Application of Intravenous Vitamin C in Adult Patients with Sepsis: A Meta-Analysis of Randomized Controlled Trials

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Research Article

Keywords: vitamin C, sepsis, mortality, meta-analysis.

Posted Date: September 7th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-850576/v1>

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Abstract

Background: The efficacy of intravenous vitamin C among sepsis patients is uncertain according to recent randomized controlled trials (RCTs). We conducted a meta-analysis to evaluate the efficacy of vitamin C application in adults with sepsis.

Methods: We performed a systematic literature search in PubMed, Web of Science, Embase and the Cochrane Library. Eligible studies were RCTs that investigated the application of intravenous vitamin C in adult patients with sepsis. We assessed the risk of bias of the included studies using the Cochrane risk of bias tool and the certainty of evidence according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, for each outcome.

Results: Fourteen trials involving a total of 1823 patients were included. We found that there was no significant effect of vitamin C on 28-day mortality [risk ratio (RR) 0.87, 95% confidence interval (CI) 0.73 to 1.04, $p = 0.12$, TSA-adjusted CI 0.70 to 1.08, low quality evidence], but among patients who were treated with vitamin C monotherapy instead of combination therapy, the mortality was reduced (RR 0.66, 95% CI 0.49 to 0.88, $p = 0.004$). Vitamin C was associated with a significant improvement of 72-h Δ SOFA score (SMD = 0.20, 95% CI 0.07 to 0.32, $p = 0.002$, $I^2=11\%$, moderate quality evidence).

Conclusions: In this meta-analysis of patients with sepsis, the use of vitamin C was not associated with reduction in 28-day mortality, but vitamin C may have a positive effect in improving organ function. As the certainty of evidence was low, Larger RCTs were needed.

Introduction

Sepsis is a life-threatening organ dysfunction resulting from dysregulated host responses to infection [1], and it is still one of the leading causes of hospital deaths in ICU patients [2]. In the United States, sepsis affects approximately 1.7 million adults each year and causes more than 250 000 deaths [3, 4]. Given the high morbidity and mortality of sepsis, new therapeutic approaches are required to improve outcomes and reduce the global burden but it should be effective, inexpensive and safe [5, 6].

Vitamin C, a free radical scavenger, is an antioxidant compound [7, 8]. It can neutralize the reactive oxygen produced by the large number of inflammatory reactions in sepsis [9]. It can regenerate other oxygen radical scavengers by acting as a donor [10]. Vitamin C also plays an important role in the synthesis of catecholamines and vasopressor, which is of great significance in maintaining adequate systemic perfusion [11]. In the initial stage of sepsis, vasopressor levels increase significantly, but as patients progress to hypotension and shock, vasopressor and vitamin C levels in the plasma gradually decrease [12]. Low plasma concentrations of vitamin C are associated with inflammation, the severity of organ failure, and mortality [13], so supplementation with vitamin C in sepsis patients is theoretically necessary.

In 2016, Marik et al [14] pointed out that early use of vitamin C, corticosteroid and thiamine through a vein may effectively prevent progressive organ dysfunction and reduce the mortality of severe sepsis and septic shock. This seems to have provided a new feasible plan for the clinical treatment of sepsis patients. A large multicenter RCT study by Fowler et al [15] also found a significant improvement in Sequential Organ Failure Assessment (SOFA) score and mortality in the vitamin C group. However, as studies on the application of vitamin C in sepsis patients have become increasingly thorough, this plan becomes controversial. Nabil Habib et al [16] and Ferrón-Celma et al [17] found that vitamin C is not beneficial or even harmful in reducing the mortality of patients with sepsis. In 2020 and 2021, A large number of randomized trials of vitamin C alone or in combination with hydrocortisone and thiamine have been published, but they have had varied design and inconsistent results [18–25]. Due to the differences in the administration time, dosage and administration method in different studies, revealing the role of vitamin C in patients with sepsis more objectively and concretely has become particularly important. Considering that previous meta-analyses including complex and diverse critically ill patients and studies that were relatively early, we think it is necessary to systematically review relevant evidence for the role of vitamin C in sepsis patients.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement [26] (Table S1). The systematic review protocol was registered with the PROSPERO International prospective register of systematic reviews (registration number CRD42020157573).

