LETTER TO THE EDITOR

Author Response

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Dear Editor,

We thank Dr Angadi and colleagues for their interest in our pilot trial and for engaging in this discussion.

At the outset, we need to clarify that our trial is a small pilot randomized controlled trial with the key and stated aim of demonstrating feasibility. While we reported secondary outcomes, as stated in our manuscript, they are to be considered exploratory. We respond below to each of their comments.

In a randomized controlled trial, any imbalances in baseline characteristics are by definition a product of chance. Current recommendations are to report them as they stand by the intervention arm and not perform any inferential testing.[1] In a large trial, it would be expected that baseline characteristics balance out between the arms. In a small trial like ours, some imbalances are only natural. As can be seen from Table 1 of our trial, median APACHE II was higher in the placebo arm whereas median SOFA was higher in the vitamin C arm. We did not adjust for these imbalances in our analysis of secondary outcomes as our trial was primarily designed to demonstrate feasibility. Differences noted in secondary outcomes as stated above are to be considered exploratory. We would also like to draw the attention of the authors to the larger and definitive parent LOVIT trial which was published in June 2022 and demonstrated a signal of harm from intravenous vitamin C.[2]

Regarding any confounding from the use of corticosteroids, again the very nature of a randomized controlled trial ensures that known and unknown confounders are balanced between arms. In our trial, a slightly lower proportion of patients in the vitamin C arm received corticosteroids on day 1 (56.3%) as compared to the placebo arm (64.3%). We would not read too much into these differences or their impact on clinical outcomes as this was a small feasibility trial. In the parent LOVIT trial, there was no difference in the use of steroids between arms and as already stated above, the trial demonstrated a signal of harm from intravenous vitamin C.[2]

Regarding additional outcomes and serum levels of vitamin C, our goals were to demonstrate feasibility, and as such, these were beyond the remit of our trial. The larger LOVIT trial did measure vitamin C levels and also performed a subgroup analysis which did not show any differential effect of the vitamin based on levels.[2]

We once again thank the authors for engaging with our study.

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