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ABSTRACT & COMMENTARY

ORANGES and ACTS Trials: No Mortality Benefit with Ascorbic Acid, Thiamine, and Hydrocortisone in Septic Shock Patients

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Dr. Longueira and Dr. Lopez Ruiz report no financial relationships relevant to this field of study.

SYNOPSIS: Two double-blinded, placebo-controlled, randomized trials involving 337 patients (ORANGES, n = 137; ACTS, n = 200) with sepsis and septic shock have shown that administration of ascorbic acid, thiamine, and hydrocortisone did not reduce organ dysfunction or improve overall mortality. However, both trials showed that this combination therapy was effective in reducing the time to achieve shock resolution or shock-free days.

SOURCES: Iglesias J, Vassallo AV, Patel VV, et al. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: The ORANGES Trial. *Chest* 2020;158:164-173.

Moskowitz A, Huang DT, Hou PC, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: The ACTS Randomized Clinical Trial. *JAMA* 2020;324:642-650.

Sepsis and septic shock remain major public health problems in the United States, with in-hospital mortality ranging from 30% to 50%.[1] The 2016 Surviving Sepsis Campaign guidelines recommend the use of fluid resuscitation, broad-spectrum antibiotics, and vasopressors in patients with sepsis or septic shock.[2] Although this approach represents the mainstay of therapy, the search for adjunctive treatments, such as the combination of intravenous (IV) ascorbic acid, thiamine,

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and hydrocortisone, has garnered interest after the encouraging preliminary results of Marik et al.[3]

Iglesias et al conducted the ORANGES trial (February 2018 to June 2019), which was a randomized, double-blinded, placebo-controlled trial in the United States involving patients with sepsis and septic shock to elucidate the role of hydrocortisone, ascorbic acid, and thiamine (HAT) therapy in sepsis management. Adult patients were eligible for inclusion in the study if they were diagnosed with sepsis or septic shock as defined by the 2016 Surviving Sepsis Campaign guidelines within 12 hours of admission to the intensive care unit (ICU).[2] Subjects were randomized to receive either ascorbic acid 1,500 mg IV every six hours, thiamine IV 200 mg every 12 hours, and hydrocortisone 50 mg IV every six hours or placebo for up to four days. Notably, intensivists were permitted to use open-label hydrocortisone in the control patients if deemed clinically necessary. The primary outcome of the study was resolution of shock defined as time from starting the study medication to discontinuation of vasopressor support and change in Sequential Organ Failure Assessment (SOFA) score. Secondary outcomes included ICU and hospital mortality, ICU and hospital length of stay (LOS), ventilator-free days, renal failure, and procalcitonin clearance.

A total of 137 patients were randomized, with 68 in the treatment arm and 69 in the control group. Ninety-six percent of the patients studied were white, with an average age of 69 ± 13 years. Overall, 64% of subjects had ascorbic acid deficiency at baseline. Groups were comparable with regard to baseline Acute Physiology and Chronic Health Evaluation (APACHE) II scores (24 vs. 24.9), SOFA scores (8.3 vs. 7.9), and APACHE IV predicted mortality (34% vs. 33.6%). Investigators found a statistically significant difference for the time to shock reversal between the HAT and control groups (34 hours vs. 54 hours, $P < 0.001$). No statistically significant difference was found for change in SOFA score (3 vs. 2, $P = 0.17$). Additionally, there were no statistically significant differences in any of the secondary outcomes. A similar incidence of acute kidney injury (AKI) (79% vs. 75%, $P = 0.68$) and renal replacement therapy (3% vs. 11%, $P = 0.098$) was reported between the groups. Investigators concluded that the combination of IV ascorbic acid, thiamine, and hydrocortisone works synergistically to significantly reduce the time to resolution of shock.

