Safety of High-Dose Vitamin C in Critically Ill Patients: A Systematic Review and Meta-analysis

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Abstract

Objective:

High-Dose Intravenous Vitamin C (HDIVC) is currently a controversial therapy for sepsis and ARDS. The published evidence regarding its efficacy in critically ill patients has shown conflicting results, and in fact, case reports have raised concerns for nephrotoxicity. The objective of this meta-analysis is to critically appraise the latest evidence regarding the safety of HDIVC in critically ill patients.

Data Sources: Structured literature search on PubMed, PubMed Central, Scopus, Embase, and Google Scholar.

Study Selection: Cross-sectional studies, case-control studies, cohort studies, randomized controlled trials, and case series with 20 or more critically ill patients who have received intravenous ascorbic acid (vitamin C), published till February 25, 2021. We identified 53 studies in our qualitative analysis and 48 studies in our quantitative analysis among a standardized search of 18,312 studies.

Data Synthesis:

We pooled data and calculated Odds Ratios (OR) and Mean Differences (MD) with their 95% confidence intervals to assess explanatory variables. Based on a random effect model from 33 studies, pooled hospital mortality outcomes showed a 19% reduction in odds for overall hospital mortality among the HDIVC group (OR, 0.81; 95% CI, 0.66-0.98). Mortality at 28/30-days, ICU mortality, length of hospital stay (LOS), new-onset AKI, and Renal Replacement Therapy (RRT) for AKI did not differ significantly across treatment and control groups. Pooled data from 30 studies disclosed 0.76 fewer ICU days in the HDIVC group than the placebo/ standard of care (SOC) group, 95% CI, -1.34 to -0.19. This significance persisted when we included RCTs only in the analysis (MD, -0.70; 95% CI, -1.39 to -0.02).

Conclusions:

Our results suggest that HDIVC treatment is renally safe and did not increase adverse kidney events, or mortality. It was associated with a slight reduction in ICU length of stay in critically ill patients.

1. Introduction

Vitamin C, also referred to as ascorbic acid, is an essential water-soluble vitamin synthesized by most animals and plants. (1) Humans, along with some mammals, such as gorillas, monkeys, guinea pigs, and bats lost the ability to synthesize vitamin C. (2) Humans cannot survive for extended periods without intake of vitamin C. (3) Recent animal and human trials proposed a plethora of mechanisms for vitamin C, including antioxidant, stress-hormone-like effects, and immune-modulating effects in a plethora of tissues and organs, including the lung, bone marrow, inflammatory cells, adrenals, pituitary glands. (4)

Over the last decade, studies have shown that high-dose intravenous vitamin C (HDIVC) attenuates systemic inflammation, corrects sepsis-induced coagulopathy, and attenuates vascular injury. (5–7). In a preliminary study conducted by Fowler et al. 2014, HDIVC decreased the magnitude of organ failure in critically ill patients with ARDS. (7) The subsequent CITRIS-ALI trial reported a significant difference in 28-day mortality as a

secondary outcome: 29.8% in the HDIVC group, compared with 46.3% in the placebo group. (8) However, it failed to improve organ dysfunction scores or alter the level of inflammatory markers and vascular injury. (9) Others demonstrated a reduction of the dose and duration of vasopressors use in surgical patients with septic shock, (10) and mortality in severe burn patients. (11)

On the other hand, well-designed trials which examined intermediate-dose vitamin C in the context of a cocktail of thiamine and hydrocortisone failed to show any outcome differences in patients with sepsis and septic shock. (12–15) Case reports have reported harms related to HDIVC, such as oxalate nephropathy (16–19) and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) (20–22). In addition, observational studies have confirmed the interference with the point-of-care glucose testing (23, 24), extrapolating a risk for life-threatening hypoglycemia. A recent structured review on the topic, which reviewed 74 studies, including nine double-blind, randomized trials, (25) confirmed that *attributed* adverse effects of vitamin C do exist. However, when they examined only randomized trials, the adverse events in the vitamin C group were the same as the control group. (25)

To further clarify evidence from anecdotal reports, we sought to critically appraise the available evidence on the harm of intravenous vitamin C by conducting this extensive systematic review and meta-analysis.

