Effect of vitamin C on the risk of mortality in patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background & Aims

Vitamin C appears to be an attractive treatment option for patients with COVID-19.

Methods

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) of vitamin C versus comparative interventions administered to patients with COVID-19. The outcome of interest was all-cause mortality.

Results

The meta-analysis of nine trials using a random-effects model revealed no significant difference in the risk of all-cause mortality with the administration of vitamin C among patients with COVID-19 relative to no vitamin C (pooled odds ratio=0.57; 95% confidence interval 0.30-1.09). However, subgroup analysis of studies which included patients with severe COVID-19, produced findings of significant mortality reduction with the administration of vitamin C relative to no vitamin C (pooled odds ratio=0.52; 95% confidence interval 0.29-0.92).

Conclusion

Overall, evidence from RCTs suggests a survival benefit for vitamin C in patients with severe COVID-19. However, we should await data from large-scale randomized trials to affirm its mortality benefits.

Keywords: ascorbic; COVID-19; mortality; Vitamin C

Introduction

Vitamin C could modulate the immune response and has been hypothesized to mitigate organ dysfunction. Hence multiple clinical trials have been conducted since the beginning of the COVID-19 pandemic to investigate the effects of vitamin C on the risk of mortality in patients with COVID-19. Therefore, we undertook a systematic review and meta-analysis to synthesize evidence from randomized controlled trials that evaluated the mortality outcomes with the use of vitamin C in patients with COVID-19.

Methods

We performed systematic literature search in the following electronic databases: PubMed, Scopus, and Web of Science, for published studies, and medRxiv, Research Square, and SSRN for preprints, from inception to November 18, 2022. The literature searchers in these electronic databases were conducted based on the following keywords and their Medical Subject Heading terms (if applicable): “COVID-19”, “SARS-CoV-2”, “COVID”, “corona”, ascorbic acid", "vitamin C", "Sodium Ascorbate", and "L-ascorbic". We also hand-searched the reference lists of included articles and relevant reviews to retrieve additional relevant records. We limited the search to human and adult studies with no restrictions on publication date or publication status.

Two investigators (CSK and SSH) independently screened all the retrieved titles and abstracts for inclusion. The two investigators (CSK and SSH) also retrieved and appraised full texts of articles that were deemed possibly eligible for inclusion. The two investigators (CSK and SSH) resolved disagreement during the review process through a discussion with a third investigator (DSR) and by consensus.

We included randomized trials which evaluated the mortality outcome with the use of vitamin C against any comparative interventions in adult participants ($\geqslant$18 years) who were infected with SARS-CoV-2. We excluded non-randomized trials, single-arm trials, observational studies, case reports, reviews, conference abstracts, animal studies, and non-English language publications.

Data extraction from each included trial was performed independently by two investigators (CSK and DSR) using a pre-specified and standardized data extraction form. Data extracted included characteristics of the included studies (first author’s surname, year of publication, and country where the trial was performed), trial design, details of the population enrolled (mean/median age and illness severity), details of the study interventions (dose, frequency, and duration), details of the comparative interventions, and

mortality events. We resolved discrepancies in the data extracted by the two investigators by discussion or, if necessary, by adjudication by a third investigator (SSH).

Two investigators (CSK and SSH) independently assessed the risk of bias for each of the included trials using the Cochrane Risk of Bias Tool version 2 [1]. Disagreements were resolved by discussion with a third investigator (DSR) and by consensus. We adjudicated the risk of bias as 'low' only if all domains were assessed as low risk of bias.

The outcome of interest was all-cause mortality.

A random-effects model meta-analysis was used to estimate the pooled odds ratio for the development of outcomes of interest with the use of vitamin C relative to the use of comparative interventions at 95% confidence intervals. To evaluate the robustness of the pooled estimate, we also fitted an inverse variance heterogeneity (IVhet) model. In addition, we conducted sensitivity analyses by excluding visible outliers studies. Subgroup analysis based on the COVID-19 severity of included patients was also performed. The heterogeneity between studies was quantified using the I^2 statistics and the χ^2 test, with substantial heterogeneity predetermined at 50% and $p < 0.10$, respectively. All analyses were conducted in Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Results

Our systematic literature search on electronic databases retrieved 660 records. After deduplication, a total of 256 records were identified, and 17 records were assessed for eligibility. Eight studies were excluded either due to observational study design or reported no mortality events. In total, we included nine randomized controlled trials [2-10] in our systematic review and meta-analysis, with 368 patients randomized to receive vitamin C and 417 patients randomized to receive comparative interventions.

