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Early administration of vitamin C in patients with sepsis or septic shock in emergency departments: a multicenter, double-blind, randomized controlled trial: the C-EASIE trial

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Abstract

Background Sepsis and septic shock are associated with high mortality and morbidity despite adequate standard care. Vitamin C deficiency is a common, potentially reversible, contributor to morbidity and mortality in sepsis. Previous studies have shown mixed and conflicting results. Our study aimed to determine the potential benefit of early administration (within 6 h after admission) of vitamin C in patients with sepsis or septic shock.

Methods This was a phase 3b prospective, multicenter, double-blinded, randomized placebo-controlled trial. Participants were enrolled in the Emergency Departments of 8 hospitals throughout Belgium. Patients were randomized to receive 1.5 g of vitamin C, or matching placebo, every 6 h for 4 days. The primary outcome was the average post-baseline patient Sequential Organ Failure Assessment (SOFA) score on day 2 to 5. Key secondary outcomes were the maximum SOFA score, 28-day mortality and length of ICU and hospital stay.

Results A total of 300 patients were recruited between June 4th, 2021, and August 19th, 2023. 292 patients, of which 147 were assigned to the vitamin C and 145 to the placebo group, completed the trial and were included in the analysis. The primary outcome (vitamin C, 1.98; placebo, 2.19) was 8.7% lower in the vitamin C group, but not significantly (ratio 0.91, 95% CI 0.77 to 1.08, $P=0.30$). In a planned subgroup analysis, patients with a baseline SOFA score of 6 or above had a significant lower average post-baseline SOFA score in the vitamin C group (ratio 0.76, 95% CI 0.86 to 0.99, $P=0.042$). Findings were similar in the two groups regarding secondary outcomes and adverse events, except for a lower probability of being on renal replacement therapy in the vitamin C group of the per protocol analysis (ratio 0.28, 95% CI 0.078 to 1.0, $P=0.05$).

Conclusions Early treatment with vitamin C did not result in a statistically significant reduction in organ dysfunction. Therefore, this study does not support the use of vitamin C in sepsis patients.

Trial registration: ClinicalTrials.gov Identifier: NCT04747795. Registered 4 February 2021.

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Key Points

Question Does early treatment with vitamin C lead to a less severe disease course in patients with sepsis or septic shock?

Findings In this randomized clinical trial that included 292 patients, treatment with intravenous vitamin C compared to placebo did not result in a lower average post-baseline patient Sequential Organ Failure Assessment (SOFA) score on day 2 to 5 (1.98 vs 2.19), except for a subgroup of patients with a baseline SOFA score of 6 or above.

Meaning Early treatment with vitamin C did not result in a significant improvement of the disease course.

Keywords Sepsis, Septic shock, Vitamin C, Ascorbic acid, C-EASIE

Background

Sepsis is a life-threatening condition characterized by a dysregulated body's response to infection causing organ dysfunction. It is the primary cause of death from infection, especially if not recognized and treated timely [1]. Current practice guidelines, based on the Surviving Sepsis Campaign, focus on early identification and appropriate management in the initial hours. It encourages clinicians to quickly obtain blood cultures, administer broad spectrum antibiotics, start adequate fluid resuscitation, measure lactate, and begin vasopressors if clinically indicated [2]. Despite implementation of these guidelines, mortality is still high. A recent meta-analysis reported a 30-day mortality of 37.2% and 24.4% for septic shock and sepsis, respectively. [3]

This has led to the investigation of targeted agents that limit the inflammatory cascade, such as vitamin C. In addition to its antioxidant and anti-inflammatory functions, vitamin C is also an essential cofactor for the metallo-enzymes involved in the biosynthesis of vasoactive catecholamines and vasopressin and may thus support endogenous vasopressor synthesis [4, 5]. It is known from previous research that critically ill patients, including those with sepsis, have significant lower vitamin C plasma levels [6–8].

Over the last decades there has been an upsurge in clinical trials evaluating vitamin C alone or as part of HAT therapy in patients with sepsis and septic shock. Initially mixed but promising results were found. Unfortunately, all the following randomized controlled trials (RCT) of HAT therapy, vitamin C and thiamine in combination or vitamin C alone did not show any significant benefit [7–23].

However, early administration of vitamin C after the onset of sepsis might be more effective as it may avoid the development of multi-organ dysfunction by preventing microvascular dysfunction, mitochondrial injury, and oxidative stress [4, 5, 16]. Nevertheless, most previous studies were conducted in intensive care units (ICU) which resulted in a significant delay, an average up to 12 h after ICU admission, in the administration of vitamin C [12, 13, 15, 17, 21–23]. This may have reduced the effectiveness of the intervention. Furthermore, in most trials, only patients with septic shock were included [12, 15, 16, 18–20, 22, 23]. By including patients at an earlier stage of disease, a more rapid solution of shock and less deterioration from sepsis to septic shock could be expected from vitamin C supplementation, hereby reducing morbidity and mortality. Therefore, the aim of this trial was to evaluate the effects of early administration, within 6 h after arrival in the emergency department (ED), of vitamin C in patients with sepsis or septic shock.