2. Methods

This systematic review was conducted according to predefined criteria as registered on PROSPERO (CRD42020222906). (26) We prepared and conducted the study as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. (27)

2.1 Search Strategy

We conducted a literature search on PubMed, PubMed Central, Scopus, Embase, and Google Scholar to collect relevant studies which assessed the use of intravenous vitamin C in critically ill patients published till February 25, 2021. We used the keywords Vitamin C, Ascorbic acid, critically ill, ICU, sepsis, lactic acidosis, antioxidant, using appropriate Boolean operators with no language restrictions. Details of the search strategy are available in Appendix 1.

2.2 Selection criteria

We included studies with the following characteristics:

1. Type of studies: Cross-sectional studies, case-control studies, cohort studies, randomized controlled trials and case series with 20 or more patients.
2. Population: Critically ill patients of all age groups.
3. Intervention: Vitamin C alone or in combination with other antioxidants. The comparator includes standard of care (SOC) or placebo.
4. Study outcome: The primary outcome examined was ICU mortality, length of ICU and hospital stay, need for mechanical ventilation and vasopressor support, improvement in clinical parameters and laboratory value, improvement in lactic acidosis, complications prevention, and adverse effects of vitamin supplementation. We used Odds Ratios (OR) and Risk Ratios (RR) to assess for explanatory variables.

We excluded studies with the following characteristics:

1. Types of studies: Meta-analysis, reviews, case reports, editorials, opinions, letters, protocols, abstracts/presentations, dissertation, and animal studies.
2. Full-text articles not available.
3. Ongoing studies.
4. Studies with incomplete data.

2.3 Data extraction

We used the Covidence platform for screening and eligibility assessment of the retrieved citations. (28) Two reviewers (SK and SS) independently reviewed the studies for eligibility, and a third reviewer (SM) resolved any conflict. The data extraction sheet was created using Microsoft Excel. One reviewer collected the data from all articles; the second reviewer verified the data for accuracy and highlighted discrepancies; the third reviewer resolved any disagreements and carried out a thorough evaluation to ensure that only the outcomes of interest were considered.

2.4 Risk of bias

We used the Cochrane Risk of Bias (ROB) 2.0 tool for RCTs and Joanna Briggs Institute (JBI) critical appraisal checklist for cohorts and case series for quality and risk of bias assessment. (29) (30) We used Review Manager (RevMan) 5.4 for creating a summary of biases for RCTs. (31) The Risk of Bias grid can be found in the eFigure 1.

2.5 Statistical analysis

We used Revman 5.4 for performing statistical analysis using Odds Ratios (OR) to estimate dichotomous outcomes whenever appropriate with 95% Confident Interval (CI). We used the fixed/random-effects model as per the heterogeneity. We analyzed the mean differences (MD) between the two groups for continuous variables. Means were calculated using the median, sample size, and inter-quartile range when mean and standard deviation were not provided in the study. (32)

2.6 Assessment of heterogeneity

The statistical heterogeneity among the studies was calculated and assessed with the I^2 test based on previously recommended stratifications (low, moderate, and high to I^2 values of 25%, 50%, and 75%, respectively). (33) In cases of heterogeneity, we used the invariance and random-effect model. We evaluated the sensitivity by rerunning the analysis to assess any unrevealed differences.

3. Results

We identified a total of 18312 studies after thorough database searching. After removing 1248 duplicates, we screened the title and abstracts of 17064 studies and excluded 16720 studies. We assessed the full text of 344 studies and excluded 291 studies with definite reasons. We included 53 studies in our qualitative analysis and 48 studies (27 randomized controlled trials and 21 observational studies) in our quantitative analysis. The PRISMA flow diagram can be found in Fig. 1.

3.1 Qualitative synthesis

Fifty-three studies were included in the qualitative synthesis. Of them, 23 were observational studies, while the rest 30 were RCTs (**Appendix 1: Tables 1 and 2**).

3.2 Quantitative synthesis

Among 48 studies included in quantitative extraction, 21 were observational studies, and 27 RCTs were used in the quantitative synthesis (**Appendix 2**).

3.2.1 Hospital Mortality

Pooled hospital mortality data with a random effect model from 33 studies showed 19% reduction in odds for overall hospital mortality (OR, 0.81; 95% CI, 0.66–0.98; $n = 4740$; $I^2 = 31\%$; $p = 0.03$). A subgroup analysis for observational and RCTs showed 33% reduction in mortality (OR 0.67, 95% CI 0.50–0.91; $n = 2603$; $I^2 = 50\%$; $p = 0.009$). Such relation was **not** seen while pooling hospital mortality among 15 RCTs only (OR 0.97, 95% CI 0.77–1.23; $n = 2137$; $I^2 = 0\%$; $p = 0.82$, Fig. 2).

