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Evaluating Vitamin C in Septic Shock: A Randomized Controlled Trial of Vitamin C Monotherapy*

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OBJECTIVES: To determine whether IV vitamin C therapy reduces 28-day mortality in patients with septic shock.

DESIGN: Multicenter, double-blinded, randomized controlled trial.

SETTING: One academic medical ICU and four community ICUs.

PATIENTS: Of 167 adult patients within 24 hours of vasopressor initiation for septic shock, 126 consented to participation, and 124 received study drug and were included in analysis.

INTERVENTIONS: IV vitamin C (10 mg/mL in normal saline) administered as a 1,000-mg bolus over 30 minutes followed by continuous infusion of 250 mg/hr for 96 hours or placebo of equal volumes of normal saline.

MEASUREMENTS AND MAIN RESULTS: Of 124 subjects receiving study drug and included in analysis, 60 received vitamin C and 64 placebo. The primary outcome of all-cause 28-day mortality (vitamin C, 26.7%; placebo, 40.6%; $p = 0.10$) was lower in the vitamin C arm but did not reach statistical significance. Initiation of renal replacement therapy was higher in the vitamin C arm (vitamin C, 16.7%; placebo, 3.3%; $p = 0.015$), as was volume of fluid administration within 6 hours of study drug initiation (vitamin C, 1.07 L; placebo, 0.76 L; $p = 0.03$). There were no statistically significant differences in other secondary outcomes. In post hoc subgroup analysis, there was a decrease in 28-day mortality in the vitamin C arm among patients requiring positive-pressure ventilation at the time of enrollment (vitamin C, 36.3%; placebo, 60.0%; $p = 0.05$). This trial is registered at clinicaltrials.gov under identifier NCT03338569.

CONCLUSIONS: Vitamin C monotherapy failed to significantly reduce mortality in septic shock patients as hypothesized. Our findings do not support its routine clinical use for this purpose.

KEY WORDS: ascorbic acid, corticosteroids, mortality, sepsis, septic shock, vitamin C

Sepsis and septic shock are common reasons for admission to the ICU with 49 million cases and 11 million sepsis-associated deaths each year worldwide (1). A therapeutic role for vitamin C (ascorbic acid) supplementation in the treatment of sepsis and septic shock has been suggested for its anti-inflammatory and antioxidant properties (2–4), and in 2017, an observational before-and-after study reported a remarkable survival benefit with the use of a combination of hydrocortisone, vitamin C (ascorbic acid), and thiamine (HAT therapy) (5). Following this, several randomized controlled trials of HAT therapy (6–11) or vitamin C and thiamine in combination (12) for sepsis and septic shock have been conducted, but these studies did not show the same dramatic effects. Although modest improvements in time to reversal of shock and organ dysfunction were occasionally noted, no study demonstrated a statistically

*See also p. 897.

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significant survival benefit (14–16). One study of vitamin C alone for treatment of patients with sepsis-induced acute respiratory distress syndrome (ARDS) did show a reduction in all-cause 28-day mortality in the vitamin C arm with a *p* value of 0.03; however, this was one of numerous secondary outcomes that obfuscates the statistical significance of the result (13).

Despite the existing trials of HAT therapy, questions about vitamin C as adjuvant monotherapy remain. First, prior investigations into vitamin C alone have been limited to small pilot studies and unblinded trials (2–4), and although the interactions between constituents in HAT therapy have been assumed to be synergistically positive (5), this has never been proven. Unexpected interactions may cancel out or otherwise convolute effects, thus limiting the ability to judge the performance of individual components from trials of a combined regimen. Second, randomized controlled trials of adjuvant corticosteroids (14–16) for septic shock have recently demonstrated clinical benefit with a consistent signal of decreased duration of vasopressor therapy, which has the potential to confound any positive results from prospective investigations of HAT therapy.

In designing our trial, we noted pharmacokinetic studies of vitamin C, which have shown that trough levels of the drug occurring with bolus dosing may result in periodic hypovitaminosis, whereas continuous vitamin C delivery resulted in more stable serum levels (17). We, therefore, designed the Evaluating Vitamin C in SepTic Shock trial to assess the effect of continuously infused vitamin C monotherapy on all-cause ICU and 28-day mortality in patients with septic shock.