Methods

Trial design

This is a prospective, multicenter double-blinded randomized placebo-controlled trial conducted in 8 Belgian hospitals coordinated by the University hospitals Leuven, Belgium. The protocol (Supplementary Material file 1) was publicly registered (ClinicalTrials.gov: NCT04747795) and published [24]. The trial protocol was approved by a central ethics committee and the Belgian Federal Agency for Medicines and Health Products.

Participants

Patients aged 18 years or older admitted to the ED with a suspected infection and a National Early Warning Score (NEWS) ≥ 5 were eligible for the trial. Suspected infection was defined as the combination of antibiotic administration and body fluid cultures within the first 6 h after ED presentation. Exclusion criteria included contraindications to vitamin C therapy, such as a known allergy, or a 'do no intubate' or 'comfort measures only' status. Further details regarding in- and exclusion criteria are provided in Supplementary Material file 1.

All patients or their legally acceptable representative (LAR) provided written informed consent. To ensure timely initiation of medication administration (within 6 h), a process of delayed consent was employed, enrolling patients in the clinical trial and obtaining consent as soon as practical from the patient or their LAR.

Randomization and masking

Patients were randomly assigned to one of two groups in a 1:1 allocation ratio stratified by site through the digital platform Randomize.net. Block size was 4. Ardena Gent NV, a Drug Product Development & Manufacturing firm blinded, packaged, relabelled the Investigational Medicinal Product (IMP) kits, and provided randomization. Treatment kits were stored at each participating site at room temperature (between 15 and 25 °C), temperature was monitored at all times.

Patients, investigators, clinicians, all trial personnel, and statisticians were blinded to study arm allocation.

Interventions

Patients in the intervention group received 1.5 g intravenous vitamin C mixed in a 50-ml solution of normal saline every 6 h for 4 days. In the control group, patients received a matching placebo infusion (normal saline). In total the patient received 16 doses of study medication.

Treatment kits contained 52 ampoules of Vitamin C 500 mg/5 ml or 52 ampoules of Normal Saline 5 ml 9 mg/ml (48 for administration and 4 spare ampoules). Once these kits were assigned, they stayed at any time with the patient and travelled from ward to ward. All ampoules had identical sizes and were blinded by a cap and sticker for an identical look.

Right before each administration, 3 ampoules of study medication needed to be dissolved in 50 ml of NaCl 0.9%. This preparation was made bedside in ICU or on the ward. (See Supplementary Material file 2 for more detailed information about the medication handling process).

A maximum of 8 h was allowed between 2 doses and only one dose could be missed. All other aspects of care, including the administration of glucocorticoids were performed at the discretion of the treating teams.

Collection of clinical data

Data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based data collection and storage tool hosted on dedicated servers of the University of Leuven, Belgium.

Parameters were obtained as part of routine clinical care. On day 1 and 4 a targeted blood sample was collected for procalcitonin determination. Baseline data were obtained as close as possible to the time of randomization. The EQ- 5D- 5L health questionnaire was obtained on admission, day 5, day 28 and after 3 months. Arterial Blood Gas (ABG) analysis was part of routine clinical care in the ICU. If the patient was discharged to the ward before day 5, ABG sampling was not considered standard of care. To be able to calculate the SOFA score in this population, we used the SpO_2/FiO_2 ratio to impute for PaO_2/FiO_2 ratio in the respiratory component.

Investigators and research coordinators collected data at the trial sites. Access was restricted to authorized and trained study personnel. Data were de-identified using a patient study code. All data entry was monitored at the coordinating center, with site visits for source data verification. DSMB members had no access to RedCap. Pseudonymized data were transferred to them via a secured method.

Outcomes

The primary outcome for this study was the average post-baseline patient SOFA score on day 2 to 5, adjusted for the baseline SOFA (d1). For patients deceased within the first 5 days, the maximum SOFA score of 24 was assigned starting at the day of death. Note that the estimate for the average was obtained based on a model (see Statistical analysis section) which can handle the presence of missing values, instead of calculating per patient its average value.

Secondary outcomes included 28-day mortality, maximum SOFA score, length of ICU stay, length of hospital stay, duration and dosage of vasopressor requirement, duration and need of RRT (renal replacement therapy), number of ventilator days, total dose of steroids given, quality of life measured using the EQ- 5D- 5L-questionnaire on d1, d5, d28 and after 3 months and time to return to work (if applicable). The EQ- 5D- 5L questionnaire was used to estimate the utility index (EQ index). An index of 1 equalled perfect health, 0 equalled death. Only adverse events (AEs) that were not expected in the disease progression needed to be recorded.