Subgroup analysis of surgical and sepsis/septic shock patients disclosed no mortality difference for neither patients with sepsis/septic shock (OR, 0.98; 95% CI, 0.76–1.26; $n = 1297$; $I^2 = 0\%$; $p = 0.86$) nor surgical patients (OR, 1.08; 95% CI, 0.63–1.86; $n = 860$; $I^2 = 4\%$, **Appendix 2: Fig. 1**).

Mortality was slightly higher in double-blind trials among HDIVC group (OR, 1.04; 95% CI, 0.76–1.43; $n = 938$; $I^2 = 0\%$; $p = 0.80$) while for single blind/open odds was slightly reduced (OR 0.92, 95% CI 0.65 to 1.29; $n = 1199$; $I^2 = 0\%$; $p = 0.61$) comparing with placebo or SOC group; it could not however reach statistical significance (**Appendix 2: Fig. 2**).

A separate analysis was done based on concomitant use of antioxidants. Analysis comparing placebo/ SOC with HDIVC (OR, 0.93; 95% CI, 0.49–1.76; $n = 207$; $I^2 = 5\%$; $p = 0.82$) and placebo/ SOC with other concomitant antioxidants use with HDIVC (OR, 0.99; 95% CI, 0.77–1.27; $n = 1930$; $I^2 = 0\%$; $p = 0.94$) also could not show significant differences in hospital mortality (**Appendix 2: Fig. 3**).

Sensitivity analysis among observational studies

In the sepsis /septic shock, group mortality was not significant (OR, 0.73; 95% CI, 0.46–1.15; $n = 340351$; $I^2 = 86\%$; $p = 0.17$), while among surgical patients (OR, 0.69; 95% CI, 0.56–0.85; $n = 5143$; $I^2 = 4\%$; $p = 0.0005$) a significant reduction in hospital mortality was observed in the HDIVC group (**Appendix 2: Fig. 4**). A comparison of concomitant antioxidants use with HDIVC showed significant reduction in hospital mortality (OR, 0.60; 95% CI, 0.38–0.95; $n = 344531$; $I^2 = 91\%$; $p < 0.0001$, **Appendix 2: Fig. 5**).

Using a fixed effect model, pooled of data from 17 studies disclosed 0.88 odds of 28/30-days mortality among HDIVC group comparing with placebo/SOC (95% CI, 0.74–1.04; $n = 3405$; $I^2 = 28\%$; $p = 0.13$), which did not reach statistical significance. Subgroup analyses based on study types showed a 0.80 odds of 28/30-days mortality among HDIVC group among RCTs (OR, 0.80; 95% CI, 0.64–1.00; $n = 2131$; $I^2 = 37\%$; $p = 0.05$) which also did not

differ significantly with placebo/SOC. Similarly, examining observational studies only also showed no significant differences across two groups (**Appendix 2: Fig. 6**).

ICU mortality

Pooled data from 14 studies which reported ICU mortality showed OR of 0.83 for overall ICU mortality (95% CI, 0.61–1.13; $n = 2448$; $I^2 = 38\%$; $p = 0.24$). Similarly, further subgroup analysis taking type of study under consideration showed similar result with RCTs (OR, 1.02; 95% CI, 0.75–1.38; $n = 1716$; $I^2 = 0\%$; $p = 0.91$) and observational studies (OR, 0.69; 95% CI, 0.41–1.17; $n = 732$; $I^2 = 55\%$; $p = 0.17$, **Appendix 2: Fig. 7**).

3.2.2 Hospital Length of Stay

Pooled data from 24 studies reporting length of hospital stay (LoHS) outcome using random effect model showed mean difference of -0.84 days comparing HDIVC group with placebo/SOC (95% CI, -2.11 to 0.44; $n = 252961$; $I^2 = 94\%$; $p = 0.20$). Similarly, further subgrouping of LoHS outcome based on type of study also could not reach level of significance for reduction in LoHS among HDIVC group comparing with placebo/SOC among RCTs (MD, -0.69; 95% CI, -1.79 to 0.41; $n = 1804$; $I^2 = 62\%$; $p = 0.22$) and observational studies (MD, -1.45; 95% CI, -3.78 to 0.87; $n = 251157$; $I^2 = 97\%$; $p = 0.22$)

Among patients in sepsis/septic shock there was no significant differences in length of hospital stay between two groups (**Appendix 2: Fig. 8**).