MATERIALS AND METHODS

Study Design and Setting

This was an investigator-initiated, randomized, placebo-controlled, double-blinded study examining the effect of IV vitamin C on outcomes in patients with septic shock. The study was performed in five hospitals, including one tertiary academic medical center and four nonteaching community hospitals (**Table S1**, http://links.lww.com/CCM/G946) between January 2018 and June 2020.

Study Population

Adult patients within 24 hours of onset of septic shock were eligible for enrollment. Main exclusion criteria were inability to obtain written consent and initiate study drug within 24 hours of eligibility, known history of nephrolithiasis, and shock occurring immediately following cardiac arrest. See **Figure 1** and the **Supplemental Methods section** (http://links.lww.com/CCM/G946) for complete inclusion and exclusion criteria and definitions.

Intervention

After giving written informed consent, subjects were randomized to two parallel groups receiving either vitamin C (10-mg/mL solution in normal saline) administered as a 1,000-mg bolus over 30 minutes followed by continuous infusion of 250 mg/hr or placebo of normal saline. The study infusion ended after 96 hours or the subject remaining vasopressor-free for 24 consecutive hours, whichever occurred sooner.

Outcomes

The primary outcome for this study was all-cause 28-day mortality. Secondary outcomes included all-cause ICU mortality, time to lactate clearance, need for renal replacement therapy (RRT), changes in severity-of-disease index scores, and durations of ICU and hospital stay following study drug initiation. The Supplemental Methods section (http://links.lww.com/CCM/G946) provides a full list of secondary outcomes.

Sample Size

Based on a prior retrospective study (5) showing a greater than 30% mortality reduction (risk difference) with vitamin C therapy, we anticipated at least a 20% reduction in absolute mortality between the groups at 28 days. Institutional data from participating centers suggested historical mortality rates for septic shock of approximately 30%. Using this baseline mortality rate and employing a two-tailed alpha of 0.05, we calculated that 124 subjects (an average of 62 per group) would be needed to detect a 20% decrease in absolute mortality with 80% power.

Randomization and Blinding

Participants, their families, study staff, and treatment teams were all blinded to group allocation. Site stratified randomization strategy and criteria for unblinding are given in the Supplemental Methods section (http://links.lww.com/CCM/G946).