Statistical analysis

To detect with at least 80% power a difference of 1 in average post-baseline patient SOFA score (calculated over day 2–5) between both groups, based on a constrained longitudinal data analysis (cLDA) model with α set at 0.05 [25], 126 patients per group (252 patients in total) were needed. The power was calculated using the approach presented by Stroup [26]. A standard deviation of the SOFA score equal to 3.5 and a correlation between the time points equal to 0.5 was assumed. These were conservative estimates, derived from reported information in two studies [7, 12]. 2.5%, 5%, 10% and 15% missing values were assumed on d2, d3, d4 and d5, respectively (combination of dropout and mortality). However, the sample size was increased to 150 patients per group to anticipate a larger variability due to the imputation of maximal SOFA scores for deceased patients.

The data and safety monitoring board reviewed the results after a planned blinded interim analysis for sample size recalculation (after 203 patients had completed follow-up for the primary outcome). The power level was at least 80% with the observed values, resulting in an unaltered sample size.

In accordance with the intent-to-treat (ITT) principle, the full analysis set (FAS) contained all randomized patients according to their randomized treatment. However, some randomized patients who did not receive any medication were excluded from the FAS, as decided during the Blind Review Meeting. Patients from the FAS with substantial protocol deviations (7 h or more between hospital admission and first administration of study medication, 2 or more successive doses missed, all planned doses missing on the first day) were excluded from the per protocol set (PPS). Both FAS and PPS were used for the evaluation of all efficacy endpoints. Only the FAS was used for the evaluation the safety endpoints.

Subgroup analyses for the primary outcome according to baseline SOFA and NEWS score were prespecified in the FAS. The aim was to investigate whether there was a distinct treatment effect across patients with mild organ dysfunction and patients with moderate to severe organ dysfunction. For the baseline SOFA score, subgroups were initially defined as SOFA < 8 vs SOFA > = 8. However, based on interim blinded descriptive data, the members of the Data Safety Monitoring Board (DSMB) deemed there would be too few patients in the SOFA > = 8 group when using a cutoff equal to 8. Therefore, the cut off was changed to SOFA < 6 vs SOFA > = 6 in the SAP (Statistical Analysis Plan: see Supplementary Material file 6).

A cLDA model was used to compare the average SOFA score (D2–D5) between both groups based on a two-sided test with $\alpha = 5\%$ (Supplementary Material file 3). Due to the right-skewed distribution of the SOFA score, a transformation was applied on the SOFA values yielding a ratio when the difference between groups was back transformed.

Linear models, Kaplan–Meier estimates, competing risks methodology, generalised linear mixed models were used for the comparison of the secondary outcomes (Supplementary Material file 3).

All analyses were performed using SAS software, version 9.4 of the SAS System for Windows. Copyright© 2002 SAS Institute Inc. SAS, Cary, NC, USA.

Results

Enrollment and patient characteristics

Between June 4th, 2021, and August 19 th, 2023, we enrolled 300 patients. Of these patients, 6 underwent randomization in error and 2 withdrew consent before administration of the study drug, which left 292 patients in the primary analysis population (147 in the vitamin C group and 145 in the placebo group) (Fig. 1). 5 patients withdrew consent to continue the trial. These patients remained part of the trial population according to the ITT principle.

The characteristics of the patients at baseline are shown in Table 1 and Supplementary Material file 4.

Patients with septic shock were identified as patients with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and having a serum lactate level > 2 mmol/L despite adequate volume resuscitation. The proportion of septic shock was slightly higher in the placebo group (15,9% vs 12.2%) than in the vitamin C group.

In the vitamin C group, there were more subjects who had a MAP < 65 mmHg on admission (57 vs 46) and more patients needed vasopressors (41 vs 37) than in the placebo group.

On the other hand, in the placebo group the proportion of lactate > 2 mmol/l was higher than in the vitamin C group (71 vs 57), while both mean values are similar. Also, the median initial procalcitonin level was slightly higher in the placebo group than the vitamin C group (4.0 vs 3.2).

Median NEWS and SOFA score at baseline were very similar in both groups.

Because the severity of sepsis is difficult to estimate with a stand-alone value and taking into account all baseline variables, we cannot conclude that 1 group was significantly sicker or healthier than the other.

