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Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis

The ORANGES Trial

Jose Iglesias, DO; Andrew V. Vassallo, PharmD, BCPS, BCCCP; Vishal V. Patel, PharmD, BCCCP; Jesse B. Sullivan, PharmD, BCPS, BCCCP; Joseph Cavanaugh, PharmD, BCPS, BCCCP; and Yasmine Elbaga, PharmD, BCPS

BACKGROUND: Sepsis is a major public health burden resulting in 25% to 30% in-hospital mortality and accounting for over 20 billion dollars of US hospital costs.

RESEARCH QUESTION: Does hydrocortisone, ascorbic acid, thiamine (HAT) therapy improve clinical outcomes in sepsis and septic shock?

STUDY DESIGN AND METHODS: This was a randomized, double-blinded, placebo-controlled trial conducted from February 2018 to June 2019, assessing an HAT treatment bundle for the management of septic and septic shock patients admitted to an ICU. The primary outcomes were resolution of shock and change in Sequential Organ Failure Assessment (SOFA) score. Secondary outcomes included 28-day mortality, ICU mortality, hospital mortality, procalcitonin clearance (PCT-c), hospital length of stay (LOS), ICU LOS, and ventilator-free days.

RESULTS: One hundred thirty-seven patients were randomized to the treatment group (n = 68) and comparator group (n = 69), respectively, with no significant differences in baseline characteristics. A statistically significant difference was found in the time patients required vasopressors, indicating quicker reversal of shock in the HAT group compared with the comparator group (27 ± 22 vs 53 ± 38 hours, $P < .001$). No statistically significant change in SOFA score was found between groups 3 (1 - 6) vs 2 (0 - 4), $P = .17$. No significant differences were found between study arms in ICU and hospital mortality, ICU and hospital LOS, ventilator free days, and PCT-c.

INTERPRETATION: Our results suggest that the combination of IV ascorbic acid, thiamine, and hydrocortisone significantly reduced the time to resolution of shock. Additional studies are needed to confirm these findings and assess any potential mortality benefit from this treatment.

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KEY WORDS: ascorbic acid; HAT therapy; hydrocortisone; sepsis; septic shock; vitamin c; thiamine

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ABBREVIATIONS: AA = ascorbic acid; AKI = acute kidney injury; ANCOVA = analysis of covariance; ANOVA = analysis of variance; HAT = hydrocortisone, ascorbic acid, thiamine; LOS = length of stay; PCT = procalcitonin; PCT-c = procalcitonin clearance; SCr = serum creatinine; SOFA = Sepsis-Related Organic Failure Assessment

AFFILIATIONS: From the Department of Critical Care, Department of Nephrology (Dr Iglesias) and the Department of Pharmacy (Drs Vassallo, Patel, and Cavanaugh), Community Medical Center, Toms River, NJ; Department of Nephrology, Jersey Shore University Medical Center, Hackensack Meridian School of Medicine at

Sepsis is a major public health burden resulting in 25% to 30% in-hospital mortality and accounting for over 20 billion dollars of US hospital costs.[1,2] It is defined as life-threatening organ dysfunction related to a dysregulated host response to infection.[1] Currently no treatments directly target the pathogenesis of sepsis; therefore, management relies on early identification and the rapid administration of antibiotics, IV fluids, and vasopressors when appropriate.[3]

Previous promising studies have demonstrated the potential benefit of co-administration of hydrocortisone, ascorbic acid (AA), and thiamine (known as HAT therapy), which may reverse shock organ dysfunction and reduce mortality.[4,5] Marik et al[5] performed a retrospective before-and-after analysis that identified a possible association between a vitamin C-based protocol and patient mortality.[5] The treatment protocol was associated with a 31.9% overall decrease in mortality and a 3-fold decrease in time to vasopressor discontinuation in patients presenting with severe sepsis and septic shock. Fowler et al[6] demonstrated that IV administration of AA decreased Sequential Organ Failure Assessment (SOFA) scores and pro-inflammatory biomarkers.[6] Currently, ClinicalTrials.gov has over half a dozen studies across the United States currently recruiting applicants or waiting to publish results on the use of a vitamin C-driven protocol on sepsis.[7] One such study published by Fujii et al[8] demonstrated that HAT therapy did not significantly improve the duration of time alive and free of vasopressor administration over 7 days.[8] To better understand the effect of HAT therapy on clinical outcomes in sepsis and septic shock, we conducted the ORANGES trial.