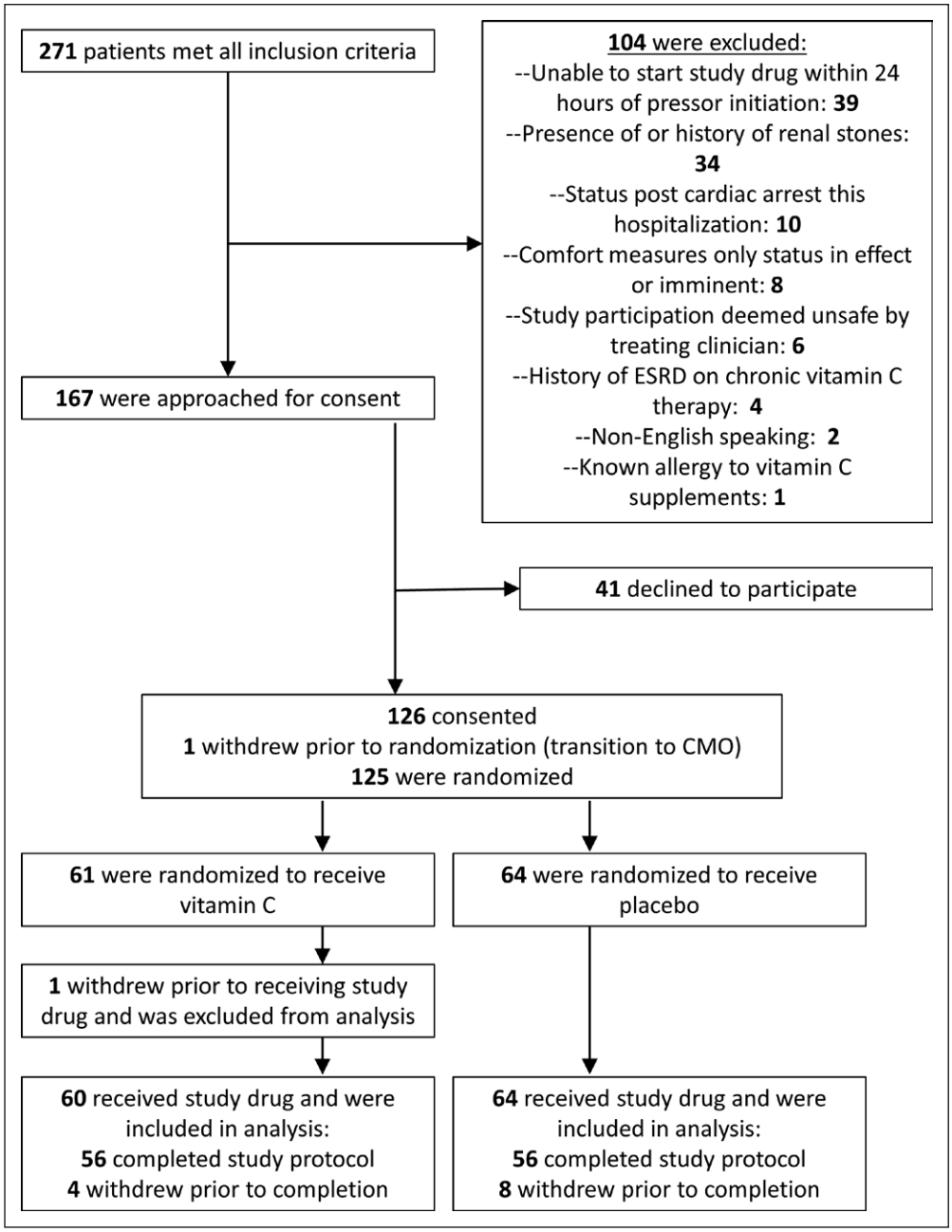

Figure 1. Subject flow through the trial: flow diagram showing subject screening, recruitment, randomization, and analysis. All subjects who withdrew prior to completing the protocol were withdrawn due to transition to comfort measures only (CMO), except one in the vitamin C group who was withdrawn due to transfer to a hospital not actively participating in the study. In almost all cases when a patient was excluded due to inability to initiate study drug within 24 hr of pressor initiation (39 excluded patients), this stemmed from the patient lacking decisional capability and inability to obtain written informed consent from the patient's legally authorized representative within the designated timeframe. ESRD = end-stage renal disease.

Data Collection and Statistical Analysis

Analysis was performed based on intention to treat. For categorical values, statistical significance was assessed using a chi-square test or Fisher exact test. For continuous variables, the median test was used. Full details of data collection, statistical analysis, and subgroup analyses are provided in the Supplemental Methods section (http://links.lww.com/CCM/G946).

Oversight and Data Availability

This study was approved by the institutional review board of the University of Minnesota, as well as the institutional review boards pertaining to each individual study site (Table S1, http://links.lww.com/CCM/G946). An independent data and safety monitoring board consisting of two intensive care physicians and one statistician who were not otherwise involved with the study met at least every 6 months and oversaw study activities. This trial is registered at clinicaltrials.gov under identifier NCT03338569. Full details of plans for data sharing can be found in the Supplemental Methods section (http://links.lww.com/CCM/G946).

RESULTS

Study Population

A total of 271 patients met inclusion criteria. Of these, 104 were excluded leaving 167 who were approached for consent. One hundred twenty-six subjects agreed to participate and were enrolled. One subject withdrew from the study following enrollment but prior to randomization, and one subject withdrew following randomization but prior to initiation of study drug. This resulted in 124