Primary outcome

The average post-baseline patient SOFA score on day 2 to 5 was slightly lower in the vitamin C group: 1.98 (95% CI 1.69 to 2.32) vs 2.19 (95% CI 1.87 to 2.56) in the placebo group but did not reach statistical significance ($P = 0.30$). With a ratio of 0.91 (95% CI 0.77 to 1.08) the SOFA score in the vitamin C group was 8.7% lower than in the placebo group. In the PPS analysis, SOFA scores on day 2 to 5 were 10.2% lower in the vitamin C group, corresponding with a ratio of 0.90 (95% CI 0.75 to 1.07), but the difference was not significant ($P = 0.23$) (Table 2).

Secondary outcomes

None of the secondary outcomes showed significant differences between vitamin C and placebo groups. In the PPS analysis, the probability of RRT was significant lower in the vitamin C group (vitamin C, 0.7%; placebo 2.4%, OR 0.28 [0.078; 0.998], $P = 0.0496$). This was not observed in the ITT analysis. To summarize visually the effects on the primary and secondary outcomes, the effect sizes

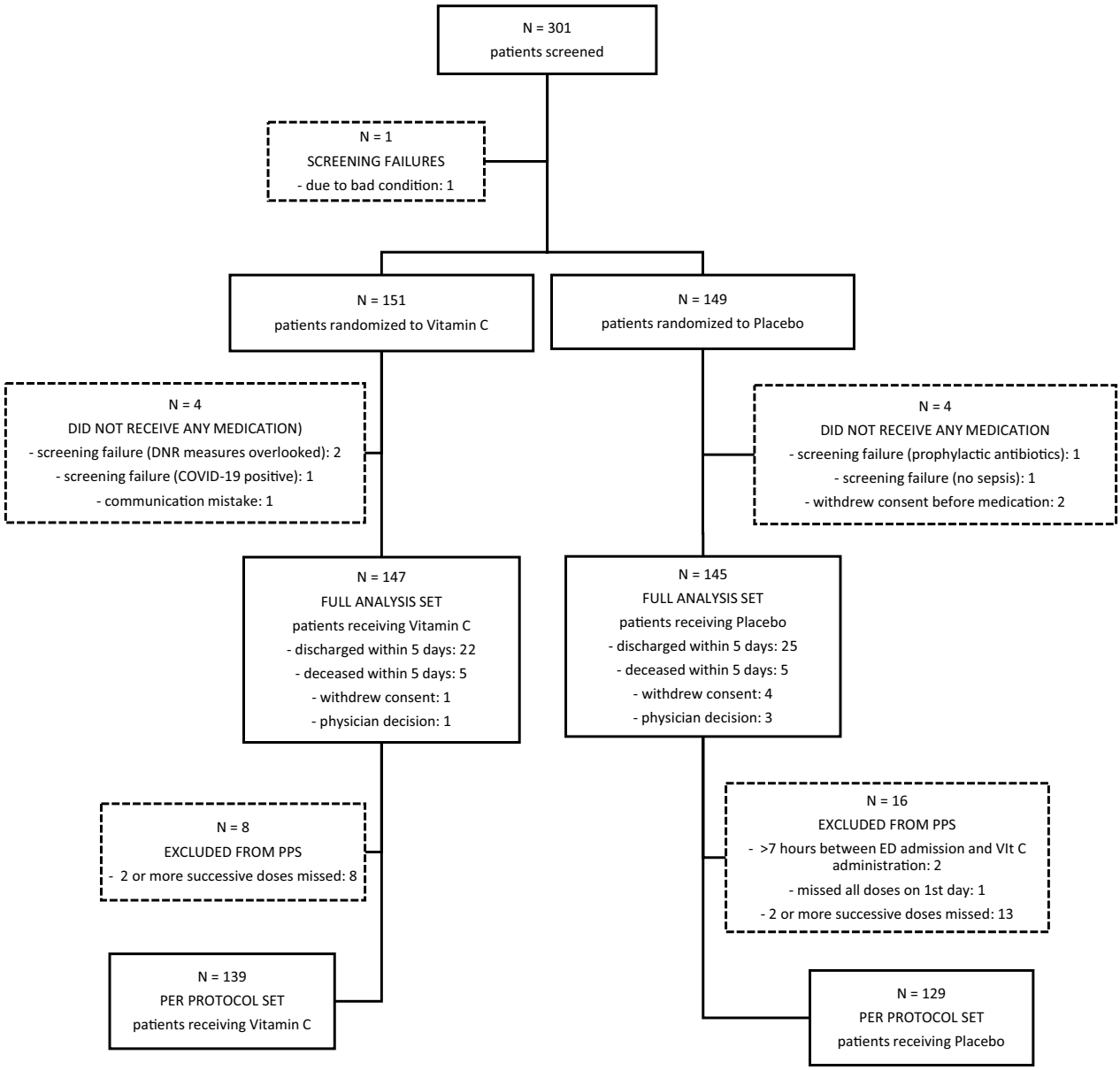

Fig. 1 Enrolment and randomisation. *DNR* Do not resuscitate, *ED* emergency department

on the original scale (see Supplementary Material file 5) were standardized (Fig. 2).