The ACTS trial was a multicenter (14 centers in the United States), randomized, double-blind, placebo-controlled trial in which patients with septic shock were assigned to combination IV ascorbic acid (1,500 mg), hydrocortisone (50 mg), and thiamine (100 mg) every six hours for four days (n = 101) or placebo (n = 99). Patients were enrolled between February 2018 and October 2019. The primary outcome was change in SOFA score between enrollment and 72 hours. Key secondary outcomes included kidney failure and 30-day mortality. Of the patients who completed the study (mean age 68 ± 15 years; 44% women), 98% received at least one dose of the study drug.

Overall, there was no statistically significant improvement in SOFA score over the 72 hours after enrollment (mean SOFA score change from 9.1 to 4.4 [–4.7] points with intervention vs. 9.2 to 5.1 [–4.1] points with placebo; adjusted mean difference, –0.8; 95% confidence interval [CI], –1.7 to 0.2; $P = 0.12$ for interaction). There was no statistically significant difference in the incidence of kidney failure (31.7% with intervention vs. 27.3% with placebo; adjusted risk difference 0.03; 95% CI, –0.1 to 0.2; $P = 0.58$) or in 30-day mortality (34.7% vs. 29.3%, respectively; hazard ratio 1.3; 95% CI, 0.8 to 2.2; $P = 0.26$). However, the median number of shock-free days was higher in the intervention group compared with the placebo group (5 [interquartile range {IQR}, 3-5] vs. 4 [IQR, 1-5] days; median difference 1.0 day; 95% CI, 0.2 to 1.8 days; $P < 0.01$).

In addition, patients in the intervention group had a significantly greater reduction in cardiovascular SOFA score during the first 72 hours (mean difference –0.5; 95% CI, –0.9 to –0.1; $P = 0.03$ for interaction). Finally, there were similar numbers of serious adverse events in each

group. The authors concluded that their data do not support the use of ascorbic acid, hydrocortisone, and thiamine in patients with septic shock.

■ COMMENTARY

Ascorbic acid in combination with hydrocortisone and thiamine (HAT therapy) has been proposed as adjunctive therapy in patients with sepsis and septic shock, given that many of these patients often have low levels of ascorbic acid and thiamine, or relative corticosteroid insufficiency.[4] Furthermore, ascorbic acid possesses anti-inflammatory and antioxidant properties that can be useful in preserving endothelial function.[5] It also serves as a cofactor for catecholamine synthesis, thereby contributing to maintain its endogenous production.[6] The combination of hydrocortisone and ascorbic acid may act synergistically, since ascorbic acid reverses the oxidative damage to glucocorticoid receptors, while glucocorticoid increases the expression of the sodium-vitamin C cotransporter-2 (SVCT2), thereby allowing more ascorbic acid to be transported into cells.[7,8] Thiamine also possesses antioxidant properties and serves as a necessary coenzyme to metabolize pyruvate inside the mitochondria and catalyzes the conversion of ascorbic acid to glyoxylate rather than oxalate, thereby preventing renal tubular injury (i.e., AKI).[3] The proposed protective mechanisms conferred by HAT therapy, along with the finding that septic patients often have deficiencies in these factors, make this therapy seem appealing and encouraging to improve ICU outcomes.

In the ORANGES trial, Iglesias et al aimed to demonstrate the benefit of HAT therapy in patients with sepsis and septic shock based on previous small, single-center studies showing that this combination was associated with significant reductions in levels of procalcitonin, C-reactive protein (CRP), and vasopressor requirements. In addition, these studies also reported improved 28-day mortality (14.2% vs. 64.2%, $P = 0.009$).[9,10]

