Dear Editor:

Sepsis continues to be leading cause of mortality among patients admitted to intensive care unit (ICU), with about 48.9 million cases of sepsis diagnosed and 11 million deaths worldwide in 2017 [1]. Despite significant advances in the understanding of the pathophysiology of sepsis, the mainstay management still relies on active fluid resuscitation for hemodynamic support, early administration of antibiotics, and identification of source and infection control [2]. Vitamin C has been suggested as a possible therapy that attenuates the pathophysiology of sepsis [2]. Multiple randomized controlled trials (RCTs) addressing effectiveness and safety of vitamin C have reported varied conclusions [3]. Previously, published meta-analysis were limited by the sample size and highlighted the need of further studies with a larger number of patients to provide further evidence [3]. The recent publication of results from LOVIT (Lessening Organ Dysfunction with Vitamin C), the largest trial to date addressing this question, justifies re-examination of the evidence [4].

PubMed and Scopus databases were searched for relevant studies by two investigators (MAT, UA) using the following keywords: “ascorbic,” “Vitamin C,” “ascorbic acid,” “sepsis,” “septic shock.” Studies were included if they were: (1) RCT (2) comprised of adult patients with Sepsis or septic shock (3) treatment arm: high-dose intravenous (IV) vitamin C (≥1.5 g every 6 hours or 25 mg/kg every 6 hours) either as monotherapy or combination therapy with thiamine and hydrocortisone, (4) control arm: placebo or standard regiment. Outcomes of interest were ICU mortality, 30-day and 90-day mortality, change in Sequential Organ Failure Assessment score (delta SOFA) within 72 hours. Subgroup analyses were conducted for vitamin C as monotherapy versus combination therapy. Review articles, non-randomized studies, conference abstracts and studies published prior to 2010 were excluded. Odds ratios (ORs) or weighted mean difference (WMD) with 95% confidence intervals (CI) were calculated using random effects model. Statistical heterogeneity in studies was assessed by $I^2$ statistics. A P<0.05 was considered significant.

The initial literature search identified 854 unique studies, 14 trials with 2,793 patients met the eligibility criteria [3-5]. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart of the study selection is shown in Supplementary Figure 1. Baseline study characteristics are shown in Supplementary Table 1. IV vitamin C in combination with thiamine and hydrocortisone significantly reduced SOFA score at 72 hours (7 RCTs, 1,318 patients; WMD: −0.52, 95% CI: −1.01 to −0.03, P=0.037, $I^2$=53%) (Figure 1D). For...
Figure 1. Forest plot showing the effect of intravenous vitamin C compared with control on (A) intensive care unit (ICU) mortality, (B) 30-day mortality, (C) 90-day mortality, and (D) change in Sequential Organ Failure Assessment (SOFA) score at 72 hours. Vit: vitamin; MH: Mantel-Haenszel; CI: confidence interval; HAT: hydrocortisone, ascorbic acid, and thiamine. A list of articles indicated in Figure 1 can be found in the online Supplementary Table 1. (Continued to the next page)
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other outcomes, IV vitamin C was not statistically significant in reducing the ICU mortality (6 RCTs, 1,284 patients; OR: 0.98, 95% CI: 0.74 to 1.30, P=0.91, I²=0.0%) (Figure 1A), 30-day mortality (14 RCTs, 2,783 patients; OR: 0.87, 95% CI: 0.69 to 1.09, P=0.22, I²=32.0%) (Figure 1B), 90-day mortality (5 RCTs, 1,740 patients; OR: 1.10, 95% CI: 0.91 to 1.34, P=0.33, I²=0.0%) (Figure 1C). The results were consistent across the subgroups.

In this meta-analysis we analyzed IV vitamin C therapy in sepsis summarizing the most recent available clinical data. Overall meta-analysis results indicate use of IV high dose vitamin C in combination with thiamine and hydrocortisone is associated with significantly improved SOFA score at 72 hours but has no effect on ICU stay and mortality. However, the clinical significance of reduction in SOFA score is still unclear and caution should be exercised when utilizing surrogate outcomes instead of patient centered outcomes such as mortality. In conclusion, this systematic review and meta-analysis provide conclusive evidence into the effects of IV vitamin C in sepsis. With marginal improvement in delta SOFA among septic patients there no mortality benefit. Little evidence exists to support the routine use of vitamin C in sepsis patients.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**ORCID**

Muhammad Ali Tariq  https://orcid.org/0000-0003-1108-0731
Hamza Amin  https://orcid.org/0000-0001-8564-4195
Uzair Ali  https://orcid.org/0000-0003-0993-0901

**AUTHOR CONTRIBUTIONS**

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**SUPPLEMENTARY MATERIALS**

Supplementary materials can be found via https://doi.org/10.4266/acc.2021.01088.

**REFERENCES**