Subgroup analysis

In a planned subgroup analysis, the average post-baseline SOFA score among patients with a baseline SOFA score of 6 or more was significantly lower in the vitamin C group compared to the placebo group (vitamin C, 4.44; placebo 5.87; ratio 0.76, $P = 0.042$) (Table 2C). Visualisation of the additional exploratory analysis treating the baseline SOFA as a continuous variable suggested that patients with a baseline SOFA score between 6 and 12 would benefit most from vitamin C, although the global interaction was not significant, only for baseline SOFA scores of 7 and 8. The same trend was observed looking at the baseline NEWS score. Patients with a NEWS score of 7 and 8 on ED admission seemed to have a treatment effect from vitamin C, but also this global interaction was not significant. (Fig. 3) No other significant differences were found in the subgroups.

Safety and adverse events

In total 45 AEs were reported of which 35 serious. There were no more SAEs in the vitamin C group than in the

Table 1 Baseline characteristics of intention-to-treat population

Characteristic	Vitamin C (N = 147)	Control (N = 145)
Age [yr]—mean (SD)	64.7 (16.2)	67.0 (13.9)
Female sex—N (%)	50 (34.0)	53 (36.6)
Weight [kg]—mean (SD)	78.2 (21.2)	78.9 (17.2)
NEWS score at admission—median (Q1, Q3)	8.0 (7.0; 10.0)	8.0 (6.0; 10.0)
Sepsis etiology—N (%)		
Respiratory	68 (46.3)	77 (53.1)
Gastro-intestinal	11 (7.5)	12 (8.3)
Urinary	28 (19.1)	34 (23.5)
Skin or soft tissue	17 (11.6)	10 (6.9)
Catheter	2 (1.4)	1 (0.7)
Other	21 (14.3)	11 (7.6)
SOFA score—median (Q1, Q3)	4.0 (2.0; 7.0)	4.0 (3.0; 7.0)
SOFA score > = 6 N (%)	51 (34.7)	53 (36.6)
Septic shock—N (%)	18 (12.2)	23 (15.9)
MAP < 65 mmHg N (%)	57 (38.8)	46 (31.7)
CRP [mg/dL]—mean (SD)	191.9 (138.2)	192.2 (144.1)
Procalcitonin [ng/mL]—median (Q1, Q3)	3.2 (0.6; 13.5)	4.0 (0.8; 22.4)
Lactate [mmol/L]—mean (SD)	2.7 (2.6)	2.8 (2.1)
Treatment—N (%)		
Corticosteroids	39 (26.5)	30 (20.7)
Mechanical ventilation needed	24 (16.3)	22 (15.2)
Vasoactive agents	41 (27.9)	37 (25.5)
RRT	3 (2.0)	3 (2.1)
Fluid balance D1 [mL]—mean (SD)	1680 (1710)	1695 (1625)
EQ Index—mean (SD)	0.452 (0.453)	0.421 (0.448)

NEWS national early warning score, *SOFA* sequential organ failure assessment, *MAP* mean arterial pressure, *CRP* C-reactive protein, *RRT* renal replacement therapy, *EQ index* EuroQol utility index: an index of 1 equals perfect health, 0 equals death

control group. None of the reported (S) AEs, abnormal laboratory values, physical findings, patient changings or other abnormal observations were possible/probably causal related to the study treatment. None of them led to dose reduction. The DSMB periodically reviewed unblinded overall safety data to identify safety issues. The first meeting took place on the 6th of December 2021 after 50 patients were included. The second meeting took place on the 1st of March 2023. During this meeting a planned blinded interim analysis for sample size recalculation was also conducted.

Discussion

In this multicenter, double-blind RCT including patients with sepsis or septic shock, early administration of vitamin C did not significantly decrease the average post-baseline patient SOFA score. This contrasts with recent meta-analyses [27, 28] which showed that vitamin C (alone or in combination with thiamine and hydrocortisone) may improve organ failure recovery, as suggested by the decrease in SOFA score within 72 h. This difference may be due to the fact that the RCT's used for the meta-analyses had small sample sizes (< 110 patients per group [29]) with the exception of the VICTAS trial. Moreover, SOFA scores from discharged or deceased patients before 72 h were managed differently across studies which may also cause survival bias.