The ORANGES trial has an important limitation: A large proportion of patients (41%) in the placebo group received open-label hydrocortisone. Given that the primary outcome of this study was time to vasopressor independence, use of hydrocortisone in the control group can significantly confound this result. Hydrocortisone has consistently been shown in previous large, randomized trials (CORTICUS – ADRENAL) to reduce the time to shock reversal and currently is recommended by the Surviving Sepsis Campaign Guidelines in patients with refractory septic shock requiring high doses of vasopressors.[2,11,12] Despite the statistical analysis and adjustment for this group of patients that received corticosteroids, the ORANGES trial found that HAT therapy still provided significant benefit in reducing the time to shock reversal, but whether this effect was a truly synergistic action of ascorbic acid with thiamine and hydrocortisone remains unclear. This beneficial effect of achieving vasopressor independence sooner with HAT therapy was not associated with improvement in any of the other outcomes, including the co-primary endpoint of reducing SOFA score. This result goes against the previous finding of Marik et al in which HAT therapy conferred significant benefit in SOFA reduction, duration and dose of vasopressor support, and ICU mortality.[3] Although the study by Marik et al was a small, single-center, and retrospective trial, the fact that reduction in vasopressor requirement was not associated with reduction in SOFA score in the ORANGES trial supports the idea that HAT therapy did not affect the severity of illness or the degree of tissue injury.

[This beneficial effect of achieving vasopressor independence sooner with HAT therapy was not associated with improvement in any of the other outcomes.]

Other important points to consider include the fact that most of the patients in the ORANGES trial were white and enrolled in two small community hospitals with low proportions of surgical septic shock. Moreover, the data on renal failure was not stratified based on severity of AKI, and it only considered those severe cases requiring renal replacement therapy (RRT). Therefore, the sample size of this study likely is too small to adequately assess the impact of HAT therapy on early stages of AKI and its progression.

The ACTS trial was a larger, multicenter trial that also failed to demonstrate any benefit of HAT therapy in reducing SOFA score or improving all-cause mortality over 30 days in patients with septic shock. In addition, the ACTS trial failed to demonstrate benefits in other secondary outcomes, such as renal failure requiring RRT, ventilator-free days, or ICU-free days. For this study, patients were not chosen because of vitamin deficiency unlike in the previous VITAMINS trial, and the study was not powered to analyze specific subgroups, such as those not requiring mechanical ventilation, those with acute respiratory distress syndrome (ARDS), or those requiring lower doses of vasopressor support (< 15 mcg/hour).[13] However, this trial, like ORANGES, demonstrated that HAT

therapy was effective in reducing the duration of vasopressor support. In fact, the median number of shock-free days was higher in the intervention group compared with the placebo group. Patients in the intervention group also had a statistically significantly greater reduction in cardiovascular SOFA score during the first 72 hours.

Overall, the current evidence after three randomized, double-blind, placebo-controlled trials (VITAMINS, ORANGES, and ACTS) using the combination of ascorbic acid, hydrocortisone, and thiamine as it was proposed by Marik et al does not support its use to improve mortality in sepsis or septic shock.[3] Subsequent trials using HAT therapy must focus on identifying a specific subgroup of patients or patient phenotype in which this therapy could be effective. Currently, there are more than 30 ongoing or planned studies investigating the role of ascorbic acid or HAT combination in patients with sepsis and septic shock. One of the next to come is the VICTAS trial, which is larger than the ACTS trial and is a multicenter, double-blinded, randomized, controlled trial enrolling 500 septic patients that will evaluate the effect of HAT therapy on ventilator- and vasopressor-free days and ICU mortality.[14] If this trial does not show benefits of HAT therapy on strong ICU endpoints, it will support the decision of abandoning this therapy from the armamentarium to manage sepsis. ■

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SPECIAL FEATURE

Considerations and Concerns with Vitamin C in Sepsis and Septic Shock

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Dr. Hammond reports no financial relationships relevant to this field of study.