Materials and Methods

Study Design

This was a randomized, double-blinded, placebo-controlled trial assessing the utilization of an ascorbic acid, thiamine, and hydrocortisone treatment bundle for the management of septic and septic shock patients admitted to an ICU. This study was performed from February 2018 to June 2019 in two community nonteaching hospitals in the United States. The study was approved by the Community Medical Center Institutional Review Board (IRB # 17-004). All participants were provided with written informed consent. For patients who presented with altered mental status or requiring mechanical ventilation, consent was obtained from the patient's legally authorized representative. Patients were randomized to receive either ascorbic acid 1,500 mg q6h, thiamine 200 mg every 12 hours, and hydrocortisone 50 mg q6h or a matching saline placebo for a maximum of 4 days. Intensivists were allowed to order open-label corticosteroid therapy for patients as deemed necessary for their usual care (ie, for respiratory failure). Study medications were discontinued if patients were discharged from the ICU before 4 days. Before study therapy initiation, baseline ascorbic acid and thiamine levels were drawn and evaluated via liquid chromatography/mass spectrometry. Study randomization and blinding was performed by the main hospital pharmacy and maintained on a password-protected file. Patients were block randomized separately at each site into 70 sets of 2, which predetermined each patient's treatment group enrollment. Investigators were blinded up until termination of patient enrollment and both primary and secondary study outcomes were met.

Ethics Statement

All procedures performed in the study were in accordance with the 1964 Helsinki declaration and its later amendments. Patients' data were kept confidential, and no patients' identifiers were included in data files handled for the purposes of this study.

Population

Participants were adults (≥18 years of age) with a primary diagnosis of sepsis or septic shock according to the 2016 Surviving Sepsis Campaign definitions.[3] Additional inclusion criteria were diagnosis of sepsis or septic shock within 12 hours of admission to the ICU and compliance with the 3-hour sepsis bundle. Once consent was obtained, treatment was allowed to begin in the ED. Although there was an update in 2018 reducing the time of the bundle to 1 hour, the 3-hour time frame was maintained because patient enrollment had already begun.[9]

Exclusion criteria included patients under the age of 18, were pregnant, had a do not resuscitate or do not intubate order on admission, had a terminal end-stage disease (eg, stage IV cancer, end-stage heart failure), did not have a primary admitting diagnosis of sepsis or septic shock, required immediate surgery, had HIV and a CD4 < 50 mm^2, had known glucose-6 phosphate dehydrogenase deficiency, were transferred from another hospital, or presented with sepsis or septic shock more than 24 hours from admission.

Outcomes

The primary outcomes of the study were resolution of shock and change in SOFA score. Resolution of shock was defined as the time from starting blinded study medications to discontinuation of all vasopressor support. Change in SOFA score was defined as the initial SOFA score minus the day 4 SOFA score. A 4-day course was chosen to align with the maximum care provided with the study medications. SOFA scores were calculated daily, starting on the first day of admission to the ICU. This difference was calculated the same way even if the patient was discharged from the ICU before day 4. If the patient was discharged from the hospital before day 4, the last known SOFA score was carried forward. If a patient died

Seton Hall (Dr Iglesias), Neptune, NJ; Fairleigh Dickinson University School of Pharmacy & Health Sciences (Dr Sullivan), Teaneck, NJ; and the Department of Pharmacy (Dr Elbaga), Monmouth Medical Center Southern Campus, Lakewood, NJ.

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CORRESPONDENCE TO: Jose Iglesias, DO, Department of Critical Care, Department of Nephrology, Community Medical Center, 99 NJ-37, Toms River, NJ 08755; e-mail: jiglesias23@gmail.com

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before day 4, their last SOFA score was also carried forward for assessment. For patients in whom the PaO_2/FIO_2 could not be obtained for SOFA score calculation, the peripheral capillary oxygen saturation/FIO_2 was used as an alternative.[10]

Secondary outcomes included ICU mortality, hospital mortality, procalcitonin clearance (PCT-c), hospital length of stay (LOS), ICU LOS, and ventilator-free days. PCT-c was calculated using the following formula: initial PCT minus PCT at 96 hours divided by the initial PCT multiplied by 100.[11,12] Ventilator-free days was calculated by the number of days free of mechanical ventilation up until day 28. Acute kidney injury (AKI) was defined on the basis of Kidney Disease: Improving Global Outcomes criteria; namely, an increase in serum creatinine (SCr) $>$ 0.3 mg/dL, a level $>$1.5 times the baseline value or the initiation of renal replacement therapy.[13] If baseline prehospitalization SCr was unknown or unavailable, we employed a prehospitalization estimated glomerular filtration rate of 75 mL/min/1.73 m^2 and "back-calculated" the SCr value using the simplified Modification of Diet in Renal Disease Equation for serial measurements of SCr. If patients required dialysis during the study or had end-stage renal disease, we arbitrarily assigned the patients an SCr of 5 mg/dL.[14] This assignment of a baseline SCr was performed only for the purpose of comparing baseline creatinine and not for the purpose of calculating acute kidney injury.

Primary safety outcomes included SCr, urine oxalate, and other reported adverse reactions documented by clinical staff. Safety evaluations included routine laboratory assessments and measurement of vital signs. Levels of urine oxalate were measured using a 24-hour urine collection on day 4 to assess for accumulation in the kidneys.