Eligibility criteria

The studies included in our meta-analysis should meet the following PICOS criteria:

1. Population: Adult patients with sepsis
2. Intervention: Intravenous vitamin C
3. Comparison: Placebo or conventional treatment
4. Outcomes:
 - a. Primary outcome: 28-day mortality
 - b. Secondary outcome: ICU LOS (days), ventilator days, duration of vasopressor use (days), change in SOFA score within 72 h after experimental intervention (72-h Δ SOFA score, SOFA score at enrolment–SOFA score after 72 h).
5. Study design: Randomized controlled trials (RCTs)

Search strategy

We performed a systematic literature search of PubMed, Web of Science, Embase and Cochrane Library databases for potentially eligible studies from inception to April 1, 2020, then updated to March 1, 2021. We searched for studies that referred to adult sepsis patients treated with vitamin C by using MeSH and free-text terms for various forms of the terms 'vitamin C' and 'sepsis'. The search was restricted to publications in English and human studies, and the electronic search strategy was shown in Table S2. In addition, we manually identified other potentially eligible trials by screening the references of included studies and other relevant systematic reviews.

All the studies we included were independently screened and read by two reviewers. By reading the abstracts and topics, we excluded unrelated literatures, and by reading the full texts, we finally included articles that fully met the requirements. When there was a disagreement about a study, the third reviewer arbitrated discussions until a decision was reached.

Data extraction

Data were collected using an author-created information extraction form. The two reviewers (HC and PC) independently extracted the required content by screening the literature. The data extracted from each trial included the following: study characteristics (first author, country, published year, and study design), baseline data (number of participants, age, sex), the risk of bias data, intervention and control details, outcomes.

Risk of bias

Two independent reviewers (HC and PC) assessed the risk of bias using the Cochrane Collaboration's tool for assessing the risk of bias in RCTs. Risk of bias was rated according to the following domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of the participants and personnel; (4) blinding of the outcome assessment; (5) incomplete outcome data; (6) selective reporting and (7) other biases. We judged the trials as 'overall low risk of bias' if all domains were at low risk, 'overall high risk of bias' if any domain was at high risk of bias, and 'unclear' if at least one domain was unclear, but no domain was at high risk of bias. We qualitatively evaluated the publication bias by funnel plots, and quantitatively analyzed by the Harbord's test, which is the modification of Egger's test [27] ($p < 0.05$ was regarded as significant evidence of publication bias).

Trial sequential analysis (TSA)

To assess the risk of random errors due to sparse data and multiple testing of accumulating data [28–30], we conducted a TSA using Trial Sequential Analysis v.0.9.5.10 beta, which could also estimate required information size (RIS) [31], thereby stopping similar research in time and preventing the waste of medical resources. We performed a two-sided TSA to summarize and analyze the data of the included studies for the primary outcome with a statistical significance level of 5%, a power of 80%, and a relative risk reduction (RRR) of 20%. The control group incidence was calculated by all included trials.

Statistical analysis

We used Review Manager 5.3 software to combine aggregate data. Given the possible clinical heterogeneity, a random-effects model was used to combine data. We calculated the pooled RR and 95% CI for dichotomous outcomes, and standardized mean difference (SMD) with 95% CI for continuous outcomes. Continuous variables in two articles were reported with median and interquartile range (IQR): for one article [15], we recalculated the mean and standard deviation (SD) from the original data in the supplementary materials; for the other [32], we did not get the original data, so we estimated the mean and SD in reference to recently established methods [33, 34]. In terms of statistical heterogeneity, a quantitative analysis was performed using the Mantel-Haenszel (MH) χ^2 test and the I^2 test; when p was < 0.05 for the MH χ^2 test or I^2 was $> 50\%$ for the I^2 test, there was obvious heterogeneity. Besides, we conducted a sensitivity analysis using STATA version 15.1 to determine whether any single study incurred undue weight in the analysis, and a fixed-effects model was only used.