An analysis for LoHS taking RCTs based on blinding of trials showed significant reduction in length of hospital stay of HDIVC group among both double blinded trials (MD, -0.54; 95% CI, -1.43 to 0.36; $n = 1247$; $I^2 = 34\%$; $p = 0.24$) and single blinded/open RCTs reduction in LoHS among HDIVC group could not reach statistical significance (**Appendix 2: Fig. 9**). Analysis comparing HDIVC only with placebo/ SOC showed on an average 1.7 day reduction in LoHS among HDIVC group (**Appendix 2: Fig. 10**).

Sensitivity analysis among observational studies

In both sepsis/septic shock group (MD, 1.34; 95% CI, -0.43 to 3.10; $n = 246631$; $I^2 = 64\%$; $p = 0.14$) and surgical group (MD, -5.25; 95% CI, -14.19 to 3.69; $n = 4526$; $I^2 = 97\%$; $p = 0.25$) reduction in LoHS could not reach statistical significance comparing HDIVC with placebo/ SOC groups (**Appendix 2: Fig. 11**).

An examination of concomitant use of other antioxidants with HDIVC among observational studies also could not show significant differences in length of hospital stay comparing placebo/ SOC with HDIVC only (**Appendix 2: Fig. 12**).

3.2.4 New-onset acute kidney injury (AKI)

A pool analysis new onset AKI outcome using fixed effect model from 12 studies showed no significant increment in new AKI (OR, 1.23; 95% CI, 0.95 to 1.59; $n = 5330$; $I^2 = 0\%$; $p = 0.12$). Similarly, considering type of study also could not show significant increment in new AKI among observational studies (OR, 1.36; 95% CI, 0.87 to 2.12; $n = 4482$; $I^2 = 37\%$; $p = 0.18$) and RCTs (OR, 1.16; 95% CI, 0.85 to 1.60; $n = 848$; $I^2 = 0\%$; $p = 0.35$, Fig. 3)

A pool analysis of new-onset AKI outcome using random-effect model also showed no significant difference in new AKI outcome (OR, 1.22; 95% CI, 0.94 to 1.58; $n = 5330$; $I^2 = 0\%$; $p = 0.14$). Similarly, the type of study could not show significant changes among observational studies and RCTs (**Appendix 2: Fig. 13**).

3.2.5 Renal replacement therapy (RRT) for AKI

In terms of requirement for RRT in AKI, a pooled analysis with random effect model from 13 studies showed no significant differences in overall requirement of RRT for AKI (OR, 0.80; 95% CI, 0.63 to 1.01; $n = 1989$; $I^2 = 0\%$; $p = 0.06$). This applied both for observational studies (OR, 0.80; 95% CI, 0.61 to 1.04; $n = 1518$; $I^2 = 0\%$; $p = 0.09$) and RCTs (OR, 0.81; 95% CI, 0.47 to 1.39; $n = 471$; $I^2 = 9\%$; $p = 0.44$).

Discussion

After a detailed systematic review of published literature, we pooled the results of 48 studies, including 27 randomized controlled trials and 21 observational studies that examined the safety of HDIVC in critically ill patients. We found a reduction in overall hospital mortality with the use of HDIVC in critically ill patients, which contrasted with the earlier meta-analyses by Langlois et al. and Wei et al. (34, 35). However, this finding may be due to the inclusion of observational studies in our cumulative analysis. This finding was not replicated when sensitivity analysis was performed separately for the randomized controlled trials. However, a reduction in mortality was seen in the analysis of observational studies alone.

Critically ill and surgical patients and patients with critical illness, including sepsis, are exposed to oxidative stress that plays a significant role in the pathophysiology of the inflammatory syndrome in both populations. A high proportion of surgical patients suffer from vitamin C deficiency, and the intense inflammatory process leads to increased turnover of vitamin C, resulting in severe deficiency. (36)·(37) Parenteral HDIVC has been investigated for its potential role in alleviating the inflammatory response and oxidative stress, improving immune function, regulating microcirculation, and preventing thrombosis. (38) However, we found no difference in mortality in patients receiving HDIVC while performing subgroup analysis among surgical patients or patients with sepsis/septic shock among RCTs. At the same time, among observational studies, the benefit is observed among surgical patients. We also found no difference in the hospital length of stay even with further subgroup analysis.

