of microvascular and macrovascular function, and reduction of inflammatory mediators. Thiamine deficiency exists in about 20% of patients with sepsis and may be associated with an increased risk of mortality. In patients with a critical illness, thiamine stores are depleted so supplementation with thiamine may improve organ function. Hydrocortisone is effective in resolving septic shock and current clinical practice guidelines recommend hydrocortisone in patients with septic shock who are not responding adequately to fluid resuscitation and vasopressors. The rationale for including hydrocortisone in HAT therapy is based on the potential synergistic effects with ascorbic acid. Because of the high mortality risk associated with sepsis, it has been a global public health priority to explore new treatment options for patients with sepsis and septic shock. The combination of hydrocortisone, ascorbic acid, and thiamine (HAT) is emerging as a potential adjunct treatment option in patients with sepsis and septic shock.[2]

Literature Review

The ORANGES trial[3] was a randomized, double-blind, placebo-controlled trial assessing the efficacy of HAT treatment in managing sepsis or septic shock in patients admitted to the intensive care unit (ICU). The trial included patients age 18 years or older with a primary diagnosis of sepsis or septic shock, defined by the 2016 Surviving Sepsis Campaign.[4] Additional inclusion criteria were compliance with the 3-hour sepsis bundle and diagnosis of sepsis or septic shock within 12 hours of admission to the ICU.[3] A total of 137 patients were randomized to receive either hydrocortisone 50 mg every 6 hours, ascorbic acid 1,500 mg every 6 hours, and thiamine 200 mg every 12 hours (n=68) or matching saline placebo (n=69) for a maximum of 4 days, in addition to standard of care. Secondary outcomes included both ICU mortality and hospital mortality. Results showed that the intervention group did not have a statistically significant reduced rate of ICU mortality (6 patients [9%] vs. 10 patients [14%], odds ratio [OR] 1.75; 95% confidence interval [CI] 0.59-5.1, P=0.37) or hospital mortality (11 patients [16.4%] vs. 13 patients [19%], OR 1.25; 95% CI, 0.5-2.97; P=0.65) compared to the placebo group. A limitation of this trial was the small sample size which limits the ability to detect differences in outcomes. Additionally, more than 90% of the patients in the study were white. This is important because the trial population does not represent the actual population of patients with sepsis or septic shock and the results may not be generalizable. A final limitation stems from 41% of the placebo group receiving corticosteroids, since the results was not-significant no adjustments were made to account per analysis protocol. The authors concluded that further randomized trials with larger and more diverse cohorts are needed to determine the effect on HAT therapy on mortality.

Chang et al[5] conducted a single-blind, randomized control trial to compare the effects of HAT therapy and placebo in preventing mortality in patients with sepsis or septic shock. Inclusion criteria were age 18 years or older, procalcitonin level of 2 ng/mL or higher, admission to the ICU, and a diagnosis of sepsis or septic shock, defined as meeting the diagnostic criteria for Sepsis-3 developed by the American Society of Critical Care Medicine and European Society of Intensive Care Medicine.[6] This trial randomized patients to receive either hydrocortisone 50 mg

TABLE 1. Summary of Literature Review

Year Published	Author	Trial design	Intervention (n)	Control (n)	Outcome(s)	Mortality Results	Conclusion
2020	Iglesias[3]	RCT, double-blind,	HAT (n=68)	Saline placebo (n=69)	ICU mortality[&] and hospital mortality[&]	ICU mortality: odds ratio (OR) 1.75; 95% confidence interval (CI) 0.59-5.1, P=0.37 Hospital mortality: OR 1.25; 95% CI, 0.5-2.97; P=0.65	No statistically significant difference in hospital mortality or ICU mortality
2020	Chang[5]	RCT, single-blind	HAT (n=40)	Saline placebo (n=40)	28-day mortality	Relative risk (RR) 0.79; 95% CI 0.41-1.52; P=0.47	No statistically significant difference in 28-day mortality
2019	Litwak[8]	Retrospective, real-world	HAT (n=47)	Standard of care (n=47)	Hospital mortality and ICU mortality[&]	ICU morality: 36.2% vs. 38.3%; P=0.83 Hospital mortality: 40.4% vs. 40.4%; P=1.0	No statistically significant difference in hospital mortality or ICU mortality
2017	Marik[7]	Retrospective before-after study	HAT (n=47)	Hydrocortisone 50 mg every 6 hours (n=47)	Hospital mortality	Propensity adjusted OR 0.13; 95% CI 0.04-0.48; P=0.002	HAT therapy had a statistically significant lower rate of mortality compared to standard of care

