Unclear reporting of secondary outcome in randomized trial of Lv et al

Arnav Agarwal¹ · François Lamontagne² · Neill K. J. Adhikari³

Received: 5 October 2021 / Accepted: 6 October 2021 / Published online: 12 October 2021
© The Author(s), under exclusive licence to Royal Academy of Medicine in Ireland 2021

To the editor: We read with interest the randomized controlled trial published by Lv and colleagues [1]. This single-centre trial randomized 117 patients admitted to the intensive care unit with sepsis to moderate-dose vitamin C (total daily dose not explicitly stated, but likely 6 g) or placebo. The trial found a statistically significant difference in 28-day mortality (15/61 [24.6%] in vitamin C group vs. 24/56 [42.9%] in the placebo group, $p = 0.002$).

Change in sepsis-related organ failure assessment (SOFA) score [2] in the first 72 h after intensive care unit admission was a secondary outcome; higher SOFA scores denote worse organ dysfunction and are associated with increased risk of mortality. Comparable baseline SOFA scores were reported (mean $\pm$ standard deviation, 8.6 ± 2.9 [vitamin C] vs. 8.9 ± 3.1 [placebo]); however, reporting of follow-up data is inconsistent. The results text and Table 2 indicate that patients receiving vitamin C had greater organ failure at 72 h than controls (median [quartile 1, quartile 3] SOFA score 4.2 [1.2, 6.6] vs. 2.1 [1.1, 4.3], $p = 0.001$). Conversely, the results and conclusion of the abstract, along with the discussion and conclusion of the paper, suggest that patients receiving vitamin C had a greater change in 72-h vs. baseline SOFA score compared to controls (change in SOFA score, as reported in the abstract, 4.2 vs. 2.1, with values implied to be reductions and the larger reduction in the vitamin C group).

The issue is important to resolve, both for the interpretation of this trial and of published meta-analyses, which have assumed that the SOFA data reported by Lv and colleagues refer to change in SOFA at 72 h [3].

We attempted to contact the authors on two occasions to clarify their data, with no success.

Author contribution AA drafted the first version of this letter. All authors revised the letter and approved the final version.

Funding None.

Data availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent to publish Not applicable.

Competing interests NKJA and FL are co-principal investigators of Lessening Organ dysfunction with VITamin C, a randomized trial of vitamin C for sepsis (NCT03680274), and of Lessening Organ dysfunction with Vitamin C-COVID, a randomized trial of vitamin C for COVID-19 (NCT04401150). AA has no conflicts of interest to declare.

References

1. Lv SJ, Zhang GH, Xia JM et al (2021) Early use of high-dose vitamin C is beneficial in treatment of sepsis. *Ir J Med Sci* 190(3):1183–1188. <https://doi.org/10.1007/s11845-020-02394-1>
2. Vincent JL, Moreno R, Takala J et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 22 (7):707–710. <https://doi.org/10.1007/BF01709751>
3. Sato R, Hasegawa D, Prasitlumkum N et al (2021) Effect of IV high-dose vitamin C on mortality in patients with sepsis: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Med*. <https://doi.org/10.1097/CCM.0000000000005263>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

✉ Neill K. J. Adhikari
neill.adhikari@utoronto.ca

¹ Division of General Internal Medicine, Department of Medicine, McMaster University, Hamilton, ON, Canada

² Department of Medicine, Université de Sherbrooke, and Centre de Recherche du CHU de Sherbrooke, Sherbrooke, QC, Canada

³ Department of Critical Care Medicine and Interdepartmental Division of Critical Care Medicine, Sunnybrook Health Sciences Centre and University of Toronto, Toronto, ON, Canada