However, some but significant reduction in ICU stay among while analyzing all studies reporting ICU stay and among RCTs only separately, although a level of statistical significance could not be achieved while analyzing observational studies separately. Prior meta-analyses by Langlois et al., Putzu et al., and Wei et al. found no difference in duration of hospital stay and ICU stay among critically ill patients with intravenous vitamin C.(34, 39) Putzu et al. found a decreased length of hospital and ICU stay among patients undergoing cardiac surgery on subgroup analysis. (39) This might be explained by the fact that HDIVC has been shown to decrease the risk of postoperative atrial fibrillation in patients undergoing cardiac surgery and thus decrease the length of hospital and ICU stay as per prior meta-analysis. (40, 41)

Excess of vitamin C has been shown to have adverse renal effects due to the increased amount of oxalate formed as a byproduct of vitamin C that accumulates in the kidney triggering acute kidney injury. (42) However, we found no increment in new-onset acute kidney injury and requirement for renal replacement therapy due to AKI among critically ill patients receiving HDIVC, which was similar to prior meta-analyses done by Putzu et al.

and Wei et al. (35, 39) Most of the trials have not reported any significant adverse effect with the use of vitamin C. Based on the best available evidence, this risk remains theoretical, and not evidence-based.

The present meta-analysis is the most comprehensive meta-analysis, including 48 studies in quantitative analysis and an abundant clinical outcome. We only included studies in which parenteral vitamin C was administered. This was because a higher dosage of oral vitamin C saturates the intestinal absorption system achieving inadequate plasma concentration. Prior meta-analyses done in the role of HDIVC among critically ill patients have included fewer studies than our analysis and included patients receiving both oral and parenteral HDIVC, which adds to the strength of our research. (34, 35, 39). Our analysis was strengthened by the findings of various subgroup analyses, based on the clinical settings of medical and surgical patients, sepsis/septic shock, of studies.

This study has several limitations. The included RCTs and observational studies have their inherent limitations. Baseline characteristics and assessment of organ dysfunction were not individually reported across studies. Formulation and dose of vitamin C is comparable and offer granularity of data in assessing individual influence. Patients could have been enrolled in different severity stages of sepsis and ARDS, where clinical outcomes could have been impacted given the stage of pathology.

Further, ICU pathophysiology is complex, and clinical outcomes are determined by several factors that are not reversed by HDIVC therapy alone and confound the results. Various included studies in our analysis had treatment with other antioxidants, thiamine, and steroids, acting as potential confounders. Our observation in terms of no difference in acute kidney injury and the need for renal replacement therapy is reassuring in terms of renal safety of HDIVC therapy. It can guide future investigators and enable further trials in specific syndromes, such as ARDS and COVID-19.

Conclusions

The present systematic review and meta-analysis interrogated 48 studies: 27 randomized controlled trials and 21 observational studies. It critically appraised the evidence and confirmed the safety of vitamin C in critically ill patients. HDIVC therapy was found to be safe from a renal standpoint since we found no significant differences in AKI and the need for RRT. Based on this analysis, the risk for AKI from oxalate nephropathy remains a theoretical and not an evidence-based risk. HDIVC reduced the length of hospitalization, although it did not reduce the number of ICU days. Furthermore, HDIVC did not increase the overall hospital or ICU mortality in surgical and sepsis patients. There was a paucity of ARDS or COVID-19 trials to make definitive inferences in those patient populations.

Declarations

Ethics approval and consent to participate: Not Applicable (meta-analysis).

Consent for publication: All authors provided consent for publication.

Availability of supporting data: The original datasets are available from the corresponding author on request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: DBS, PB, and YRS, MGK contributed to the concept and design, analysis, and interpretation of data. MGK, XQ, AA DBS, PB, YRS, SM, SS, and SK contributed to the review and initial manuscript drafting. All authors were involved in drafting and revising the manuscript and approved the final version.