TABLE 1.
Baseline Characteristics of Subjects Included in Analysis

Characteristic	Vitamin C Group ($n = 60$)	Placebo Group ($n = 64$)	p
Age, yr, median (IQR)	68.9 (60.1–79.9)	73.0 (60.8–80.0)	0.47
Sex male, *n* (%)	30 (50)	33 (52)	0.71
Race, *n* (%)			
Asian	2 (3.3)	2 (3.1)	0.95
Black or African American	0 (0.0)	2 (3.1)	0.50
White	58 (96.7)	59 (91.8)	0.28
Unknown or declined to answer	0 (0.0)	1 (2)	> 0.99
Ethnicity, *n* (%)			
Latino/Latina	0 (0.0)	0 (0.0)	> 0.99
Baseline Sequential Organ Failure Assessment score, median (IQR)	10 (7–11)	9 (7–12)	0.63
Baseline Acute Physiology and Chronic Health Evaluation II score, median (IQR)	22 (16.5–28)	23 (17–28.5)	0.38
Source of infection, *n* (%)			
Pulmonary	13 (21.6)	16 (25.0)	0.66
Urinary	16 (26.6)	14 (21.9)	0.53
Gastrointestinal/biliary	12 (20.0)	14 (21.9)	0.80
Soft tissue/skin	4 (6.7)	7 (10.9)	0.40
Primary bacteremia	6 (10.0)	4 (6.2)	0.44
Endocarditis	1 (1.7)	2 (3.1)	0.60
Bacterial meningitis	1 (1.7)	0 (0.0)	0.48
Other/unknown	8 (13.3)	7 (10.9)	0.68
Time to antibiotics,[a] hr, *n* (%)			
< 1	32 (53.3)	28 (43.8)	0.29
1–3	22 (36.7)	24 (37.5)	0.92
3–6	5 (8.3)	9 (14.1)	0.31
> 6	2 (3.3)	3 (4.7)	0.70
Total fluid administered preenrollment (mL), median (IQR)	4,270 (3,305–5,781)	3,810.5 (3,000–5,800)	0.40
Positive-pressure ventilation (noninvasive or via endotracheal tube) at enrollment, *n* (%)	34 (56.7)	37 (57.8)	0.90
Received steroids, *n* (%)	30 (50.0)	42 (65.6)	0.08
Received thiamine, *n* (%)	4 (6.7)	5 (7.8)	0.81
Time from pressor initiation to study drug initiation (hr), median (IQR)	11.4 (5.4–17.3)	8.8 (5.4–17.4)	0.21

IQR = interquartile range.

[a]Defined as the amount of time between the patient meeting criteria for sepsis (either two or more systemic inflammatory response syndrome criteria positive or decrease from baseline Sequential Organ Failure Assessment score of 2 or more) and administration of antibiotics.

subjects receiving study drug: 60 in the vitamin C cohort and 64 in the placebo cohort. Of these subjects, 112 completed the protocol and 12 were withdrawn prematurely from the drug portion of the study (11 upon transition to comfort measures only and one on transfer to a nonparticipating hospital). All of these 12

subjects received at least one dose of study drug and were included in the final analysis (Fig. 1).

Baseline characteristics between the two groups including demographics, baseline laboratory values, initial disease acuity, time to antibiotics, preenrollment fluid administration, ventilatory needs, and past medical history were similar (**Table 1**; and **Table S2**, http://links.lww.com/CCM/G946). Pneumonias and infections of the gastrointestinal/biliary system and urinary system were the predominant sources of sepsis in both groups with similar distribution of infectious sources between the groups. Although the source of septic shock was not able to be identified in all cases, the rates at which this occurred (13.3% of vitamin C group subjects and 10.9% of placebo group) were similar to those observed in prior sepsis epidemiological studies (18, 19). The time from vasopressor administration to study drug initiation was similar in the vitamin C and placebo groups with median times of 11.4 hours (interquartile range [IQR], 5.4–17.3 hr) versus 8.8 hours (IQR, 5.4–17.4 hr), respectively ($p = 0.21$). Thirty patients (50%) received steroids in the vitamin C group, whereas 42 (65.6%) received steroids in the placebo group ($p = 0.08$).

Primary and Secondary Outcomes

Sixteen of 60 subjects (26.7%) in the vitamin C arm had died at 28 days versus 26 of 64 subjects (40.6%) in the placebo arm ($p = 0.10$) (Table 2). Kaplan-Meier survival analysis showed a similar result with a log-rank score of 0.10 (**Fig. 2**). There was also no statistically significant difference between the two arms in ICU mortality (23.3% vs 31.1%; $p = 0.32$).

Improvement in Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores over the 96-hour study period was similar between arms, as were time to lactate clearance, vasopressor duration, and mechanical ventilation duration (Table 2). Subjects in the vitamin C arm received more IV fluids within the first 6 hours after study drug initiation (1.07 L [IQR, 0.72–1.64 L] vs 0.76 L [IQR, 0.36–1.26 L]; $p = 0.03$); however, the clinical significance of this 310-mL difference is unclear, and by 24 hours, there were no statistically significant differences in total volume administered (3.59 L [IQR, 2.52–5.02 L] vs 3.37 L [IQR, 1.98–4.70 L]; $p = 0.47$) nor net total fluid balance (2.12 L [IQR, 1.10–3.59 L] vs 2.05 L [IQR, 1.24–3.11 L]; $p = 0.93$). ICU length of stay (2.9 d [IQR, 1.8–7.5 d] vs 2.6 d [IQR, 1.5–5.3 d]; $p = 0.47$) and hospital length of stay (8.9 d [IQR, 4.0–20.0 d] vs 6.3 d [IQR, 3.8–12.5 d]; $p = 0.15$) following study drug initiation were similar between the two arms. Although there was no statistically significant difference between the arms in serum creatinine changes over the study drug period, there was an increased need for RRT in the vitamin C arm compared with the placebo arm (16.7% vs 3.3%; $p = 0.02$).