The characteristics of the included randomized trials are shown in **Table 1**. The regimen of vitamin C in the intervention group differed across the included trials. Most of the included trials (n = 5) [2,4,7,8,10] administered vitamin C intravenously as a fixed non–weight-based dose ranging from 2 g to 24 g daily for a duration of 4 to 7 days. One trial [3] administered vitamin C intravenously as a weight-based dose of 50 mg/kg daily. The remaining three trials [5,6,9] administered vitamin C orally/enterally as a fixed non–weight-based dose ranging from 0.2 g to 8 g daily for a duration of 10 to 14 days.

We adjudicated three trials [5,9,10] as having a low risk of bias in all domains and, thus an overall low risk of bias. We rated the remaining trials as having overall some concerns of bias (some concerns of bias in

at least one domain): the four trials reported by Zhang et al. [2], by JamaliMoghadamSiahkali et al. [4], by Tehrani et al. [7], and by Beigmohammadi et al. [8] respectively, had some concerns of bias in the domain of 'deviations from intervention' due to open-label/single-blind trial design; the trial reported by Kumari et al. [3] had some concerns of bias in the domain of 'randomization' due to inadequate information on allocation concealment and in the domain of 'deviations from intervention' due to single-blind trial design; the trial reported by Cao et al. [6] had some concerns of bias in the domain of 'deviations from intervention' due to single-blind trial design and in the domain of 'selection of the reported results' since no information on whether the trial was analyzed as pre-specified.

The meta-analysis of nine trials [2-10] using a random-effects model revealed no significant difference in the risk of all-cause mortality with the administration of vitamin C among patients with COVID-19 relative to no vitamin C; the pooled odds ratio though indicated mortality benefits (**Figure 1**; pooled odds ratio = 0.57; 95% confidence interval 0.30 to 1.09; I^2 = 26%), but is without evidence to refute the null hypothesis of 'no significant difference', at the current sample size. The IVhet model also produced non-significant evidence of mortality reduction (pooled odds ratio = 0.57; 95% confidence interval 0.29 to 1.10; I^2 = 26%) with similar heterogeneity.

Nevertheless, the sensitivity analyses by excluding visible outliers studies [5,6] revealed mortality benefits with the administration of vitamin C among patients with COVID-19 relative to no vitamin C; the pooled odds ratio indicated mortality reduction (pooled odds ratio = 0.48; 95% confidence interval 0.28 to 0.82; I^2 = 0%), and is with adequate evidence to refute the null hypothesis of 'no significant difference', at the current sample size. The IVhet model with visible outliers studies [5,6] removed also produced significant evidence of mortality reduction (pooled odds ratio = 0.48; 95% confidence interval 0.28 to 0.82; I^2 = 0%) with similar heterogeneity.

Subgroup analysis of studies [2-4,6-10] which included patients with severe COVID-19, produced findings of significant mortality reduction with the administration of vitamin C relative to no vitamin C (pooled odds ratio = 0.52; 95% confidence interval 0.29 to 0.92; I^2 = 11%). Likewise, significant evidence of mortality reduction (pooled odds ratio = 0.53; 95% confidence interval 0.29 to 0.93; I^2 = 11%) with similar heterogeneity is observed when an inverse variance heterogeneity (IVhet) model was fitted.

Discussion

In this systematic review and meta-analysis, we found significant mortality benefits with the use of vitamin C in patients with COVID-19, especially in the subgroup of patients with severe illness. The findings of our

review concur with the widely hypothesized benefits of vitamin C in patients with COVID-19 since the beginning of the COVID-19 pandemic. Vitamin C is deemed to have conducive effects in patients with COVID-19 by virtue of its immunomodulatory role. Vitamin C may have a role in various immunity pathways against COVID-19 by controlling the growth and function of innate and adaptive immune cells and producing antibodies. Besides, as a robust antioxidant, vitamin C can help ameliorate oxidative stress, which is considered a pivotal point in the pathophysiology of COVID-19. By scavenging reactive oxygen species produced in polymorphonuclear neutrophils, vitamin C may inhibit neutrophil extracellular traps (NET) production or NETosis, which contributes to the development of multiorgan injury in patients with COVID-19.