Statistics

Based on the results of the preliminary study of Marik et al,[5] we projected that the combination of ascorbic acid, thiamine, and hydrocortisone could reduce time to vasopressor discontinuation from 54 (±30 hours) vs 30 hours. For the additional primary outcome, we projected a greater change of SOFA score of 4 (±3) vs 2. Assuming a type 1 error of 5% (alpha of 0.05) and a power of 80%, this study would require a sample size of 94 patients. To account for dropouts and patients not requiring vasopressor therapy, we aimed for a sample size of 140 patients. Sample size was calculated based on both primary outcomes, and the larger of the two calculations was used.

The primary analysis was intention to treat. Summary statistics were computed for both study arms. Continuous variables were expressed as mean ± SD. Differences between HAT and comparator arms were compared by the Student *t* test or the Wilcoxon rank-sum test, as appropriate for non-normally distributed data. Variables that were serially measured during the study period such as procalcitonin levels, SOFA scores, vasopressor requirements, and laboratory parameters were compared by employing repeated-measures analysis of variance (ANOVA) with HAT therapy and the comparator being the between-subjects' factor. When the assumptions of the repeated-measures ANOVA were not met, a Student *t*-test with a Bonferroni correction was employed. Categorical values were compared with Pearson χ^2 test or Fischer χ^2 test when indicated. Significance was set at a *P* value of less than .05. Because 41% of patients in the comparator group received corticosteroids, any outcomes found to be significant were reanalyzed by adjusting for corticosteroid therapy use. Kaplan-Meier survival curves and log-rank analyses were employed to compare survival difference between HAT and comparator groups. Cox regression analysis was employed to compare differences in time with reversal of shock between groups.

Statistical analysis was performed using SPSS and R (IBM; R Foundation for Statistical Computing). We performed checks on the assumption of proportionality of hazards by evaluating Schoenfeld residuals and the Therneau, Grambsch global test on the summed Schoenfeld residuals.[15]

Results

Study Population

Between February 14th, 2018 and April 29th, 2019, 140 patients consented to participate in the study. Three patients were withdrawn from analysis after randomization because of a new diagnosis of terminal cancer. One hundred thirty-seven patients were randomized. Sixty-eight patients and 69 patients were randomized to the treatment arm (HAT) and comparator arms, respectively (Fig 1). Most of the patients received their first dose of study treatment between 3 and 14 hours (mean, 9.9 ± 4.5 hours) from presentation to the ED once enrolled and randomized. At the time of enrollment, there were no significant baseline differences in demographics, comorbidities, laboratory values, Acute Physiology and Chronic Health Evaluation II scores, SOFA scores, between the treatment arms (Table 1). This was a predominantly white patient population, representing 96% of the population. There were 43% male and 57% female participants in the study. The mean age of the participants was 69 ± 13 years. The major sources of infection were pulmonary 43%, urogenital 31%, primary bacteremia 14%, and GI/other 12%. There were 23 (17%) episodes of gram-negative bacteremia, 21 (15%) episodes of gram-positive bacteremia, and 1 (0.7%) episode of non-albicans candidemia. At time of enrollment 50% of the patients were on mechanical ventilation and 75% were on vasopressors. A total of 28 (41%) patients in the comparator arm received corticosteroids. The mean SOFA score was 8.1 ± 3.3, and the Apache II score was 24.5 ± 8.2, with an estimated mortality of 34% ± 2%, which is comparable to similar sepsis trials.[4,5,16] Hypovitaminosis, defined as an AA level of ≤23 μmol/L, was present in 50% of participants, and severe AA deficiency, defined as an AA level ≤ 11.3 μmol/L, was present in 14% of participants. Only one patient was discharged alive from the hospital before day 4.

Primary End points

A significant difference was seen in the time patients required vasopressors, indicating reversal of shock in the HAT arm compared with the comparator arm, 27 ± 22 vs 53 ± 38 hours, $P < .001$. Kaplan-Meier curves

comparing reversal of shock in HAT therapy, comparator arm without steroids, and comparator arm receiving open-label steroids showed a significant difference, log rank $P = .009$ (Fig 2). A Cox regression was performed with HAT therapy and corticosteroid therapy in the comparator group as factors. This identified an independent effect of HAT therapy on reversal of shock, $P = .007$, HR, 1.79, 95% CI, 1.17-2.75 (Fig 2).