To further characterize the increased use of RRT in the vitamin C arm, we performed a post hoc analysis comparing the time of study drug initiation with the time that RRT was planned or initiated (**Table S3**, http://links.lww.com/CCM/G946). In the vitamin C group, six of the 10 patients receiving RRT already had it established or immediately planned prior to initiation of study drug. In the placebo group, one of the two patients did. Only four patients required unplanned initiation of RRT post study drug administration in the vitamin C group compared with one patient in the placebo group ($p = 0.17$). Additionally, although there were no immediate plans for RRT, all five of these patients had oliguric (less than 500-mL urine output over 24 hr) acute kidney injury prior to study initiation.

Subgroup Analysis by Corticosteroid Administration

Corticosteroids were given to 72 subjects as part of usual clinical care. Overall, there were no statistically significant differences in 28-day or ICU mortality between the vitamin C and placebo arms in either the steroid or nonsteroid subgroups (**Tables S4** and **S5**, http://links.lww.com/CCM/G946). There was an increased incidence in requirement of RRT in the vitamin C arm relative to that of the placebo arm in both the steroid (23.3% vs 4.8%; $p = 0.02$) and nonsteroid (10.0% vs 0%; $p = 0.27$) subgroups. These findings reflect the increased incidence of RRT requirement in the vitamin C arm overall. Otherwise, there were no significant differences between the vitamin C and placebo arms in acuity score improvement, duration of pressors, duration of mechanical ventilation, or lactate clearance within each subgroup (Tables S4 and S5, http://links.lww.com/CCM/G946). In the steroid-receiving

TABLE 2.
Primary and Secondary Outcomes

Outcome	Vitamin C Group	Placebo Group	*p*
Primary outcome			
28-d mortality, *n* (%)	16 (26.7) (*n* = 60)	26 (40.6) (*n* = 64)	0.10
Secondary outcomes			
ICU mortality, *n* (%)	14 (23.3) (*n* = 60)	20 (31.1) (*n* = 64)	0.32
Organ failure scores			
Paired improvement in Sequential Organ Failure Assessment score,[a] median (IQR)	3.5 (1–6) (*n* = 58[b])	4 (1–6) (*n* = 61[b])	0.68
Paired improvement in Acute Physiology and Chronic Health Evaluation II score,[a] median (IQR)	4.5 (2–9) (*n* = 58[b])	7 (–2 to 11) (*n* = 61[b])	0.22
Renal function outcomes			
Paired improvement in creatinine (mg/dL),[a] median (IQR)	0.4 (0–0.7) (*n* = 49[b–d])	0.3 (–0.1 to 0.7) (*n* = 56[b–d])	0.55
Renal replacement therapy required during 96-hr study period, *n* (%)	10 (16.7) (*n* = 60[d])	2 (3.3) (*n* = 60[d])	0.02
Lactate clearance,[e] *n* (%)			
Within 24 hr	12 (27.9) (*n* = 43[f])	13 (28.9) (*n* = 45[f])	0.92
Within 48 hr	16 (37.2) (*n* = 43[f])	18 (40.0) (*n* = 45[f])	0.79
Within 72 hr	18 (41.9) (*n* = 43[f])	18 (40.0) (*n* = 45[f])	0.86
Within 96 hr	18 (41.9) (*n* = 43[f])	19 (42.2) (*n* = 45[f])	0.86
Hospital length of stay following study drug initiation (d), median (IQR)	8.9 (4.0–20.0) (*n* = 60)	6.3 (3.8–12.5) (*n* = 64)	0.15
ICU length of stay following study drug initiation (d), median (IQR)	2.9 (1.8–7.5) (*n* = 60)	2.6 (1.5–5.3) (*n* = 64)	0.47
Duration of pressors following initiation of study drug (hr), median (IQR)	27.7 (13.6–47.6) (*n* = 60)	27.1 (16.4–45.2) (*n* = 64)	0.79
Duration of mechanical ventilation following initiation of study drug (hr), median (IQR)	0 (0–60) (*n* = 60)	5 (0–48) (*n* = 64)	0.45
Total IV fluid administration (L), median (IQR)			
6 hr after study drug initiation	1.07 (0.72–1.64) (*n* = 60)	0.76 (0.36–1.26) (*n* = 64)	0.03
24 hr after study drug initiation	3.59 (2.52–5.02) (*n* = 60)	3.37 (1.98–4.70) (*n* = 64)	0.47
Fluid balance (total intake minus output, L), median (IQR)			
24 hr after study drug initiation	2.12 (1.10–3.59) (*n* = 60)	2.05 (1.24–3.11) (*n* = 64)	0.93
96 hr after study drug initiation	2.87 (1.70–4.30) (*n* = 60)	2.69 (0.69–4.84) (*n* = 64)	0.53