Further, the early administration of vitamin C was assumed to be associated with patients' survival improvement [8, 11], however it did not result in a survival benefit in our trial. This is similar to the report of another recent trial [18] that focused on early administration, except they investigated the potential benefit of HAT therapy and included only patients with septic shock, as in most other preceding trials. Important to mention is that they only started randomizing patients in this study once admitted to the ICU after a median length of stay of 0,5 days. Moreover, they reported a 2-h median time from randomisation to 1st administration of study drug.

Looking at all previous vitamin C studies reporting a study drug administration time frame, the average time to treatment varies between 3.3 and 18 h (or < 24 h) after ICU admission [12–17, 20, 21, 23]. The strength of our study lies in the fact that the mean time to 1st study drug

Table 2 Primary outcome

	Vitamin C	Control	Treatment effect	*P*-value
(A) Intention-to-treat analysis (FAS)				
Day 1	3.86 (3.55;4.19)	3.86 (3.55;4.19)		
Day 2	2.79 (2.42;3.20)	3.04 (2.65;3.49)	0.92 (0.79;1.07)	
Day 3	2.26 (1.92;2.66)	2.34 (1.98;2.75)	0.97 (0.81;1.16)	
Day 4	1.70 (1.40;2.06)	1.93 (1.59;2.32)	0.90 (0.73;1.11)	
Day 5	1.40 (1.11;1.73)	1.66 (1.33;2.04)	0.87 (0.68;1.09)	
Average D2–D5	1.98 (1.69;2.32)	2.19 (1.87;2.56)	0.91 (0.77;1.08)	0.300
(B) Per-protocol analysis (PPS)				
Day 1	3.87 (3.55;4.22)	3.87 (3.55;4.22)		
Day 2	2.82 (2.45;3.24)	3.14 (2.72;3.62)	0.90 (0.78;1.05)	
Day 3	2.26 (1.91;2.66)	2.39 (2.00;2.83)	0.95 (0.79;1.15)	
Day 4	1.70 (1.38;2.07)	1.93 (1.56;2.35)	0.90 (0.72;1.12)	
Day 5	1.41 (1.11;1.75)	1.72 (1.37;2.14)	0.84 (0.66;1.07)	
Average D2–D5	1.99 (1.69;2.34)	2.24 (1.90;2.64)	0.90 (0.75;1.07)	0.233
(C) Subgroup analysis (FAS) baseline SOFA score > = 6				
Day 1	3.87 (3.55;4.22)	3.87 (3.55;4.22)		
Day 2	2.82 (2.45;3.24)	3.14 (2.72;3.62)	0.90 (0.78;1.05)	
Day 3	2.26 (1.91;2.66)	2.39 (2.00;2.83)	0.95 (0.79;1.15)	
Day 4	1.70 (1.38;2.07)	1.93 (1.56;2.35)	0.90 (0.72;1.12)	
Day 5	1.41 (1.11;1.75)	1.72 (1.37;2.14)	0.84 (0.66;1.07)	
Average D2–D5	1.99 (1.69;2.34)	2.24 (1.90;2.64)	0.90 (0.75;1.07)	0.233

Estimates of SOFA (95%CI) obtained from the cLDA model fitted on inverse hyperbolic sign transformed data. Means and 95% confidence intervals are obtained after back transformation to the original scale. Due to the transformation, the comparison of both groups refers to a ratio

administration was 3.7 h after ED presentation, making it the only trial recruiting patients in the ED and investigating a true early administration effect. This early administration effect might be a plausible explanation for the observation that patients with a higher baseline SOFA score (6 or above) may benefit from the early administration of vitamin C.

We also focused on patients at an earlier stage of disease to investigate a potential preventive role of vitamin C leading to less deterioration from sepsis to septic shock. This is confirmed by a low ICU admission rate of 48.3% and 45.5% for the vitamin C and placebo groups, respectively, as well as a low median baseline SOFA score of 4 in both groups. This low average is partly due to rapid detection of sepsis in our EDs. The preventative role vitamin C, however, could not be established, since there was no benefit observed in patients with lower SOFA scores.

Taking into consideration all observed outcome parameters, we can stipulate that the early administration of vitamin C has no clinical impact. No hard claims can be made upon an only just significant reduction in need for RRT in the PPS (3.6% in the vitamin C group vs 9,3% in the placebo group, $P = 0.0496$), since no key secondary outcomes were defined, and this result was not confirmed in the FAS. The lower average post-baseline SOFA score among patients with a baseline SOFA score of 6 or above may have been found to be statistically significant but lacks clinical relevance. This exploratory result might be hypothesis generating. However, given the fact that the administration of vitamin C in sepsis and septic shock has been extensively studied in recent years [7–23], further targeted research probably will not have much added value.