To compare whether the effectiveness of HAT therapy on resolution of shock was not solely an effect of corticosteroid administration, we performed a one-way analysis of covariance (ANCOVA) adjusted for corticosteroid use as a covariate. The outcome was time to discontinuation of vasopressors. Preliminary analysis revealed that the assumptions of the ANCOVA test were not met. We therefore employed a nonparametric rank ANCOVA described by Quade.[17,18] In the rank ANCOVA, the dependent variable (time to reversal of shock/time to discontinuation of vasopressors) is rank transformed, and parametric analysis is performed on the rank values.[17,18]

Adjusting for corticosteroid use, HAT therapy remained significant in resolution of shock. The grand mean time to discontinuation of vasopressors and reversal of shock was 44 hours, with a mean time in HAT therapy being 34 hours compared with the control arm mean of 54 hours, demonstrating that patients in the control arm remained in shock 59% longer ($F_{1,84} = 28.6$, $P < .001$, adjusted $R^2 = 0.147$). Vasopressor dosage (norepinephrine equivalents) over time decreased; however, this difference did not meet traditional thresholds of statistical significance ($F_{1,19} = 4.28$, $P = .052$) (Fig 3).[19,20] These results suggest that HAT therapy has a significant effect on decreasing the time to reversal of shock, which is independent of corticosteroid effects.

During the study, no statistically significant change in SOFA score was seen between the HAT arm and the

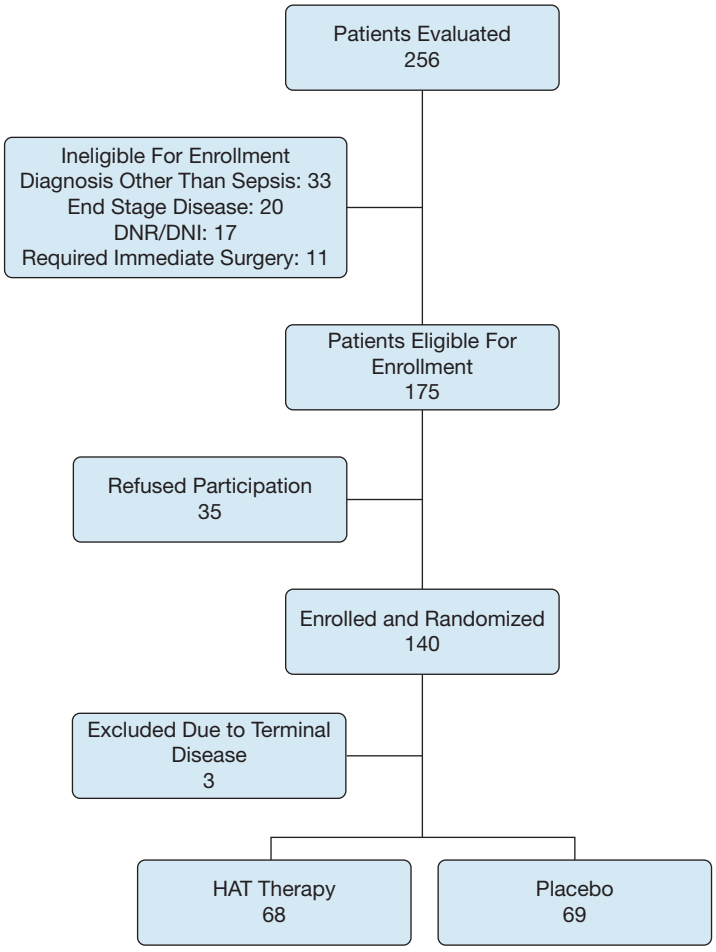


Figure 1 – *Flow diagram for patient enrollment.*

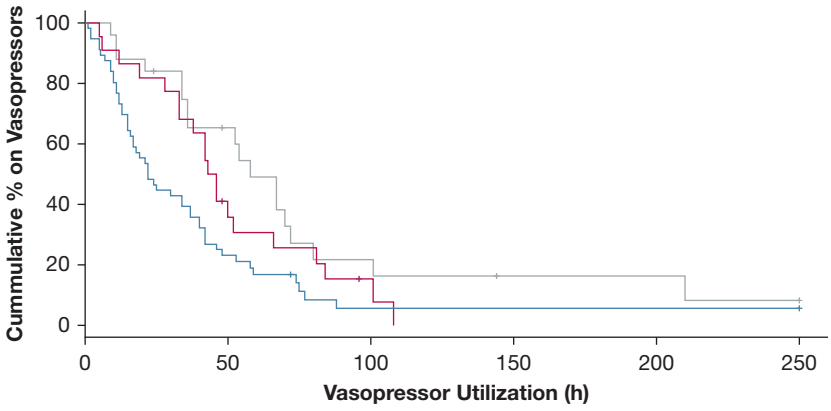
comparator arm, with decreases in SOFA of 3 (1-6) vs 2 (0-4), $P = .17$. Repeated-measures ANOVA demonstrated that there was no statistically significant change in SOFA score throughout the study (Fig 4) ($F_{3,103} = 1.3$, $P = .27$).