Subgroup analyses

In order to assess the reliability of the results and explore the impact of different clinically meaningful subgroups on the results, we performed a subgroup analysis for primary outcome based on a pre-defined subgroup: (1) Low risk of bias versus high risk of bias; (2) low dose (< 5 g/d) versus high dose (≥ 5 g/d) [35]; (3) vitamin C monotherapy versus combination therapy.

Assessment of quality of evidence

We assessed the quality of evidence by using the GRADE approach [36], the certainty of evidence was classified into high, moderate, low, or very low for each outcome. Well-conducted RCTs were considered as high-quality evidence but can be downgraded based on the following five domains: risk of bias, inconsistency, indirectness, imprecision and reporting bias.

Results

Study selection

We screened a total of 1921 studies through electronic search and manual search, 47 studies were selected for full-text review after removal of duplicates and reading titles and abstracts. Finally, fourteen studies with 1823 participants were included in the systematic review. The search process and the reasons for excluding the ineligible studies are provided in Fig. 1, The major exclusions were showed in Table S3.

Characteristics of the included studies

The characteristics of the included studies were summarized in Table 1. All the studies were published between 1997 and 2021, with samples ranged from 20 to 501 patients. Vitamin C monotherapy was used in 6 trials [15–17, 22, 32, 37] and combination therapy in 8 trials [18–21, 23–25, 38], six of them were combination of vitamin C, thiamine, and hydrocortisone [18, 19, 21, 23–25]. One was combination of vitamin C, vitamin E, NAC [38]. One was combination of vitamin C and thiamine [20]. The dose of vitamin C ranged from 0.45 g/d to 12 g/d (we convert mg/kg/d to g/d based on a typical adult's weight of 60 kg). All the studies included mortality, ten studies [15, 16, 18, 20–22, 24, 25, 32, 37] reported ICU LOS, six studies [15, 16, 18, 20, 32, 37] reported ventilator days, and seven studies [16, 18, 21, 22, 24, 32, 37] reported duration of vasopressor use, seven studies [18, 20–25] reported 72-h Δ SOFA score.

Table 1
Characteristics of included studies

Study	Country	Design	Population		Age		Experimental Intervention	VC Dose (original data)	VC Dose (g/d)	CON
			VC	CON	VC	CON				
Chang 2020	China	Single center	40	40	60 ± 15	64 ± 13	vitamin C hydrocortisone thiamine	1.5 g qid for 4 d or until ICU discharge	6	saline
Ferrón-Celma 2009	Spain	Single center	10	10	68 ± 5	65 ± 4	vitamin C	450 mg qd for 6 d	0.45	Placebo (5%GS)
Fowler 2014	United States	Single center	16	8	60 ± 10	61 ± 4	vitamin C	12.5 or 50 mg/kg qid for 4 d	3 or 12*	Placebo (5%GS)
Fowler 2019	United States	multicenter	84	82	53 ± 21	57 ± 20	vitamin C	50 mg/kg qid for 4 d	12*	Placebo (5%GS)
Fujii 2020	Australia	multicenter	107	104	62 ± 16	62 ± 14	vitamin C hydrocortisone thiamine	1.5 g qid	6	hydrocortisone
Galley 1997	United Kingdom	Single center	16	14	67 ± 14	70 ± 17	vitamin C vitamin E NAC	1,000 mg qd for 1 d	1	Placebo (5%GS)
Hwang 2020	Korea	multicenter	53	58	70 (62–76)	69 (62–74)	vitamin C thiamine	daily dose 6 g	6	Placebo (0.9% saline)
Iglesias 2020	United States	multicenter	68	69	70 ± 12	67 ± 14	vitamin C hydrocortisone thiamine	1,500 mg qid	6	Placebo (0.9% saline)
Lv 2020	China	Single center	61	56	58.7 ± 14.3	60.2 ± 14.1	vitamin C	3.0 g, bid	6	5% dextrose
Moskowitz 2020	United States	multicenter	101	99	68.9 ± 15.0	67.7 ± 13.9	vitamin C hydrocortisone thiamine	1500 mg every 6 hours	6	Placebo (0.9% saline)
Nabil Habib 2017	Egypt	Single center	50	50	43 ± 9	42 ± 10	vitamin C	1,500 mg qid until ICU discharge	6	conventional sepsis treatment
Sevransky 2021	United States	multicenter	252	249	62 (51–69)	61 (50–72)	vitamin C hydrocortisone thiamine	1.5g every 6 hours	6	placebo
Wani 2020	Indian	Single center	50	50	51 ± 36	52 ± 36	vitamin C hydrocortisone thiamine	1.5 g qid	6	standard care
Zabet 2016	Iran	Single center	14	14	64 ± 16	64 ± 14	vitamin C	25 mg/kg qid for 3 d	6*	Placebo (5%GS)