Equal to previous studies [7, 9] and recent meta-analyses [27, 28] the use of vitamin C seems to be safe, with the finding of no treatment-related AEs in our trial. This contrasts with the recent LOVIT trial, where serious anaphylactic reactions as well as a higher risk of death or persistent organ dysfunction at 28 days were observed in patients on vasopressor treatment receiving vitamin C [21]. In this trial, they used higher doses of vitamin C (50 mg/kg) and had a late onset of administration. In addition, there was a higher baseline severity of illness, and a higher death rate (44.6%) compared to ours.

Other strengths of this study include an interim analysis for sample size recalculation which checked and confirmed the power of our study and include blinding to limit ascertainment bias.

Limitations

Nonetheless, this trial also has some limitations. First, the large variety in study set-ups, mixed outcomes, and the inconsistency in the reported results, have made

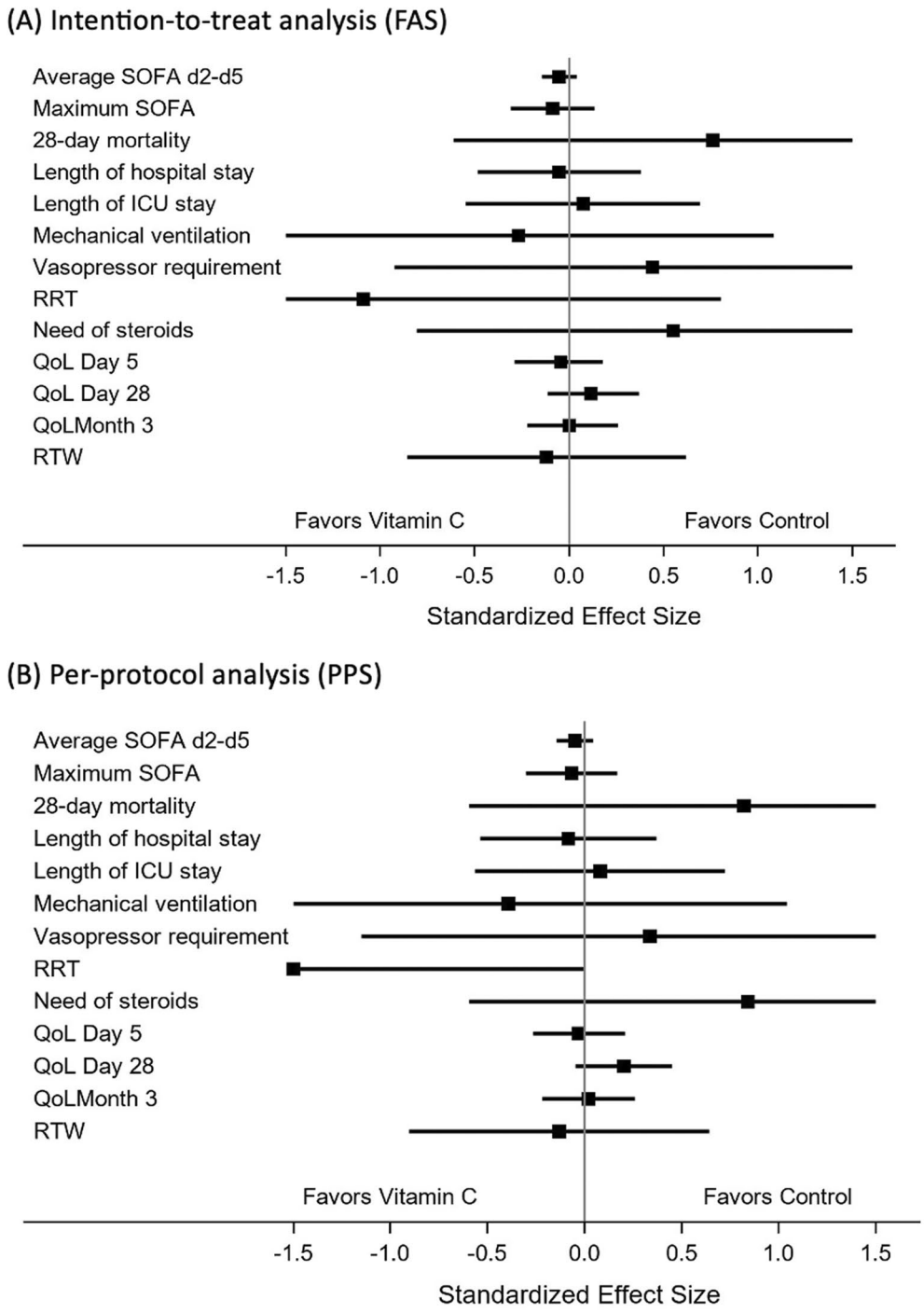

Fig. 2 Standardized effect sizes for primary and secondary outcomes for FAS (**A**) and PPS (**B**). All effect sizes on the original scale were converted into Cohen's 'd'

it difficult to estimate the optimal dose and timing of vitamin C administration. As a result of increased metabolism due to enhanced inflammatory response, high doses of vitamin C, up to 3 to 6 g daily, are needed to normalize the vitamin C plasma level [30, 31]. Based on published clinical data and the pharmacokinetics of vitamin C most studies decided to administer 6 g of vitamin C per day divided in four equal doses i.e. every 6 h [8, 11, 12, 14–17, 19, 29]. Other trials have chosen to give even higher doses of vitamin C [10, 18, 20–23], because Fowler et al. [7] reported that the SOFA score reduction was most remarkable in patients receiving the