To account for patients who died before 72 hours or did not have values at each time period (24-72 hours) we also determined the mean change in SOFA score, the difference between the mean SOFA scores at 72 hours, and the mean SOFA score at baseline.

TABLE 1] Baseline Characteristics of HAT Therapy and Comparator Group

Characteristic	HAT Treatment (n = 68)	Comparator (n = 69)	*P*	OR	95% CI
Age	70 ± 12	67 ± 14	.17		
Race (white)	66 (97%)	65 (94%)	.68	0.49	0.2-2
Weight, kg	82 ± 27	82 ± 30	.37		
Sex (male)	32 (47%)	27 (39%)	.35	0.72	0.36-1.42
Comorbidities					
CAD	25 (37%)	21 (30%)	.43	0.75	0.37-1.5
Diabetes	24 (35%)	33 (48%)	.14	1.68	0.85-3.33
Dementia	7 (10 %)	4 (5.8%)	.33	0.53	0.15-1.9
Heart failure	18 (26%)	13 (19%)	.29	0.65	0.28-1.44
Malignancy	15 (22%)	11 (16%)	.36	0.67	0.30-1.6
COPD	23 (34%)	17 (25%)	.24	0.64	0.30-1.34
Cirrhosis	0 (0)	3 (2.2%)	.25	0.49	0.41-0.58
ESRD	3 (0.4%)	0 (0%)	1.2	0.48	0.40-0.57
CKD	10 (7%)	4 (2.9%)	.08	0.36	0.11-1.2
Morbid obesity (BMI > 40)	16 (23.5%)	13 (19%)	.5	0.75	0.33-1.71
Immunocompromised[a]	6 (8.8%)	5 (7.2%)	.73	0.87	0.23-2.8
Primary diagnosis					
Pneumonia	29 (43%)	30 (44%)	.92	1.03	0.53-2.03
Urosepsis	18 (26.5%)	25 (36%)	.21	1.58	0.76-3.3
Primary bacteremia	9 (13%)	11 (16%)	.65	1.24	0.48-3.23
GI/biliary	9 (13%)	8 (12%)	.8	0.66	0.31-2.4
Other	13 (19%)	9 (13%)	.33	0.63	0.25-1.6
Mechanical ventilation	34 (50%)	35 (51%)	.93	1.03	0.53-2
Vasopressors	56 (82%)	47 (68%)	.05	0.45	0.20-1.02
Acute kidney injury	54 (79%)	52 (75%)	.57	0.76	0.35-1.77
Positive blood cultures	22 (32%)	23 (33%)	.93	1.05	0.51-2.13
WBC × 10^9/L	16 ± 10	19 ± 9.7	.1		
Lactate (mM/L)	4.45 ± 3.5	4.8 ± 4.2	.49		
Creatinine (mg/dL)	2.1 ± 1.5	2 ± 1.51	.68		
Ascorbic acid level (mg/dL)[b]	0.52 ± 1	0.48 ± 0.4	.79		
Procalcitonin (ng/mL)	44 ± 72	23 ± 38	.61		
Thiamine (mg/dL)	193 ± 144	148 ± 53	.09		
Day 1 SOFA	8.3 ± 3	7.9 ± 3.5	.47		
APACHE II	24 ± 7.6	24.9 ± 8.7	.53		
APACHE IV	88 ± 28.3	87.5 ± 29.7	.84		
APACHE IV predicted mortality	34 ± 3	33.6 ± 2.6	.8		

APACHE = Acute Physiology and Chronic Health Evaluation; CAD = coronary artery disease; CKD = chronic kidney disease; ESRD = end stage renal disease; PLT = platelets; tBili = total bilirubin; SOFA = Sepsis-Related Organ Failure Assessment.
[a]HIV infection, neutropenia, posttransplantation, immunoglobulin deficiency etc.
[b]To convert ascorbic acid from mg/dL to μmol/L multiply by conversion factor 56.82.



No. at risk						
No steroids	25	12	4	2	2	1
Steroids	22	8	2	0	0	0
HAT	56	11	2	2	2	2

Figure 2 – *Cox proportional hazards and corresponding Kaplan–Meier survival curves (n = 103 patients with 3 factors; HAT therapy (blue line), comparator group patients who did (red line) and did not (gray line) receive corticosteroids; log rank P = .009. Cox proportional hazards analysis demonstrates an independent effect of HAT therapy on reversal of shock, P = .007 (Beta, 0.58, SE, 0.218, HR, 1.79, 95% CI, 1.17-2.75). HAT = Hydrocortisone, Ascorbic acid, Thiamine.*

There was no statistical difference found in the change in mean SOFA score (3.4 ± 4.4 vs 2.3 ± 5.2, $P = .18$).