IQR = interquartile range.

[a]Baseline-to-final measured value within 96-hr study period.

[b]Patients for whom only baseline values were obtained were excluded from this analysis.

[c]Patients receiving renal replacement therapy at any point during the 96-hr study period were excluded from this analysis.

[d]Patients with dialysis dependence prior to hospital admission were excluded from this analysis.

[e]Clearance is defined as reaching a serum lactate level of 2.0 mmol/L or less.

[f]Patients whose serum lactate level had cleared prior to study drug initiation, and those for whom only a baseline value was obtained were excluded from this analysis.

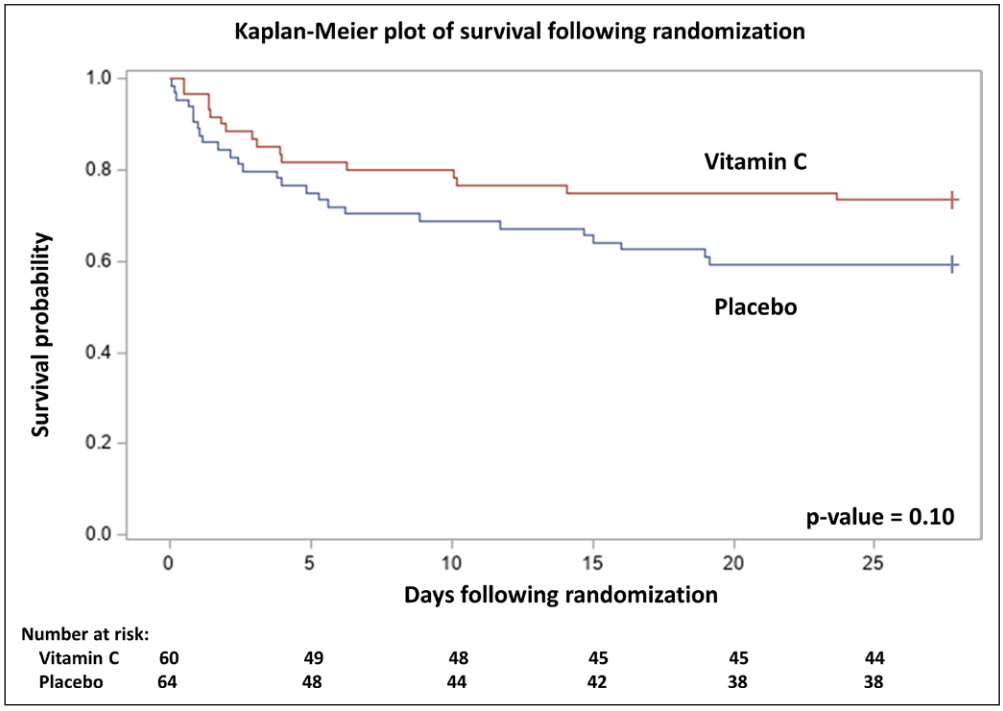

Figure 2. Comparison of survival in the 28-d study follow-up period: Kaplan-Meier survival analysis comparing survival over 28 d following study drug initiation for patients in the vitamin C and placebo groups. Log-rank testing *p* value is 0.10.

subgroup, there was a trend toward increased hospital length of stay in the vitamin C arm compared with the placebo arm (10.8 d [IQR, 4.2–20.5 d] vs 6.3 d [IQR, 2.6–13.0 d]; $p = 0.06$), which was not seen in the non-steroid subgroup (7.9 d [IQR, 3.8–19.7] vs 6.7 d [IQR, 4.7–12.1]; $p = 0.58$). ICU length of stay did not significantly differ between the arms in either subgroup.