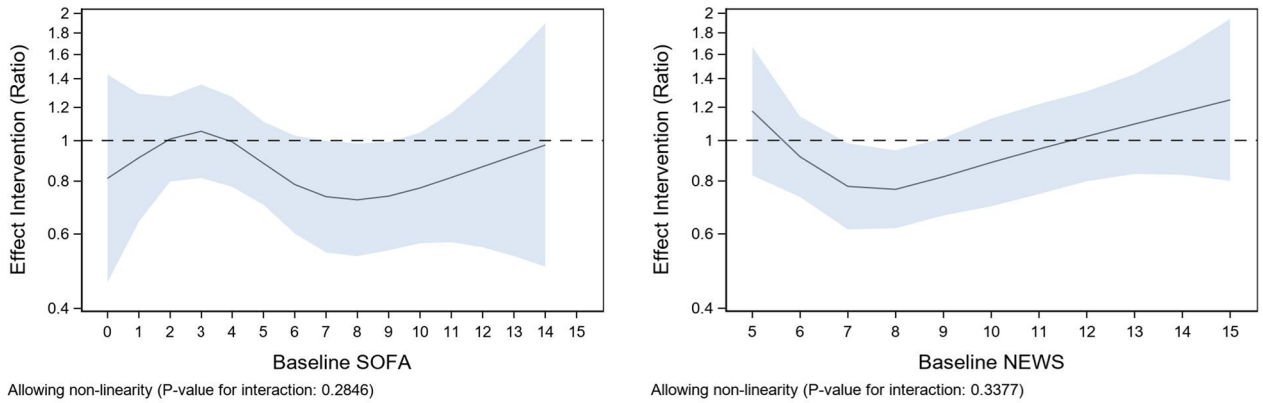

Fig. 3 Interaction model for continuous baseline SOFA and baseline NEWS scores (FAS)

highest dose of vitamin C, 200 mg/kg/day, despite this was a phase I safety trial what obfuscates its statistical significance.

Secondly, since this was a pragmatic trial, we did not measure the baseline levels of vitamin C in patients. A recent prospective pharmacokinetic study on the patients in treatment group of the VITAMINS trial showed that the 6-hourly doses regimen of 1.5 g was sufficient to achieve and maintain normal to supranormal vitamin C plasma levels [32]. We can assume that the lack of significant reduction in our primary outcome is not due to an insufficient dose.

Third, despite this trial is multicentric, one hospital included about 40% of the patients. The DSMB judged the distribution of the baseline SOFA scores to be similar to that of the other centers and recommended further recruitment at this site. Also, final results were adjusted per study site.

Conclusion

Among patients with sepsis or septic shock, incorporating the early administration of vitamin C did not improve organ dysfunction as assessed by the average post-baseline patient SOFA score on day 2 to 5. Therefore, these data do not support the use of vitamin C in adults with sepsis or septic shock.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05383-x.

Supplementary Material file 1
Supplementary Material file 2
Supplementary Material file 3
Supplementary Material file 4
Supplementary Material file 5
Supplementary Material file 6

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Author contributions

SV, JB, DD, SF, LW conceived and designed the study. SV, LW and DD obtained funding. SF carried out the statistical analysis. SV, SF, DD and WM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SF, SV, BC, WE and DD were responsible for the acquisition, analysis, and interpretation of the data. SV, BC, SF and WE drafted the manuscript. SM, PV and DD conducted a critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

Any request by a third party to receive the study data, shall be registered at our institution and the proper arrangements in line with GDPR shall be put in

place between the parties. Such transfer means that personal data is being processed. A data transfer agreement will be completed to that extent.

Declarations

Ethics approval and consent to participate

The trial protocol was approved by a central ethics committee and the Belgian Federal Agency for Medicines and Health Products through the Clinical Trial Regulation (CTR) pilot procedure. CTR Pilot Number: 389. All patients or their legally acceptable representative (LAR) provided written informed consent. To ensure timely initiation of medication administration (within 6 h), a process of delayed consent was employed, enrolling patients in the clinical trial and obtaining consent as soon as practical from the patient or their LAR.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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