Secondary End points

No significant differences in secondary end points and laboratory markers were obtained during the first 4 days of treatment between study arms (Table 2, Table 3). ICU mortality was 9% (6 patients) in the HAT arm and 14% (10 patients) in the comparator arm ($P = .37$, OR, 1.75, 95% CI, 0.59-5.1). Hospital mortality was 16.4% (11 patients) in the HAT arm and 19% (13 patients) in the comparator arm ($P = .65$. OR, 1.25, 95% CI, 0.5-2.97) (Figs 5, 6).

Renal Outcomes and Adverse Events

Renal outcomes were similar in both arms, with AKI occurring in 54 (79%) in the HAT arm and 52 patients (75%) in the comparator arm ($P = .68$, OR, 0.79, 95% CI, 0.35-1.77). Renal replacement therapy was required in 2 (3%) in the HAT arm and 8 patients (11%) in the comparator arm ($P = .098$, OR, 4.1, 95% CI, 0.84-20.3). Measurement of urinary oxalate on day 4 was not significant, with HAT arm 24-hour oxalate excretion 51 ± 35 mg/1.73 m^2 vs 40 ± 28 mg/1.73 m^2 in the

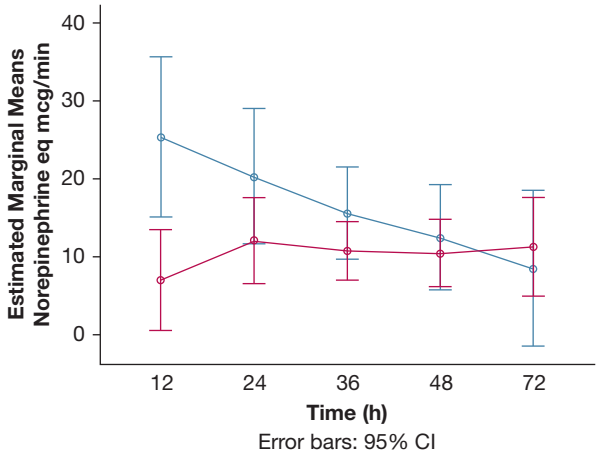


Figure 3 – *Graph displaying change in vasopressor dose in norepinephrine equivalents during the course of treatment in HAT arm (blue lines) and comparator arm (red lines) analysis of variance (ANOVA), F (1, 19 = 4.28, P = .052). SOFA = Sepsis-Related Organic Failure Assessment. See Figure 2 legend for expansion of other abbreviation.*

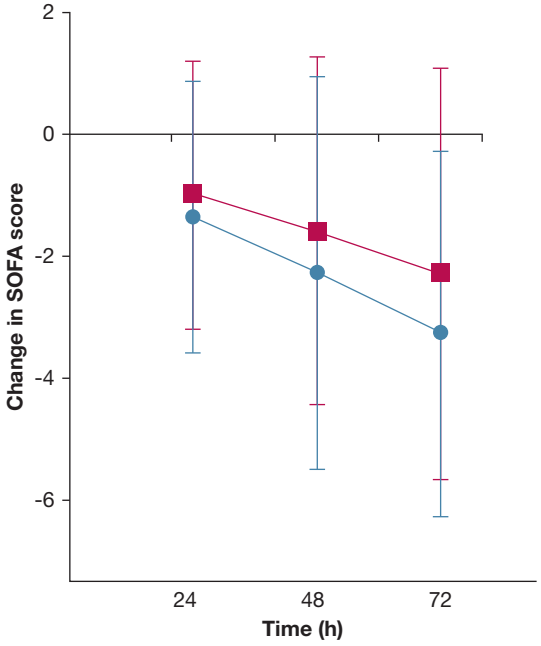


Figure 4 – *Graph of SOFA score kinetics during study period in HAT arm (blue line) and comparator arm (red line) analysis of variance (ANOVA), (F3, 103 = 1.3, P = .27). See Figure 2 and 3 legends for expansion of other abbreviations.*