Subgroup Analyses by Respiratory Status and Severity Index Score at Enrollment

In light of recent findings of the Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury (CITRIS-ALI) trial (13), we wished to further investigate the effects of vitamin C on subjects with respiratory failure. Although we did not collect data for all criteria necessary to determine an ARDS diagnosis, we were able to stratify our study population by the presence of positive-pressure ventilation at enrollment (either mechanical ventilation or non-invasive support) and by the presence of hypoxemic respiratory failure at enrollment, defined as positive-pressure ventilation and a Pao_2/Fio_2 ratio of 300 or less. A post hoc subgroup analysis of 28-day and ICU mortality showed a statistically significant reduction in 28-day mortality in patients with positive-pressure ventilation at baseline (36.3% vs 60.0%; $p = 0.05$); however, the reduction observed in patients with hypoxemic respiratory failure did not achieve statistical significance (33.3% vs 56.0%; $p = 0.11$), nor did reductions in ICU mortality (**Table 3**). Given the post hoc nature of this analysis, these results should be interpreted as hypothesis generating only.

To investigate whether respiratory status at enrollment is simply a surrogate for disease severity in the above analysis, we dichotomized the total population by enrollment SOFA and APACHE II scores and compared these populations with those obtained by respiratory status stratification using Spearman rank correlation testing. We found low-to-moderate correlation in all comparisons (**Table S6**, http://links.lww.com/CCM/G946). To further explore the degree to which severity of illness at enrollment could influence the efficacy of vitamin C therapy, we performed post hoc subgroup analyses of 28-day and ICU mortalities using the stratifications by enrollment severity index scores described above (**Tables S7** and **S8**, http://links.lww.com/CCM/G946). Although greater reductions in absolute mortality were seen in the groups with higher acuity, the differences were not statistically significant.

Adverse Events

Overall, 27 adverse events were reported, 15 in the vitamin C arm and 12 in the placebo arm. Distribution of these events by system and event type shows no significant differences between the vitamin C and placebo arms (**Table S9**, http://links.lww.com/CCM/G946). Most events were attributed to sequalae of septic shock. Only three events were reported as being possibly related to study drug: one report of nausea (mild severity, vitamin C arm), one report of bradycardia (mild severity, placebo arm), and one report of loose stools (moderate severity, placebo arm).

TABLE 3.
Post Hoc Subgroup Analysis of Mortality Outcomes by Positive-Pressure Ventilation Status and Presence of Acute Hypoxemic Respiratory Failure at Enrollment

	Stratification by Positive-Pressure Ventilation[a] Status at Enrollment						Stratification by Presence of Hypoxemic Respiratory Failure[b] at Enrollment					
	Positive-Pressure Ventilation Needed at Enrollment			Positive-Pressure Ventilation Not Needed at Enrollment			Hypoxemic Respiratory Failure Present at Enrollment			Hypoxemic Respiratory Failure Not Present at Enrollment		
Outcome	Vitamin C Group ($n = 33$)	Placebo Group ($n = 35$)	p	Vitamin C Group ($n = 27$)	Placebo Group ($n = 29$)	p	Vitamin C Group ($n = 24$)	Placebo Group ($n = 25$)	p	Vitamin C Group ($n = 36$)	Placebo Group ($n = 39$)	p
28-d mortality, *n* (%)	12 (36.3)	21 (60.0)	0.05	4 (14.8)	5 (19.2)	> 0.99	8 (33.3)	14 (56.0)	0.11	8 (22.2)	12 (30.8)	0.40
ICU mortality, *n* (%)	10 (30.3)	17 (48.6)	0.12	4 (14.8)	3 (10.3)	0.70	7 (29.2)	11 (44.0)	0.28	7 (19.4)	9 (23.1)	0.70

[a]Positive-pressure ventilation provided by either noninvasive positive-pressure ventilation or mechanical ventilation.
[b]Acute hypoxemic respiratory failure defined as Pao_2/Fio_2 ratio less than 300 and need for positive-pressure ventilation with positive end-expiratory pressure or expiratory positive airway pressure of at least 5 cm H_2O.