Sepsis remains a major healthcare problem associated with significant morbidity and mortality.[1] Standard septic shock therapies include fluid resuscitation, antimicrobials, and vasopressors.[2] Roles for hydrocortisone, ascorbic acid (vitamin C), and thiamine (HAT therapy) as potential adjuvants remain controversial.[3-18]

The reduced form of vitamin C, ascorbate, affects both cellular regulation and immune system

function.[19,20] It acts as an antioxidant and free radical scavenger to improve microvascular and macrovascular function, reduce endothelial permeability, regulate macrophage function, and decrease cellular apoptosis.[19-21] Vitamin C is an essential co-factor for catecholamine and vasopressin synthesis and may be depleted in critically ill patients.[22,23]

VITAMIN C AND HAT THERAPY EFFICACY

Mortality

Several randomized controlled trials (RCTs) and observational studies have evaluated vitamin C alone or as part of HAT therapy in sepsis and septic shock.[3-18] Only two RCTs reported positive mortality outcomes.[13,15] The VITAMINS trial compared HAT therapy (n = 109) vs. hydrocortisone (n = 107) alongside usual care in septic shock.[16] No differences in mortality, median time alive, or vasopressor-free days up to day 7 were found between the groups. Two recently published RCTs, the Combined treatment with HYdrocortisone, Vitamin C, and Thiamine for the Treatment of Sepsis and Septic Shock (HYVCTTSSS) trial and the Outcomes of metabolic Resuscitation using Ascorbic acid, thiamiNe, and Glucocorticoids in the Early treatment of Sepsis (ORANGES) trial, failed to demonstrate mortality benefit with vitamin C.[17,18] HYVCTTSSS was terminated early because of a significantly higher incidence of severe hypernatremia with HAT therapy.[17] However, data from 80 enrolled patients did not demonstrate a mortality benefit at 28 days (27.5% vs. 35%, $P = 0.47$). The subgroup of patients diagnosed with sepsis within 48 hours had lower mortality compared to placebo (13.6% vs. 47.6%, $P = 0.02$).

The ORANGES trial (n = 137) evaluated HAT therapy in patients diagnosed with sepsis or septic shock within 12 hours from hospital admission.[18] The primary endpoint was updated after patient enrollment from hospital mortality to resolution of shock and change in Sequential Organ Failure Assessment (SOFA) score at 96 hours from baseline. The authors reported a significant reduction in duration of vasopressor use in patients who received HAT therapy (27 ± 22 vs. 53 ± 38 hours, $P < 0.001$) but no difference in intensive care unit (ICU) (9% vs. 14%, $P = 0.37$) and hospital mortality (16.4% vs. 19%, $P = 0.65$) compared to placebo. Both HYVCTSSS and ORANGES did not control for hydrocortisone use between groups, which potentially could have confounded these outcomes.

The second largest multicenter, placebo-controlled RCT, CITRIS-ALI (n = 167), randomized septic patients with acute respiratory distress syndrome (ARDS) to vitamin C (50 mg/kg intravenous [IV] every six hours) or placebo for 96 hours.[15] Even though there was no difference in the co-primary endpoint of change in SOFA score, serum C-reactive protein, and thrombomodulin at 96 hours from baseline, the 28-day mortality was lower in the vitamin C group (29.8% vs. 46.3%, 95% confidence interval [CI], between-group difference 2% to 31%, $P = 0.03$).[15] However, the mortality analyses did not account for multiple comparisons.

Eight observational studies have evaluated mortality, and only three of these studies reported positive mortality findings.[3-10]

Resolution of Organ Failure

The presumed protective effect of vitamin C on organ function also has been evaluated in both observational studies and RCTs.[3-8,12-18] Only three out of seven RCTs that assessed improvement in organ function (i.e., improvement in SOFA scores or need for renal replacement therapy) reported greater improvement with vitamin C. However, these significant improvements should be interpreted cautiously, since these were secondary endpoints assessed without adjustment for multiple comparisons. Only one observational study assessed this endpoint and observed that patients who received vitamin C had a greater change in SOFA scores at 72 hours (4.8 ± 2.4 vs. 0.9 ± 2.7, $P < 0.001$).[3]