NAC = N-acetylcysteine, qd = once a day, qid = four times a day, IV = Intravenous, VC = Vitamin C, CON = Control

* We convert mg/kg/d to g/d based on a typical adult's weight of 60 kg

Risk of bias assessment

Figure S1 and Figure S2 present the risk of bias assessment of the included studies, and the reasons for judgment of each item were shown in Table S4. Five studies [15, 21, 23, 25, 32] were adjudicated as overall low risk of bias, four [17, 20, 22, 38] were 'unclear', and five [16, 18, 19, 24, 37] were 'high'.

Quality of the evidence

As was shown in Table 2, the overall quality of evidence was assessed as very low for mortality, ICU LOS, ventilator days and duration of vasopressor use, and moderate for 72-h Δ SOFA score according to GRADE. Mainly because of high heterogeneity, co-interventions and limited sample size.

Table 2
GRADE evidence profile

Certainty assessment							No. of patients		Effect	
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin C	Control	Relative (95% CI)	Absolute
Mortality										
14 ^a	Randomised trials	Not serious	Not serious	serious ^b	Serious ^c	None	241/921 (26.2%)	270/902 (29.9%)	RR 0.87 (0.73 to 1.04)	39 fewer per 1000 (from 81 fewer to 12 more)
ICU LOS										
10 ^d	Randomised trials	Serious ^e	Not serious	serious ^b	Serious ^f	None	679	666	-	SMD 0.09 lower (0.25 lower to 0.06 higher)
Ventilator days										
6 ^g	Randomised trials	Serious ^h	Very serious ⁱ	serious ^b	Serious ^j	None	227	218	-	SMD 0.29 lower (0.79 lower to 0.22 higher)
Duration of vasopressor use										
7 ^k	Randomised trials	Serious ^l	Very serious ^m	serious ^b	Not Serious	None	299	287	-	SMD 0.83 lower (1.28 to 0.38 lower)
ΔSOFA score										
7 ⁿ	Randomised trials	Not Serious	Not serious	serious ^b	Not Serious	None	615	611	-	SMD 0.2 higher (0.07 to 0.32 higher)
CI confidence interval; RR risk ratio; SMD standardised mean difference										
^a Chang et al. [18], Ferrón-Celma et al. [17], Fowler et al. [32], Fowler et al. [15], Fujii et al. [19], Galley et al. [38], Hwang et al. [20], Iglesias et al. [21], Lv et al. [22] al. [23], Nabil Habib et al. [16], Sevransky et al. [25], Wani et al. [24], Zabet et al. [37].										
^b Most of the included trails are co-interventions.										
^c The total sample size is small, and the 95% CI includes significant benefit and harm (0.73, 1.04).										
^d Chang et al. [18], Fowler et al. [32], Fowler et al. [15], Iglesias et al. [21], Lv et al. [22], Nabil Habib et al. [16], Sevransky et al. [25], Wani et al. [24], Zabet et al. [37].										
^e 4/10 trials had overall high risk of bias.										
^f The total sample size is small, and the 95% CI includes significant benefit and harm (-0.25, 0.06).										
^g Chang et al. [19], Fowler et al. [18], Fowler et al. [28], Hwang et al. [20], Nabil Habib et al. [17], Zabet et al. [37].										
^h 3/6 trials had overall high risk of bias.										
ⁱ I ² = 83%, P < 0.0001. Substantial heterogeneity.										
^j The total sample size is small, and the 95% CI includes significant benefit and harm (-0.79, 0.22).										
^k Chang et al. [18], Fowler et al. [32], Iglesias et al. [21], Lv et al. [22], Nabil Habib et al. [16], Wani et al. [24], Zabet et al. [37].										