HAT: Hydrocortisone 50 mg every 6 hours, ascorbic acid 1,500 mg every 6 hours, and thiamine 200 mg every 12 hours; ICU: Intensive Care Unit; RCT: Randomized Control Trial
[&]Secondary study outcomes

every 6 hours for 7 days, vitamin C 1,500 mg every 6 hours for 4 days, and thiamine 200 mg every 12 hours for 4 days (n=40) or normal saline as placebo (n=40), in addition to standard care.[5] The primary outcome was 28-day mortality and the results showed that there was no statistically significant difference in mortality between the two groups (relative risk [RR] 0.79; 95% CI 0.41-1.52; P=0.47). This trial had a small sample size and was underpowered to detect a difference in the clinical outcomes. The interim analysis showed severe hypernatremia in the treatment group, which was thought to be caused by hydrocortisone administration, and the study was terminated early. Additionally, the HAT regimen was the same as a previous retrospective study[7], so it is unclear what is truly the optimal therapeutic regimen. The authors concluded that HAT therapy did not appear to reduce 28-day mortality in patients with sepsis or septic shock compared to placebo and that larger, multicentered, randomized controlled trials are required to validate the efficacy of HAT therapy.

A retrospective, real-world study by Litwak et al[8] compared HAT therapy versus standard of care in patients with severe sepsis and septic shock. Retrospective chart review was conducted for patients age 18 years and older with an International Classification of Disease (ICD) code for septic shock who were admitted to the ICU. All patients included in the study were treated with the standard of care, which included fluids, vasopressors, and empiric broad-spectrum antibiotics. Patients who received hydrocortisone 50 mg every 6 hours or 100 mg every 8 hours, vitamin C 1,500 mg every 6 hours, and thiamine 200 mg every 12 hours were included in the HAT group (n=47) and patients who received standard of care alone were included in the control group (n=47). The primary outcome was hospital mortality and a secondary outcome was ICU mortality. There was no statistically significant difference in hospital mortality (40.4% vs. 40.4%; P=1.0) or ICU mortality (36.2% vs. 38.3%; P=0.83) between the two groups. A limitation of this study was that 27 patients (57%) in the HAT group did not receive the full treatment duration of four days mainly due to either discontinuation of therapy by the primary team or patient death. Another limitation was that 40.4% of patients in the control group received hydrocortisone therapy. Due to early treatment discontinuation and hydrocortisone administration in the control group, the effects of HAT therapy may not have been fully observed. The authors concluded that a randomized controlled trial is necessary before implementing HAT therapy as a standard of care in patients with septic shock.

Marik et al[7] conducted a retrospective before-after clinical study to evaluate hospital survival in patients treated with HAT versus standard of care after the implementation of a Vitamin C protocol. Patients age 18 years or older admitted to the ICU with a diagnosis of sepsis or septic shock and a procalcitonin level of 2 ng/mL or higher were included in the retrospective chart review. During the treatment period, 47 patients were treated with the Vitamin C protocol (hydrocortisone 50 mg every 6 hours for 7 days, vitamin C 1,500 mg every 6 hours for 4 days or until ICU discharge, and thiamine 200 mg every 12 hours for 4 days). During the control period, 28 patients (59.6%) received hydrocortisone 50 mg every 6 hours at the discretion of the attending physician. Results showed that the treatment group had a statistically significant lower rate of mortality compared to the control group (propensity adjusted OR 0.13; 95% CI 0.04-0.48; P=0.002).

Limitations of this study include the small sample size, the retrospective nature of the study, and the treatment and control periods occurring during different seasons. While the results demonstrate a mortality benefit in HAT therapy, the authors conclude that larger trials are needed to validate these findings.

Evidence-based Answer

Combination therapy with HAT does not reduce mortality in critically ill patients with sepsis or septic shock compared to standard of care or placebo (Strength of recommendation = B, based on limited quality-patient oriented evidence from small-scale randomized controlled trials and retrospective cohort studies).[9] Results from the included studies[3,5,7,8] share a common conclusion that additional larger RCTs are needed to truly assess the effects of HAT therapy in patients with sepsis or septic shock. Additionally, studies that look at the efficacy of the individual components of HAT therapy may be beneficial.

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