TABLE 2] Laboratory Values and SOFA Score During Study Period

Laboratory Values	HAT Treatment (n = 68)		Comparator (n = 69)		*P*
WBC-initiation ($\times 10^9$/L)[a]	16 ± 10		19.0 ± 9.7		.18
WBC-24 h	16 ± 8.8		17.2 ± 8.2		.49
WBC-48 h	13.3 ± 7		14 ± 6.2		.61
WBC-72 h	12.8 ± 6		12.4 ± 6.4		.78
PLT-initiation ($\times 10^9$/L)[b]	233.41 ± 131.8		264.6 ± 147.15		.2
PLT-24 h	196.4 ± 127		216.36 ± 120.31		.31
PLT-48 h	172.12 ± 109.6		199.1 ± 112.6		.11
PLT-72 h	171.81 ± 103		193.5 ± 107.01		.1
Tbili-initiation (mg/dL)[c]	1.13 ± 1		1.44 ± 1.74		.32
Tbili-24 h	0.9 ± 0.6		1.24 ± 1.69		.21
Tbili-48 h	0.72 ± 0.6		0.9 ± 1.32		.52
Tbili-72 h	0.7 ± 0.72		0.71 ± 0.68		.58
PO/FiO-initiation[d]	267.2 ± 115.53		243.43 ± 127.35		.17
PO/FiO-24 h	287 ± 118.59		283.78 ± 132.6		.38
PO/FiO-48 h	288.54 ± 114.61		276.34 ± 119.22		.41
PO/FiO-72 h	265.42 ± 109.02		273.39 ± 127.46		.83
Lactate-initial[e]	4.45 ± 3.5		4.80 ± 4.2		.59
Lactate-24 h	2.39 ± 2.84		2.88 ± 3.87		.44
Lactate-48 h	2.5 ± 3.7		2.04 ± 2.34		.32
Lactate-72 h	2.01 ± 2.56		1.74 ± 2.57		.52
SOFA initial[f]	8.3 ± 3		7.9 ± 3.5		.34
SOFA-24 h	7.1 ± 3.35	n = 61	7 ± 3.38	n = 61	.62
SOFA-48 h	6.32 ± 3.82	n = 60	6.42 ± 3.6	n = 59	.83
SOFA-72 h	4.93 ± 3.14	n = 62	5.58 ± 3.78	n = 63	.51
SCr initial[g]	2.1 ± 1.5		2 ± 1.51		.82
SCr 24 h	1.74 ± 1.21		1.85 ± 1.6		.65
SCr 48 h	1.62 ± 1.32		1.8 ± 1.71		.53
SCr 72 h	1.47 ± 1.3		1.67 ± 1.71		.45
SCr at discharge	1.32 ± 1.13		1.37 ± 1.18		.78
Procalcitonin at enrollment	44 ± 72		23 ± 38		.61

See Table 1 legend for expansion of abbreviations.
[a-f]For repeated measurements, no statistically significant differences were found between groups by independent Student t test with Bonferroni correction. For SOFA calculations, "n" at each time interval includes patients alive and with all laboratory values available for calculation of SOFA score.

comparator arm, respectively ($P = .35$). No adverse events were noted that were deemed related to the study drug. One patient developed worsening hypoxia in the setting of severe COPD and gram-negative sepsis with mildly elevated methemoglobin levels with no evidence of hemolysis. This was reviewed by the adverse events committee and deemed unrelated to study treatment.

Discussion

This randomized double-blinded controlled study of HAT therapy demonstrated a marked acceleration in the reversal of shock. This effect remained significant after adjusting for corticosteroid administration in the comparator group, accounting for approximately 15% of the variability observed. This suggests both an independent and synergistic effect of AA in the reversal of shock and in augmenting the hemodynamic effects of corticosteroids.[5,21,22] This was in contrast to the recently published study by Fujii et al,[8] which showed no benefit. This may be due to differences in the patient population studied and trial design. Liberation from vasopressor support has numerous advantages, potentially preventing the immunosuppressive effects of catecholamines minimizing the risk of mesenteric, limb, and end-organ ischemia.[2,5,23]

TABLE 3] Treatment and Clinical Outcome

Treatments	HAT Treatment (n = 68)	Comparator (n = 69)	*P*	OR	95% CI
Days of HAT therapy or placebo	3.3 ± 0.8	3.25 ± 1	.94		
Fluid balance at 24 hours (mL/kg)	53 ± 26	46 ± 24.1	.09		
Fluid balance at 72 hours (mL/kg)	83 ± 97	80 ± 75	.82		
Vasopressors at time of enrollment	56 (82%)	47 (68%)	.05	0.45	0.2-1.02
Vasopressor initiated after study enrollment	4 (6%)	10 (14.5%)	.16	2.7	0.8-9.1
Renal replacement therapy for AKI	2 (3%)	8 (11.5%)	.1	4.1	0.84-20.3
Primary outcome					
Δ SOFA score at 72 hours	2.9 ± 3.3	1.93 ± 3.5	.1		
Duration of vasopressors, h	27 ± 22	53 ± 38	<.001		
Secondary outcomes					
Hospital mortality (%)	11 (16%)	13 (19.4)	.6	1.2	0.50-2.97
ICU mortality (%)	6 (9%)	10 (14%)	.3	1.7	0.59-2.63
Hospital LOS, d	11.5 ± 6.8	11 ± 6.2	.75		
ICU LOS, d	4.76 ± 4.3	4.66 ± 3.45	.88		
Procalcitonin clearance, %	63 ± 170	58 ± 66	.44		
Ventilator-free days	22 ± 6.2	22.4 ± 4.3	.63		
AKI	54 (79%)	52 (75%)	.57	0.76	0.35-1.77

AKI = acute kidney injury; LOS = length of stay. See Table 1 legend for expansion of other abbreviations.