Certainty assessment							No. of patients		Effect	
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin C	Control	Relative (95% CI)	Absolute
^l 4/7 trials had overall high risk of bias.										
^m $I^2 = 84\%$, $P < 0.00001$. Substantial heterogeneity.										
ⁿ Chang et al. [18], Hwang et al. [20], Iglesias et al. [21], Lv et al. [22], Moskowitz et al. [23], Sevransky et al. [25], Wani et al. [24].										

Primary outcome: 28-day mortality

28-day mortality was reported in 14 studies, two of them reported 30-day mortality, we approximated them to the 28-day mortality. They included a total of 1823 patients. The mortality was not significantly different between the vitamin C group and the control group (RR 0.87, 95% CI 0.73 to 1.04, $p = 0.12$) (Fig. 2). The contour-enhanced funnel plot supported by Harbord's test showed no publication bias ($p = 0.483$) (Figure S3).

TSA

TSA showed that the adjusted CI for mortality was 0.70 to 1.08 ($I^2 = 30\%$, $D^2 = 32\%$, $n = 1823$), and the diversity-adjusted RIS was 2530 (Fig. 3). The cumulative Z score didn't cross the traditional boundary or adjusted boundaries for benefit, and the RIS had not been reached (72 %).

Subgroup analyses for mortality

Table 3 showed the subgroup analyses for mortality based on a pre-defined subgroup, and the details were shown in Figures S4-6. The mortality was lower in the vitamin C group than in the control group among patients who were treated with vitamin C monotherapy (RR 0.66, 95% CI 0.49 to 0.88, $p = 0.004$) (Figure S6), and there was a significant difference between vitamin C monotherapy subgroup and vitamin C combination therapy subgroup ($p = 0.01$, $I^2 = 83.9\%$) (Figure S6).

Table 3 Subgroup analyses for mortality

Subgroups	No. of trials	No. of participants	RR	95% CI	<i>p</i>	I ²	Test of subgroup differences	
							<i>p</i>	I ²
Risk of bias								
Low risk of bias	5	1028	0.85	0.67-1.09	0.20	25%	0.84	0%
High risk of bias	5	517	0.82	0.58-1.14	0.24	31%		
Dose of vitamin C								
Low dose (≥ 5 g/d)	3	66	1.12	0.73-1.73	0.61	0%	0.22	32.6%
High dose (< 5 g/d)	12	1765	0.84	0.70-1.00	0.05	23%		
Vitamin C regimen								
Monotherapy	6	455	0.66	0.49-0.88	0.004	17%	0.01	83.9%
Combination therapy	8	1368	1.01	0.85-1.20	0.91	0%		

RR risk ratio; CI confidence interval

Secondary outcomes

Seven trials with a total of 586 patients reported on duration of vasopressor use. When pooled, the vitamin C was associated with a reduction in duration of vasopressor use (SMD = -0.83, 95% CI -1.28 to -0.38, $p = 0.0003$, $I^2 = 84\%$) (Figure S7). 72-h Δ SOFA score data was available from 7 studies (1226 patients). When pooled, the vitamin C was associated with an increase in 72-h Δ SOFA score (SMD = 0.20, 95% CI 0.07 to 0.32, $p = 0.002$, $I^2 = 11\%$) (Figure S8). ICU LOS was not significantly associated with vitamin C (SMD = -0.09, 95% CI -0.25 to 0.06, $p = 0.24$, $I^2 = 41\%$) when 10 studies were combined (1345 patients) (Figure S9). Ventilator days was not significantly associated with vitamin C (SMD = -0.29, 95% CI -0.79 to 0.22, $p = 0.26$, $I^2 = 83\%$) when 6 studies were combined (445 patients) (Figure S10).