Nonetheless, we believe our findings are still not adequate to warrant the routine use of vitamin C in patients with COVID-19 for mortality reduction. Our evaluation revealed that most of the randomized trials investigating the mortality outcomes with the use of vitamin C in patients with COVID-19 had some concerns of bias. In addition, other than the trial reported by Majidi et al. [9], none of the individual trials [2-8,10] reported significant mortality reduction with the administration of vitamin C in patients with COVID-19. Also, variation in the dosing regimen of vitamin C used across the included trials precludes the recommendation of the most appropriate vitamin C administration methods in patients with COVID-19 to reduce their risk of mortality. Therefore, further randomized trials with large sample sizes should be performed to confirm the mortality benefits of vitamin C and to determine the optimal dosing strategy in this population of patients.

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Declaration of competing interest: All authors have no conflicts of interest to declare.

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Table 1: Characteristic of included studies

Study (year)	Study design	Country	Age (mean/median)	Severity of COVID-19	Regimen of vitamin C and other study interventions	Regimen of comparative intervention	Mortality events		Risk of bias[1]
							Vitamin C (n/N; %)	Non-vitamin C (n/N; %)	
Zhang et al. (2021)	Randomized, single-blind, controlled trial	China	Vitamin C group=66.3 Non-vitamin C group=67.0	Severe (baseline PaO_2/FiO_2 < 300 mmHg)	12 g twice daily intravenously for 7 days	Placebo	6/27; 22.2	11/29; 37.9	Some concerns
Kumari et al. (2020)	Randomized controlled, open-label trial	Pakistan	Vitamin C group=52.0 Non-vitamin C group=53.0	Severe (mean baseline oxygen saturation < 90%)	50 mg/kg daily intravenously + standard of care	Standard of care (antipyretics, dexamethasone, prophylactic antibiotics)	7/75; 9.3	11/75; 14.6	Some concerns
JamaliMoghadamSiahkali et al. (2021)	Randomized controlled, open-label trial	Iran	Vitamin C group=57.5 Non-vitamin C group=61.0	Severe (baseline oxygen saturation < 93%)	1.5 g every 6 hours intravenously for 5 days + standard of care	Standard of care (lopinavir/ritonavir, hydroxychloroquine)	3/30; 10.0	3/30; 10.0	Some concerns
Thomas et al. (2021)	Randomized controlled, open-label trial	United States	Vitamin C group=45.6 Vitamin C + zinc group=48.7 Zinc group=44.1 Non-vitamin C/zinc group=42.0	Mild (received outpatient care)	8 g daily orally for 10 days ± zinc gluconate + standard of care	Standard of care ± zinc gluconate	3/106; 2.8	0/108; 0	Low
Cao et al. (2020)	Randomized, single-blind, controlled trial	China	Vitamin C group=64.0 Non-vitamin C group=63.0	Severe (defined according to the Chinese management guideline for COVID-19)	0.1 g twice daily orally + standard of care	Standard of care (antiviral therapy, corticosteroid, antibiotics)	3/21; 32.6	0/20; 0	Some concerns
Tehrani et al. (2021)	Randomized controlled, open-label trial	Iran	Vitamin C group=58.0 Non-vitamin C group=61.0	Severe (mean baseline oxygen saturation < 90%)	2 g every 6 hours intravenously for 5 days + standard of care	Standard of care (lopinavir/ritonavir, hydroxychloroquine, interferon beta-1a)	0/18; 0	4/26; 15.4	Some concerns
Beigmohammadi et al. (2021)	Randomized, single-blind, controlled trial	Iran	Vitamin C group=51.0 Non-vitamin C group=53.0	Severe (admitted to intensive care unit)	0.5 g four times daily intravenously for 7 days + vitamin A, vitamin B,	Placebo	0/30; 0	4/30; 13.3	Some concerns

					vitamin D, and vitamin E				
Majidi et al. (2021)	Randomized, double-blind, controlled trial	Iran	Vitamin C group=59.4 Non-vitamin C group=63.8	Severe (admitted to intensive care unit)	0.5 g daily enterally for 14 days	Placebo	26/31; 83.9	67/69; 97.1	Low
Kumar et al. (2022)	Randomized, double-blind, controlled trial	India	Vitamin C group=57.0 Non-vitamin C group=63.3	Severe (admitted to intensive care unit)	1 g every 8 hours intravenously for 4 days	Placebo	10/30; 33.3	13/30; 43.3	Low
Labbani-Motlagh et al. (2022)	Randomized, double-blind, controlled trial	Iran	Vitamin C group=57.8 Non-vitamin C group=58.9	Moderate-to-severe	12 g every 12 hours intravenously for 4 days	Placebo	4/37; 10.8	6/37; 16.2	Low
Leal-Martínez et al. (2022)	Randomized, double-blind, controlled trial	Mexico	Vitamin C group=51.5 Non-vitamin C group=53.9	Severe (baseline oxygen saturation < 93%)	1 g twice daily orally + vitamin B complex, Spirulina maxima, folic acid, glutamine, brewer's yeast, amaranth, zinc, selenium, cholecalciferol, resveratrol, omega-3 fatty acids, L-Arginine, magnesium, Probiotic	Standard of care	1/40; 2.5	7/40; 17.5	Low