DISCUSSION

In this trial of IV vitamin C therapy for septic shock, the observed reduction in absolute risk of 28-day mortality in the experimental arm of 13.9% (p = 0.10) did not meet the primary endpoint of reducing absolute 28-day mortality by 20% as hypothesized. Analysis of our secondary outcomes showed a modest increase in fluid administered within 6 hours of study drug initiation in the vitamin C arm that reached statistical significance but is of unclear clinical significance and statistically higher incidence of RRT use in the vitamin C arm. Post hoc analysis examining the relative times of study drug initiation and RRT initiation indicates that the majority of patients requiring RRT in the vitamin C group had it initiated or planned prior to study drug initiation. This suggests that vitamin C was noncausal; however, we cannot assess the extent to which this difference between the groups may have influenced other outcomes.

We did not note any statistically significant differences in ICU mortality, improvements in SOFA or APACHE II scores between the groups, time to resolution of shock, time to lactate clearance, or duration of ICU or hospital stay; however, attrition bias due to uneven mortality between the groups may have reduced any potential differences in the latter four outcomes. Also, because SOFA and APACHE II scores are routinely only determined once per day, this metric may not fully appreciate precipitous deterioration of status leading to death.

We attempted to determine whether there may be some synergistic effect between vitamin C and steroids by performing a subgroup analysis comparing mortality between arms in subgroups of patients receiving or not receiving steroids. In the subgroup of patients receiving steroids, the observed reductions in absolute 28-day and ICU mortality were greater than those in the full study cohort (14.3% and 11.4%, respectively); however, statistical significance was not reached. Additionally, the use of steroids was not protocolized but rather at the discretion of the treating provider, which may introduce selection bias.

Several trials of vitamin C-based therapies for sepsis and septic shock have recently been completed. Among trials of HAT therapy or vitamin C and thiamine, the maximum reduction in 28- or 30-day absolute mortality observed has been 7.5% (9), and none have shown a statistically significant reduction in mortality (6, 8–12). Individual trials of HAT therapy have suggested a reduction in 28-day mortality when the therapy is initiated within 48 hours of onset of sepsis (9), and quicker resolution of shock associated with HAT therapy (4, 7, 10); however, these findings have not been uniformly reproduced.

The CITRIS-ALI trial of vitamin C monotherapy for patients with sepsis and acute lung injury demonstrated a reduction in 28-day absolute mortality of 16.6% ($p = 0.03$) (13); however, this was one of multiple secondary outcomes that obfuscates its statistical significance, and the primary outcomes of reductions in SOFA score and plasma inflammatory markers were not met. Subgroup analysis of patients requiring positive-pressure ventilation in our study similarly suggested a heightened mortality benefit for this group relative to the general study population, but potential conclusions from this analysis are tempered by its post hoc nature. Additional trials of vitamin C for patients with septic shock and sepsis-induced respiratory dysfunction employing short-term mortality as a primary outcome could further inform whether vitamin C carries an enhanced therapeutic effect for this population.

Our trial had several limitations. Although it benefitted from its multicenter design, all included centers were in a single geographical area, and our enrollment demographics reflected this with significant underrepresentation of non-White subjects. This limits the generalizability of our findings. Second, the size of our study population was chosen based on a large survival benefit observed in a retrospective study (5) that has not been reproduced in prospective trials. Our study is, therefore, underpowered to detect potentially smaller differences between the groups. Third, we did not measure serum vitamin C levels, so we are unable to assess the degree of preexisting hypovitaminosis in study subjects nor the degree to which vitamin C levels were increased by supplementation. However, prior studies have suggested that even patients with normal vitamin C levels at admission become deficient with onset of septic shock (20). Fourth, although we enrolled subjects within 24 hours of vasopressor initiation, we were frequently unable to assess the amount of time a subject may have been in untreated shock prior to vasopressor initiation, leading to immeasurable variations in the time between shock onset and study drug initiation. Fifth, there was a statistically significant difference in RRT use between the arms of our study. Although RRT was underway for many of these subjects prior to study drug initiation, it is unclear the extent to which this may have influenced other outcomes.

CONCLUSIONS

Vitamin C monotherapy failed to significantly reduce mortality in septic shock patients as hypothesized. Our findings do not support its routine clinical use for this purpose.

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