Comment

Vitamin C for Cardiac Surgery Patients: Several Errors in a Published Meta-Analysis. Comment on “Effects of Vitamin C on Organ Function in Cardiac Surgery Patients: A Systematic Review and Meta-Analysis. Nutrients 2019, 11, 2103”

Harri Hemilä 1,* and Elizabeth Chalker 2

1 Department of Public Health, University of Helsinki, POB 41, FI-00014 Helsinki, Finland
2 School of Public Health, University of Sydney, Sydney 2006, Australia; elizabeth.chalker@gmail.com
* Correspondence: harri.hemila@helsinki.fi

Received: 2 December 2019; Accepted: 31 December 2019; Published: 24 February 2020

Keywords: ascorbic acid; atrial fibrillation; artificial respiration; cardiac surgical procedures; critical care; meta-analysis; systematic review

We recently published a meta-analysis on vitamin C and the length of intensive care unit [ICU] stay [1] and so were interested to read Hill et al.’s meta-analysis on randomized trials of vitamin C for cardiac surgery patients published in Nutrients in September 2019 [2]. However, we have some methodological concerns.

The abstract states that “vitamin C significantly decreased . . . ventilation time ($p < 0.00001$)” [2]. We believe that this conclusion is incorrect based on the evidence presented. This particularly small p-value from Figure 6 [2] is associated with the test of heterogeneity, not with the test of overall effect ($p = 0.02$, $Z = 2.27$). In the abstract, this same error occurs for ICU length of stay and hospital length of stay in that the reported p-values are from the heterogeneity tests, not from the tests of overall effect.

Furthermore, Hill states in Figure 6 that the ventilation time in the Safaei trial [3] was 15.1 h with 1.0 h standard deviation (SD) in the vitamin C group and 22.9 h (SD 3.8 h) in the control group. These dispersion estimates were published by Safaei, however, as standard errors (SE) and not SDs: “All continuous variables are expressed as mean ± standard error of mean” [3] (p. 47) and “Values are mean ± SEM” [3] (Table 2). Thus, the use of SE in Figure 6 led to an erroneous p-value for the vitamin C effect [2]. Hill made the same error (using SE from the Safaei trial) in their meta-analysis on ICU length of stay. This same error (using SE instead of SD) was repeated in Figures 6, 8, 12, 14, 18, and 20 [2]. Consequently, they are incorrect.

Hill states that “Analyses were carried out on an intention-to-treat [ITT] basis for all outcomes, as far as possible” [2] (p. 3). The ITT principle means that investigators include in the analysis all participants who underwent randomization in the groups to which they were originally allocated [4–6]. However, Hill’s Figure 6 includes the Sadeghpour trial [7], which recruited 500 participants, but reported only 113 vitamin C participants and 177 placebo participants [1] (p. 3). The 42% dropout rate was very high and there were significant differences in the dropout rates between the treatment groups. Therefore, the Sadeghpour trial [7] should not be included in a meta-analysis that intends to follow the ITT principle.

Excluding the Sadeghpour trial [7] and using the SD values for the Safaei trial [3] (calculated from the published SE values), the p-value for the overall effect of vitamin C on ventilation time remained at 0.02; however, the heterogeneity disappeared (from $p < 0.00001$ to $p = 0.39$), see Figure S3 in the supplementary file. Several other concerns with the Hill meta-analysis [2] are described in the supplementary file.
Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/12/2/586/s1, Supplementary file describing further concerns in the Hill meta-analysis [2].

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Hemilä, H.; Chalker, E. Vitamin C can shorten the length of stay in the ICU: A meta-analysis. Nutrients 2019, 11, 708. [CrossRef] [PubMed]
2. Hill, A.; Clasen, K.C.; Wendt, S.; Majoros, Á.G.; Stoppe, C.; Adhikari, N.K.J.; Heyland, D.K.; Benstoem, C. Effects of vitamin C on organ function in cardiac surgery patients: A systematic review and meta-analysis. Nutrients 2019, 11, 2103. [CrossRef] [PubMed]
3. Safaei, N.; Babaei, H.; Azarfarin, R.; Jodati, A.R.; Yaghoubi, A.; Sheikhalizadeh, M.A. Comparative effect of grape seed extract (vitis vinifera) and ascorbic acid in oxidative stress induced by on-pump coronary artery bypass surgery. Ann. Cardiac. Anaesth. 2017, 20, 45–51. [CrossRef]
4. McCoy, C.E. Understanding the intention-to-treat principle in randomized controlled trials. West. J. Emerg. Med. 2017, 18, 1075–1078. [CrossRef] [PubMed]
5. DeMets, D.L.; Cook, T. Challenges of non-intention-to-treat analyses. JAMA 2019, 321, 145–146. [CrossRef] [PubMed]
6. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. BMJ 2010, 340, c869. [CrossRef] [PubMed]
7. Sadeghpour, A.; Alizadehasl, A.; Kyavar, M.; Sadeghi, T.; Moludi, J.; Gholizadeh, F.; Totonchi, Z.; Ghadrdoost, B. Impact of vitamin C supplementation on post-cardiac surgery ICU and hospital length of stay. Anesth. Pain Med. 2015, 5, e25337. [CrossRef] [PubMed]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).