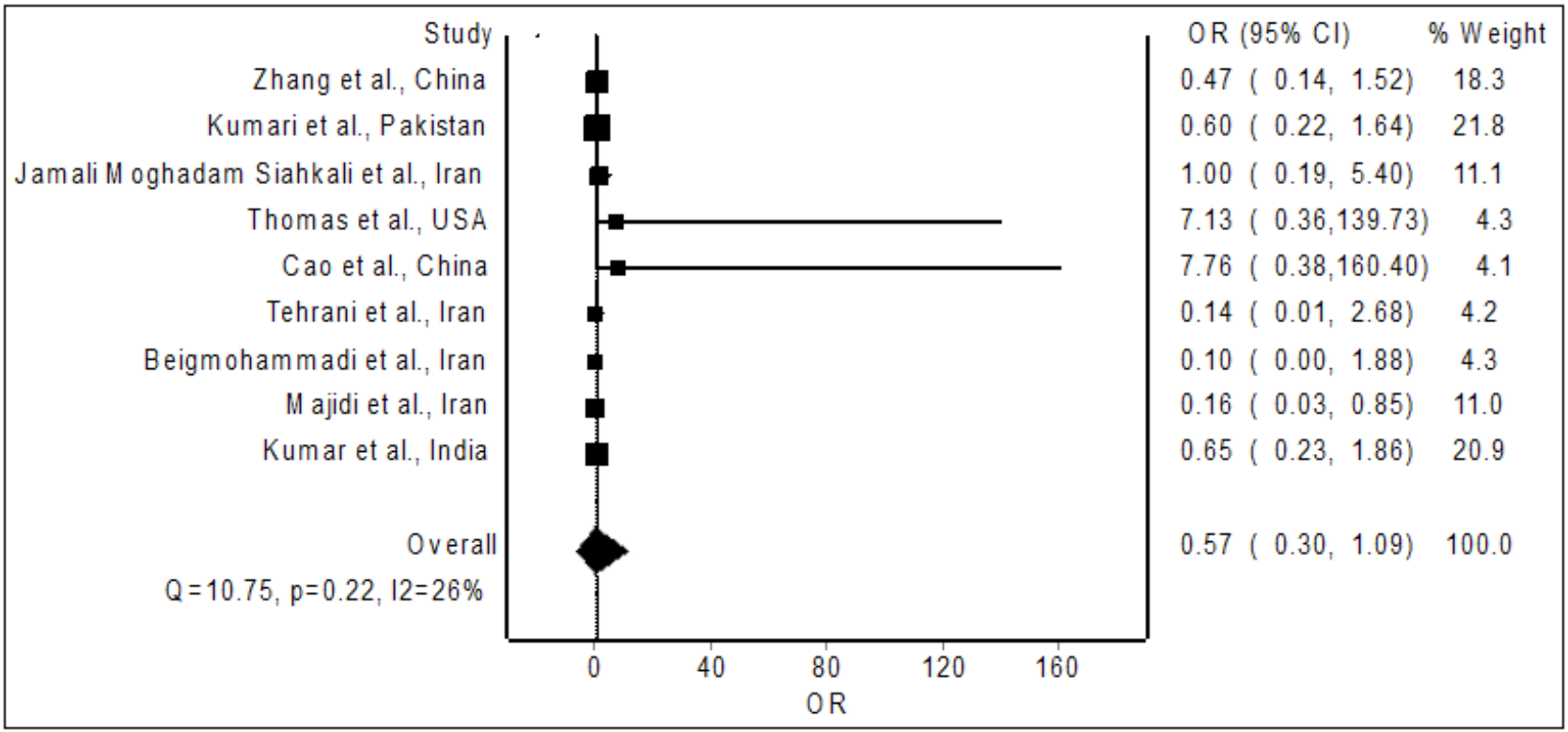

Figure 1: Pooled odds ratio for all-cause mortality with the administration of vitamin C among patients with COVID-19 relative to comparative interventions