Sensitivity analyses

We systematically and qualitatively analyzed the sensitivity across the included studies to determine the influence of individual trials on the results. We did not detect a significant impact from any single study in the results of mortality, ICU LOS and 72-h Δ SOFA score (Figures S11-12, Figure S15). In the results of

ventilator days and duration of vasopressor use, we found that the trial of Nabil Habib et al may led to the high heterogeneity (Figures S13-14), but deleted the trial did not result in significant deviations from the original overall estimate.

Discussion

Our meta-analysis systematically evaluate whether vitamin C improves the prognosis of adult patients with sepsis in randomized controlled trials. Through an analysis of 1823 patients from the 14 included studies, we found that when vitamin C is used as an adjunct method in patients with sepsis, it may not significantly reduce mortality, but when vitamin C is administered monotherapy instead of combination therapy, it may be beneficial for reducing mortality. In addition, we found a statistically significant reduction in SOFA score during the first 72 hours after enrollment.

Two recent meta-analyses showed that vitamin C does not have a positive therapeutic role in critically ill patients [39, 40], but these meta-analyses included various patients, not sepsis patients only; thus, there may have greater heterogeneity. Last year and this year, two meta-analyses showed that the use of vitamin C did not reduce mortality in sepsis patients[41, 42], but they included many retrospective studies, which may have led to lower evidence quality, and several recently published high-level large RCTs was not included, especially the largest study to date including 501 patients (the VICTAS Randomized Clinical Trial) was not included[25].

In animals, studies have shown that when animals are stressed, the synthesis of endogenous vitamin C increases [43, 44], as it does in mice exposed to tumors [45]. Other studies have shown that the synthesis of vitamin C is eight times greater than it is in animals exposed to drugs [46, 47]. It can be seen that when animals are affected by diseases and drugs, the demand for vitamin C increases significantly. This is especially obvious for humans who cannot synthesize vitamin C themselves. Long et al confirmed that the levels of vitamin C are very low in plasma after trauma and infection [48]. In patients with sepsis, as the disease worsens, an excessive inflammatory response increases the metabolism of vitamin C, and vitamin C levels gradually decline [12, 49]. Carr et al found that 88% of septic shock patients had hypovitaminosis C, and 38% were deficient in vitamin C [50]. Therefore, vitamin C supplementation is particularly important for patients with sepsis.

The amount of vitamin C that sepsis patients need to be supplemented with is still inconclusive, ranging from 0.45 g/d to 12 g/d. Under normal physiological conditions, 100–300 mg of vitamin C per day can meet daily needs [51]. However, critically ill patients may need more, and studies have shown that critically ill patients need more than 3 g daily doses to restore normal vitamin C levels [48]. We tried to explore whether the dose of vitamin C affects mortality, but we found that there was no significant difference between the high-dose vitamin C subgroup (≥ 5 g/d) and the low-dose vitamin C subgroup (< 5 g/d). In recent years, Wang et al found that medium doses (3–10 g/d) of vitamin C were associated with decreased mortality in critically ill patients, with neither low doses (< 3 g/d) nor high doses (≥ 10 g/d) having a significant impact [39]. According to the grouping method of Wang et al, we found that high doses can significantly reduce mortality in patients with sepsis, while medium or low doses cannot (Figure S16). However, what is worth to notice is that both studies in the high-dose group used vitamin C monotherapy, this may be a confounding factor.

Recently, cocktail therapy combining vitamin C, thiamine, and corticosteroids has become a hot topic among new therapies for sepsis. Since vitamin C, thiamine, and corticosteroids have the same cellular signaling pathways and metabolic cascades [52], this cocktail therapy is theoretically justified. Since the treatment was proposed by Marik et al in 2016, the combination therapy of vitamin C, thiamine, and corticosteroids in patients with sepsis has received increasing attention. They found that the early use of intravenous vitamin C, together with corticosteroids and thiamine, is effective in preventing progressive organ dysfunction and in reducing the mortality of patients with severe sepsis and septic shock [14]. However, a recent retrospective observational cohort study suggests that incorporating vitamin C, hydrocortisone, and thiamine into standard practice may not improve patient outcomes [53], what is worth to notice is that non-sequential patients were included in the vitamin C group in this study resulting in a severe selection bias which may limit the interpretation. Since these two studies are observational studies, we did not include them in our meta-analysis. Excitingly, several large RCT studies on this cocktail therapy have been published recently, providing new evidence for our meta-analysis. Fujii et al found that the combination of vitamin C, thiamine, and hydrocortisone did not reduce mortality or vasopressor time in a study of 216 sepsis patients [19]. Recent years, Iglesias et al [21], Chang et al [18], Moskowitz et al[23] and Sevransky et al[25] used similar methods and found no significant change in mortality or SOFA score.