VITAMIN C TIME TO INITIATION IN SEPTIC SHOCK

The effect of time to initiation of vitamin C therapy on outcomes remains controversial. In patients with septic shock, early vitamin C administration may prevent over-resuscitation and subsequent negative sequelae.[24-26] Marik et al evaluated patients who received vitamin C within 24 hours of ICU admission and showed a decrease in hospital mortality with vitamin C.[3] HYVCTTSSS found a 34% improvement in mortality in a predefined subgroup analysis of patients with sepsis within 48 hours (n = 22).[17] These findings were not replicated in other RCTs.[4,5,16]

In the VITAMINS trial, the median time from meeting Sepsis-3 criteria to vitamin C initiation in the intervention group was 12.1 hours (IQR, 5.7-19.0 hours).[16] Despite all patients receiving vitamin C within 24 hours of sepsis diagnosis, no mortality benefit was detected. ORANGES recruited patients within 12 hours of development of septic shock, and patients received their first dose of the study treatment between three and 14 hours (mean, 9.9 ± 4.5 hours). Again, there was no observed difference in mortality.[18] Although the proposed mechanisms of benefit for vitamin C in septic shock support early administration, the differences in timing of vitamin C and outcomes in many RCTs make

deciphering optimal timing of vitamin C initiation difficult.

PATIENT POPULATIONS THAT MAY BENEFIT FROM HIGH-DOSE VITAMIN C

Currently, clinical equipoise exists regarding high-dose vitamin C use in sepsis and septic shock, both with and without the use of other metabolic resuscitation agents, because of variable findings and methodological quality in RCTs and studies.[3-18] However, there may be specific patient populations for whom beneficial outcomes are more likely.

[Although few safety events and adverse events have been reported in studies, vitamin C is not a benign therapy.]

Severity of Critical Illness

Patients in the Marik study were less severely ill than those in the VITAMINS trial.[3,16] Patients in both received similar HAT therapy regimens, although some patients enrolled in the VITAMINS trial had therapy initiated beyond the first 24 hours of ICU admission, and Marik et al did not describe time to receipt of HAT therapy.[3,16] Patients in the VITAMINS trial were randomized after being on IV vasopressors for at least two hours, whereas only 46% of patients in the Marik et al study were on IV vasopressors at baseline. Additionally, baseline lactate values were lower in the Marik et al study (mean 2.7 mmol/L ± 1.5 vs. median 4.2 mmol/L; IQR, 2.8-5.9]).[3,16] The benefit seen in the Marik study may have been more profound because of the increased likelihood of recovery in these less severely ill patients. However, vitamin C has shown mortality benefit in more severely ill patients in an observational before-and-after study.[8] In a subgroup analysis of this study, vitamin C was significantly associated with lower in-hospital mortality in patients with SOFA scores > 10 points (adjusted odds ratio [OR], 0.53; 95% CI, 0.29-0.97, $P = 0.03$) and baseline albumin level < 3.0 mg/dL (adjusted OR, 0.53; 95% CI, 0.30-0.93, $P = 0.02$).[8]

Acute Respiratory Distress Syndrome in Sepsis

The CITRIS-ALI trial randomized patients with sepsis who developed ARDS to high-dose vitamin C (50 mg/kg IV every six hours for four days) or placebo.[15] Two-thirds of patients were in shock at enrollment, and two-thirds of patients received corticosteroids. Although the primary outcome, change in SOFA score, was similar between groups, an exploratory secondary outcome of 28-day mortality was lower in patients randomized to vitamin C (29.8% vs. 46.3%, $P = 0.03$). Because mortality also was lower on day 4 after the trial intervention was completed (4% vs. 23%), this survivorship bias could have affected other short-term outcomes (e.g., change in SOFA score). Further trial data in ARDS that is powered to determine a potentially moderate mortality benefit is necessary before vitamin C can be confidently recommended in these patients.