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References

1. Smirnoff N, Conklin PL, Loewus FA: Biosynthesis of ascorbic acid in plants: A renaissance [Internet]. *Annual Review of Plant Biology* 2001; 52:437–467[cited 2021 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/11337405/>.
2. Drouin G, Godin J-R, Page B: The Genetics of Vitamin C Loss in Vertebrates [Internet]. *Current Genomics* 2011; 12:371–378[cited 2021 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/22294879/>.
3. Bartholomew M: James lind's treatise of the scurvy (1753). [Internet]. *Postgraduate Medical Journal* 2002; 78:695–696 Available from: <http://pmj.bmj.com/cgi/doi/10.1136/pmj.78.925.695>.
4. Kashiouris MG, L'heureux M, Cable CA, et al.: The emerging role of vitamin C as a treatment for sepsis. *Nutrients* 2020; 12.
5. Fisher BJ, Kraskauskas D, Martin EJ, et al.: Mechanisms of attenuation of abdominal sepsis-induced acute lung injury by ascorbic acid. *American Journal of Physiology - Lung Cellular and Molecular Physiology* 2012; 303.
6. Fisher BJ, Seropian IM, Kraskauskas D, et al. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury*. *Crit Care Med.* 2011;39:1454–60.
7. Fowler AA, Syed AA, Knowlson S, et al.: Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *Journal of Translational Medicine* 2014; 12.
8. Fowler AA, Truwit JD, Hite RD, et al.: Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients with Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. *JAMA - Journal of the American Medical Association* 2019; 322.
9. Truwit J, Hite R, Morris P, et al.: Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS. *jamanetwork.com*.
10. Zabet M, Mohammadi M, Ramezani M, et al. Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. *Journal of Research in Pharmacy Practice.* 2016;5:94.
11. Kato R, Nakajima K, Takahashi T, et al. A case of advanced systemic sclerosis with severe GERD successfully treated with acotiamide. *Surgical case reports.* 2016;2:36.
12. Fujii T, Luethi N, Young PJ, et al.: Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support among Patients with Septic Shock: The VITAMINS Randomized Clinical Trial [Internet]. In: *JAMA - Journal of the American Medical Association.* American

- Medical Association; 2020. p. 423–431.[cited 2021 May 6] Available from: <https://pubmed.ncbi.nlm.nih.gov/31950979/>.
13. Sevransky JE, Rothman RE, Hager DN, et al. Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- And Vasopressor-Free Days in Patients with Sepsis- And VICTAS Randomized Clinical Trial. *JAMA - Journal of the American Medical Association*. 2021;325:742–50.
 14. Moskowitz A, Huang DT, Hou PC, et al.: Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock: The ACTS Randomized Clinical Trial [Internet]. *JAMA* 2020; 324:642–650[cited 2021 May 6] Available from: <https://pubmed.ncbi.nlm.nih.gov/32809003/>.
 15. Hager DN, Hooper MH, Bernard GR, et al.: The Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) Protocol: A prospective, multi-center, double-blind, adaptive sample size, randomized, placebo-controlled, clinical trial [Internet]. *Trials* 2019; 20[cited 2021 May 6] Available from: <https://pubmed.ncbi.nlm.nih.gov/30953543/>.
 16. Lawton JM, Conway LT, Crosson JT, et al.: Acute Oxalate Nephropathy After Massive Ascorbic Acid Administration [Internet]. *Archives of Internal Medicine* 1985; 145:950–951[cited 2021 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/3994472/>.
 17. Buehner M, Pamplin J, Studer L, et al.: Oxalate nephropathy after continuous infusion of high-dose Vitamin C as an adjunct to burn resuscitation [Internet]. *Journal of Burn Care and Research* 2016; 37:e374–e379[cited 2021 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/25812044/>.
 18. Cossey LN, Rahim F, Larsen CP: Oxalate nephropathy and intravenous vitamin C [Internet]. *American Journal of Kidney Diseases* 2013; 61:1032–1035[cited 2021 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/23548555/>.
 19. WONG K, THOMSON C, BAILEY RR, et al.: Acute oxalate nephropathy after a massive intravenous dose of vitamin C [Internet]. *Australian and New Zealand Journal of Medicine* 1994; 24:410–411[cited 2021 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/7980244/>.
 20. Rees DC, Kelsey H, Richards JDM: Acute haemolysis induced by high dose ascorbic acid in glucose-6-phosphate dehydrogenase deficiency [Internet]. *British Medical Journal* 1993; 306:841–842[cited 2021 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/8490379/>.
 21. Mehta JB, Singhal SB, Mehta BC: Ascorbic-acid-induced haemolysis in G-6-PD deficiency [Internet]. *The Lancet* 1990; 336:944[cited 2021 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/1976956/>.
 22. Campbell GD, Steinberg MH, Bower JD: Ascorbic acid induced hemolysis in G 6 PD deficiency [Internet]. *Annals of Internal Medicine* 1975; 82:810[cited 2021 May 5] Available from: <https://pubmed.ncbi.nlm.nih.gov/1138591/>.
 23. Smith KE, Brown CS, Manning BM, et al. Accuracy of Point-of-Care Blood Glucose Level Measurements in Critically Ill Patients with Sepsis Receiving High-Dose Intravenous Vitamin C. *Pharmacotherapy*. 2018;38:1155–61.
 24. Sartor Z, Kesey J, Dissanaik S. The effects of intravenous vitamin C on point-of-care glucose monitoring. *Journal of Burn Care Research*. 2015;36:50–6.
 25. Yanase F, Fujii T, Naorungroj T, et al.: Harm of IV High-Dose Vitamin C Therapy in Adult Patients: A Scoping Review. *Critical Care Medicine* 2020; E620–E628.

