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Vitamin C for patients with sepsis?

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The intensive care medicine rapid practice guideline (ICM-RPG) panel recently published a clinical practice guideline on the use of vitamin C for adult patients with sepsis. The panel recommended against its use (1). However, there are several factors which the panel seems not to have considered.

Specificity is important when looking at evidence for any intervention. If we want to determine whether vitamin C has an effect on sepsis, the comparison should be between vitamin C and a control, and not between vitamin C combined with other substances and a control (2). The panel considered that their most informative analysis was in their Supplementary Figure S1, but four of the six included trials administered vitamin C with other substances (1). This criticism is not speculative. A Korean cohort study by Jung et al. found that vitamin C alone was beneficial for patients with sepsis, whereas the combination of vitamin C and hydrocortisone was not (3). Trials of vitamin C and hydrocortisone combined are not appropriate surrogates for trials of vitamin C alone (2).

The panel "had more confidence in estimates of mortality at 90 days than at shorter time periods" though they were puzzled by "the potential difference between estimates of short- and long-term mortality". However, the 90-day follow-up is misguided.

The largest trial in their Supplementary Figure S1 (1), the LOVIT trial, administered vitamin C for just 4 days (4). In the placebo group, there were 179 deaths by 90 days, which gives SD = 13 deaths, assuming a Poisson distribution. By the end of day 4, there were 51 deaths (5), which means that 72% of the deaths within 90 days occurred after vitamin C administration had ceased. Thus, 72% of the analyzed deaths cannot be attributed to the effects of ongoing vitamin C administration. The large SD at 90 days can hide substantial and genuine effects during and shortly after the 4-day ongoing vitamin C administration. This is also not speculative.

In the LOVIT trial, there was a significant increase in mortality in the vitamin C arm immediately after the vitamin was stopped, such that during days 5–7 there were 18 extra deaths in the vitamin C arm (5). This harm can be explained by the rebound effect, which has also been observed in a guinea pig study (5, 6). However, over the follow-up of the LOVIT trial, the short 3-day period during which the 18 extra deaths occurred is not apparent within the random variation over the 90 days. Some treatments such as vaccination cause long-lasting effects and long follow-ups are appropriate. However, there is no justification to assume similar long-term effects with vitamin C administration. The effect of vitamin C on mortality of patients with sepsis should be analyzed over the period of vitamin administration and shortly thereafter (Figure 1), and should not include several months without vitamin C.

Moreover, the Korean study found that vitamin C was beneficial if the administration was ≥5 days, but ineffective if the administration was shorter (3). Although we need to be cautious about drawing treatment conclusions from cohort studies, the 4-day administration in the LOVIT trial may have been too short for patients with sepsis, one quarter of whom had ICU stays ≥ 12 days (4, 5).

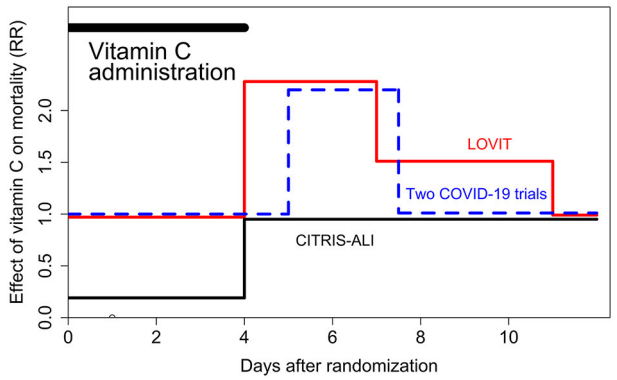

FIGURE 1
Change in mortality when 4-day intravenous vitamin C was abruptly terminated. RR = 1.00 indicates the level of the control group. This figure is based on the re-analyses of the LOVIT (4, 5), CITRIS-ALI (7, 8), and Two Harmonized Randomized Clinical Trials with COVID-19 patients (9, 10). In all trials, the vitamin C dose was 50 mg/kg body weight every 6 h (16 g/day for an 80 kg person) for 4 days. The CITRIS-ALI trial observed a significant reduction in mortality over the first 4 days, but thereafter the groups did not differ. The other two studies found no difference when vitamin C was administered, but after the abrupt termination of the vitamin there was a significant increase in mortality for a few days, after which the difference leveled off. In each study, there was significant difference in the RR before and after the end of the 4-day vitamin C administration (5, 8, 10) indicating that the abrupt termination of vitamin C had a harmful effect on mortality.

The panel writes: "there may be patient populations where vitamin C has beneficial effects, such as … patients with confirmed low or low–normal plasma vitamin C levels" (1). However, no information was provided regarding the levels that are considered low or low-normal by the ICM-RPG panel. Usually, plasma vitamin C levels lower than 11 μM are considered deficient, but scurvy has also been observed with higher plasma levels (5, 11). In the LOVIT trial, 25% of patients had baseline vitamin C levels <5.37 μM, which is half of 11 μM. One half of the LOVIT trial patients had plasma vitamin C levels below 12.38 μM (4). Should such patients be administered vitamin C routinely on the basis of low or low–normal plasma levels? The panel did not provide any guidance on this issue (1). If these patients need to be administered vitamin C on the basis of "confirmed low or low–normal plasma vitamin C levels" then it is unethical to randomize one quarter or one half of patients with low-vitamin C, similar to patients in the LOVIT trial, to the placebo group (5, 11).

There are numerous recent reports of patients suffering from scurvy and several of them were in the ICU (5, 10–20). Scurvy can cause dyspnea, edema, chest pain, and other pains, whereas gum pathology is not always present (5, 11). We are concerned that the ICM-RPG panel guideline may discourage the use of vitamin C for critically ill patients on the basis of statistically unsound analyses. Further research on vitamin C and sepsis is needed, but it is clear from the three trials which terminated 4-day vitamin C abruptly, that sudden termination is not appropriate if the patient is still critically ill (Figure 1).

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Conflict of interest

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