Through subgroup analysis, we found that the combined results of six studies using vitamin C monotherapy showed a significant reduction in mortality in patients with sepsis, while the combined results of the other eight studies using vitamin C combined with other drugs, including thiamine and hydrocortisone, mainly showed no significant effect on mortality. We speculate that patients with sepsis using vitamin C monotherapy instead of combination therapy may play a more active role.

It should be noted that our research still has many limitations. First, the included study included a 25-year time span during which significant changes in the recognition and management of sepsis may have had different effects on the trial populations. Second, many studies mentioned that the initial time of vitamin C application in patients with sepsis may have a significant impact on the results, such as mortality. We tried to perform subgroup analysis according to the initial time of medication; unfortunately, it was difficult for us to extract this part of the data. Third, since the vitamin C regimen and control regimen in each study are not the same, it will lead to greater clinical heterogeneity. Fourth, some of the included studies were co-intervention (vitamin E, NAC, etc), it will weaken the relative contribution of vitamin C. Fifth, some secondary results (duration of vasopressor use and 72-h Δ SOFA score) were not reported in the protocol, they were exploratory outcomes and may led to several bias. Sixth, although we performed a comprehensive database search and a manual search and made a funnel plot, which had symmetry, we did not search the gray literature or contact authors to confirm whether there were any unpublished studies. Therefore, we still cannot rule out the existence of publication bias. Additionally, TSA shows that the sample size did not reach the RIS, so the sample size was not enough to draw firm conclusions about the clinical efficacy of vitamin C, and more large multicenter RCTs are needed.

Conclusions

In this meta-analysis of patients with sepsis, the use of vitamin C was not associated with reduction in 28-day mortality, but vitamin C may have a positive effect in improving organ function. As the certainty of evidence was low, Larger RCTs were needed.

Abbreviations

CI: Confidence interval; GRADE: The Grading of Recommendations, Assessment, Development, and Evaluation; ICU: Intensive care unit; LOS: Length of stay; RCTs: Randomized controlled trials; RIS: required information size; RR: Risk ratio; SOFA: Sequential Organ Failure Assessment; SMD: standardized mean difference; TSA: Trial sequential analysis

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analysed during the current study are available from the corresponding author upon a reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

None

Authors' contributions

HC and PC conceived and designed the research questions, searched the scientific literature, collected the data, assessed quality of the studies. HC drafted the manuscript. PC played an important role in drafting the key questions. HC and KL performed statistical analyses. KL and JS contributed to the data interpretation and differences resolution. JS participated in the design, helped to revise the manuscript and provided technical or material support. All authors have read and approved the final manuscript, and agreed to be accountable for all aspects of the article in ensuring that questions related to the accuracy or integrity of any part of the article were appropriately investigated and resolved.

Acknowledgements

Not applicable.

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Figures

Figure 1

We screened a total of 1921 studies through electronic search and manual search, 47 studies were selected for full-text review after removal of duplicates and reading titles and abstracts. Finally, fourteen studies with 1823 participants were included in the systematic review. The search process and the reasons for excluding the ineligible studies are provided in Fig. 1.

Figure 2

28-day mortality was reported in 14 studies, two of them reported 30-day mortality—we approximated them to the 28-day mortality. They included a total of 1823 patients. The mortality was not significantly different between the vitamin C group and the control group (RR 0.87, 95% CI 0.73 to 1.04, $p = 0.12$).

Figure 3

TSA showed that the adjusted CI for mortality was 0.70 to 1.08 ($I^2 = 30\%$, $D^2=32\%$, $n = 1823$), and the diversity-adjusted RIS was 2530 (Fig. 3).

Supplementary Files

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