26. (No Title) [Internet]. [cited 2021 Feb 24] Available from:
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=228312.
27. Liberati A, Altman DG, Tetzlaff J, et al.: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical research ed)* 2009; 339.
28. How. can I cite Covidence? [Internet]. [cited 2021 January 26] Available from:
<https://support.covidence.org/help/how-can-i-cite-covidence>.
29. Sterne JAC, Savović J, Page MJ, et al.: RoB 2: A revised tool for assessing risk of bias in randomised trials. *The BMJ* 2019; 366.
30. critical-appraisal-tools. - Critical Appraisal Tools | Joanna Briggs Institute [Internet]. [cited 2020 Dec 18] Available from: <https://joannabriggs.org/critical-appraisal-tools>.
31. RevMan for non-Cochrane reviews | Cochrane Training [Internet]. [cited 2021 Jan 26] Available from:
<https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-non-cochrane-reviews>.
32. Mean Variance Estimation [Internet]. [cited 2021 Feb 16] Available from:
<https://web.archive.org/web/20181224162602/http://www.comp.hkbu.edu.hk/~xwan/median2mean.html>.
33. 9.5.2. Identifying and measuring heterogeneity [Internet]. [cited 2020 Dec 18] Available from:
https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm.
34. Langlois PL, Manzanares W, Adhikari NKJ, et al. Vitamin C Administration to the Critically Ill: A Systematic Review and Meta-Analysis. *Journal of Parenteral Enteral Nutrition*. 2019;43:335–46.
35. Wei X, Wang Z, Liao X, et al.: Efficacy of vitamin C in patients with sepsis: An updated meta-analysis. *European Journal of Pharmacology* 2020; 868.
36. Doll S, Ricou B. Severe vitamin C deficiency in a critically ill adult: A case report. *Eur J Clin Nutr*. 2013;67:881–2.
37. Luo M, Fernandez-Estivariz C, Jones DP, et al. Depletion of plasma antioxidants in surgical intensive care unit patients requiring parenteral feeding: effects of parenteral nutrition with or without alanyl-glutamine dipeptide supplementation. *Nutrition*. 2008;24:37–44.
38. Fowler AA, Syed AA, Knowlson S, et al.: Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *Journal of Translational Medicine* 2014; 12.
39. Putzu A, Daems A-M, Lopez-Delgado JC, et al. The Effect of Vitamin C on Clinical Outcome in Critically Ill Patients. *Crit Care Med*. 2019;47:774–83.
40. Hemilä H, Chalker E. Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis. *Nutrients*. 2019;11:708.
41. Shi R, Li ZH, Chen D, et al. Sole and combined vitamin C supplementation can prevent postoperative atrial fibrillation after cardiac surgery: A systematic review and meta-analysis of randomized controlled trials. *Clin Cardiol*. 2018;41:871–8.
42. Colliou E, Mari A, Delas A, et al. Oxalate nephropathy following vitamin C intake within intensive care unit. *Clin Nephrol*. 2017;88:354–8.

Figure 1. PRISMA Flow Diagram

Figure 1

PRISMA Flow Diagram

Figure 2

Forest plot showing overall hospital mortality using a random-effect model.

Figure 3

Forest plot of Acute Kidney Injury (AKI) in vitamin C vs. Placebo.

Supplementary Files

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