AA possesses antioxidant, antiinflammatory, and immune-enhancing functions, while also serving as a co-factor in the synthesis of endogenous catecholamines, steroidogenesis, vasopressin synthesis, and enhancing adrenergic receptor activity.[24,25] Approximately 90% of septic shock patients have hypovitaminosis C, and 40% have AA deficiency. These rates are significantly higher than nonseptic critically ill patients.[26] The use of hydrocortisone in the treatment of septic shock has been controversial, with studies yielding mixed results.[3] Glucocorticoids and AA may synergistically protect against or reverse vascular endothelium dysfunction from damage due to endotoxins.[27]

In contrast to the Marik et al[5] and Fowler et al[6] studies, the current study did not demonstrate a difference in SOFA kinetics or PCT clearance. We postulate that this can potentially be attributed to less severity of AA hypovitaminosis (ORANGES = 21.7 ± 14.8 μmol/L, Marik et al[5] = 14.7 ± 11.8 μmol/L, Fowler et al[6] = 17.9

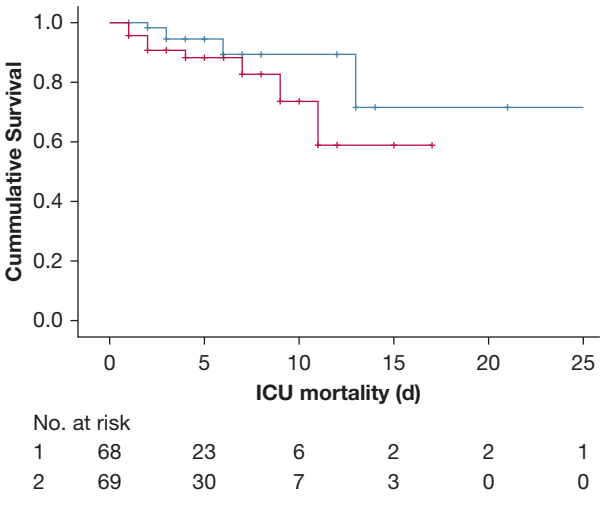


Figure 5 – *Kaplan-Meir survival curves of ICU mortality rate in days in HAT arm (blue lines) and comparator arm (red lines), P = .168. See Figure 2 legend for expansion of other abbreviation.*

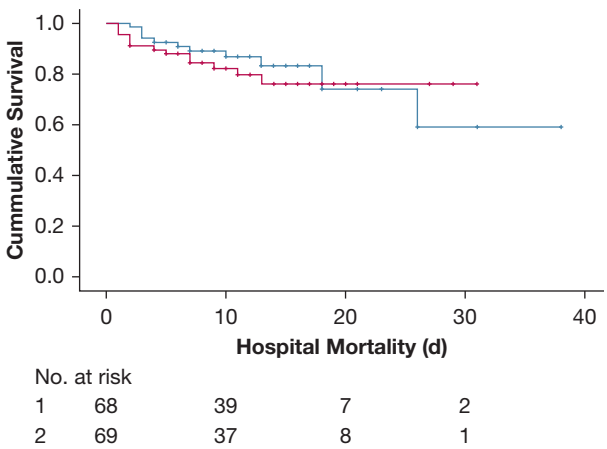


Figure 6 – *Kaplan-Meir survival curves of hospital mortality in days of HAT arm (blue lines) and comparator arm (red lines), P = .568.*

± 2.4 μmol/L) and shorter duration of HAT therapy in the current study.[5,6]

Administering AA is considered relatively safe; however, prolonged intake of high IV doses in the presence of impaired renal function increases the risk of oxalate kidney stones, resulting in nephropathy or death in rare cases.[24] Thiamine may reduce the risk of hyper-oxalosis because of its function as a cofactor in the oxidation of glyoxylate by the enzyme glyoxylate aminotransferase.[23] Additionally, correction of thiamine deficiency may help mitigate oxidative stress and inflammation, as shown in an animal model of sepsis.[28] Thiamine deficiency has been shown to occur in 10% to 70% of patients presenting with sepsis.[29] Although oxalate excretion was higher in the HAT therapy group, no significant differences were seen between groups or differences in the development of AKI. Therefore, short-term parenteral AA administration in patients with sepsis was safe from a renal standpoint.

The strengths of our study include that it was performed in a non-teaching community hospital setting with minimal resource utilization reflecting real-world clinical management. The relative weakness was its small, homogenous (primarily white) cohort size, limiting the ability to detect differences in hospital mortality and length of stay.

Conclusions

HAT therapy is safe and decreases the duration of shock in patients with sepsis. This effect appears to be due to the ascorbic acid component of HAT therapy rather than the mineralocorticoid effect of steroids alone. Further randomized trials are needed, with larger cohorts to determine whether HAT therapy translates to improved mortality or a decrease in ICU length of stay.

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