International Journal of Surgery 64 (2019) 66

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Letter to the Editor

Errors in a meta-analysis on vitamin C and post-operative atrial fibrillation

There are several errors in the meta-analysis on vitamin C and post-operative atrial fibrillation (POAF) by Hu et al. [1].

Hu et al. stated in their methods that "studies that met the following criteria were included: randomized controlled trials (RCTs) of adult patients who underwent cardiac surgery; patients randomly assigned to receive vitamin C or placebo … Any studies of non-randomized designs … were excluded" [1, p. 59]. However, Hu included the study by Carnes et al. although that was not an RCT, instead "an age- and gender-matched control group (not receiving ascorbic acid) was retrospectively selected" [2, p. 3]. In addition, Hu did not include the data of two so far largest vitamin C and POAF trials that found no effect of vitamin C against POAF and therefore remained unpublished, leading to publication bias [3]. Hu claimed that "funnel plots showed no evidence of publication bias" (p. 60), but the existence of those 2 unpublished large negative trials obviously proves that there is publication bias.

Hu et al. calculated that the effect of vitamin C on POAF was OR = 0.47. However, Altman [4] pointed out that "the odds ratio [OR] should not be interpreted as an approximate relative risk [RR] unless the events are rare in both groups (say, less than 20–30%)". In Hu's Fig. 2, the lowest incidence of POAF in the placebo groups was 19%, and 6 out of 8 studies had incidence of POAF over 30% in their placebo groups [1]. In such a case the OR does not properly approximate RR. Instead, the OR can substantially exaggerate the effects for common outcomes [4]. Thus, Hu's OR = 0.47 does not indicate that vitamin C reduced the risk of POAF by 53%. Hu should have calculated the effect of vitamin C on the RR scale instead.

In their Fig. 4, Hu et al. stated that the standard devation (SD) of the mean duration of ICU stay in the vitamin C group was 24.9 hours in the trial by Colby et al. [5]. However, Colby reported in their Table 1 and text that the SD for the duration of ICU stay was 249.9 hours in their vitamin C group, i.e. 10 times greater than Hu claimed. Evidently, such a big error leads to a large error in the pooled estimate of effect, but also generates great exaggeration of the heterogeneity between the included trials. Hu wrote "compared with placebo group, vitamin C administration was not associated with any length of stay, including in the ICU" [1, p. 60]. However, I calculated that there was strong evidence from 10 RCTs that vitamin C shortened the ICU stay in the POAF trials by 7.4% (P = 0.002) [3]. This divergence in conclusions seems to be largely caused by Hu's 10-fold error in the SD value of the Colby trial mentioned above.

Although the general conclusion of Hu et al. that vitamin C has some efficacy against POAF is consistent with trial reports, there is very strong evidence of heterogeneity in the effect [3], even though Hu claimed that there was "no significant heterogeneity (I^2 = 44%; P = 0.09)" [1, p. 60]. High level heterogeneity has important implications as it guides further research. Five trials in the USA found no benefit, discouraging further research in the USA [3]. However, positive findings in less wealthy countries suggest that the effect of vitamin C should be further studied in such countries [3].

Provenance and peer review

Not Commissioned, internally reviewed.

Ethical approval

NA.

Source of funding

No funding currently.

Author contribution

I am the only author.

Conflicts of interest

No conflicts of interest.

Research registration number

NA.

Guarantor

I am the only author.

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https://doi.org/10.1016/j.ijsu.2019.01.025
Received 20 December 2018; Accepted 2 January 2019
Available online 02 March 2019