SAFETY CONCERNS WITH VITAMIN C AND THIAMINE

Although few safety events and adverse events have been reported in studies, vitamin C is not a benign therapy. Adverse effects are rare, but they may include oxalate nephropathy, hypernatremia, fictitious hyperglycemia, and hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.[27]

Vitamin C is metabolized into oxalate, which binds with calcium to form a precipitate in renal tubules that can cause acute and chronic tubular injury, interstitial fibrosis, and renal failure.[28] Doses of 10 g carried an increased risk of oxalate crystal formation.[29] At least five cases of oxalate nephropathy have been reported in patients receiving IV vitamin C.[27]

Prior to the HYVCTTSSS trial, there have been five reported cases of hypernatremia with IV vitamin C administration. Hypernatremia can occur with large doses of vitamin C because marketed products of IV vitamin C are sodium ascorbate.[27] The HYVCTTSSS trial was terminated early because of the incidence of severe hypernatremia (> 160 mmol/L) in addition to ineffectiveness of the treatment.[17] Thirteen patients in the treatment group compared with three patients in the placebo group experienced severe hypernatremia (relative risk [RR] 4.43; 95% CI, 1.34-14.1; $P = 0.05$).

Vitamin C also may cause fictitious hyperglycemia.[30] This is because of an interaction with the mechanism of some point-of-care blood glucose machines that use glucose dehydrogenase-pyrroloquinoline quinone amperometric methods.[30] When vitamin C is oxidized at the electrode surface, it causes more electron production that potentiates a larger current, causing interference with glucose biosensors.[31]

G6PD deficiency is an exclusion criterion in many of the ongoing trials for vitamin C because of the potential risk of hemolysis with very high doses (> 60 g).[32] However, doses used in the protocols for sepsis (up to 6 g/day) should not achieve blood concentrations typical of causing harm.[33]

CONCLUSION

The role of vitamin C in sepsis has been evaluated in observational and randomized controlled trials.

Vitamin C produces early reductions in pro-inflammatory mediators and slows the progression of endothelial injury in patients with severe sepsis. There is inconsistency in the vitamin C dosing regimens used in clinical trials, making it challenging to draw definitive conclusions on its role in sepsis. In general, vitamin C appears to be safe. However, patients should be monitored for nephropathy and glucose monitoring errors when high-dose vitamin C is administered. Overall, there is insufficient evidence to support the routine use of vitamin C in sepsis. Future studies are warranted to identify subgroups of sepsis patients that may benefit from vitamin C therapy. ■

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CME/CE INSTRUCTIONS

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CME/CE QUESTIONS

1. Which of the following intensive care unit (ICU) outcomes have been achieved with the use of ascorbic acid, thiamine, and hydrocortisone in the ORANGES and ACTS trials?
a. Reductions in Sequential Organ Failure Assessment (SOFA) score at 72 hours
b. Increase in vasopressor-free days
c. Reduced renal failure requiring renal replacement therapy
d. Reduced ventilator-free days

2. Which of the following statements is correct regarding the ACTS trial?
a. It compared ascorbic acid and hydrocortisone (treatment arm) vs. placebo.
b. Treatment therapy was initiated at the same time as vasopressor support.
c. Treatment did not affect the rate of renal failure or ICU-free days.
d. Patients were enrolled if they had low levels of ascorbic acid.

3. In the CITRIS-ALI trial, which secondary endpoint was significantly different favoring vitamin C administration?
a. Change in SOFA score
b. Twenty-eight-day mortality
c. Decrease in serum C-reactive protein
d. Decrease in thrombomodulin

4. In the HYVCTTSSS trial, why was the trial terminated early?
a. Increased hyperkalemia with hydrocortisone, ascorbic acid, and thiamine (HAT) therapy
b. Increased hypernatremia with HAT therapy
c. Increased metabolic acidosis with HAT therapy
d. Increased mortality with HAT therapy

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.