Editorial

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Quick response code

Does my septic patient have scurvy?

Recent literature on the use of vitamin C in critically ill patient with sepsis has generated much interest. Analysing the scientific rationale for the increasing use of this molecule in the intensive care units (ICUs) around the world and differentiating it as a real hope for such patients from hype needs to proceed in a logical sequence of understanding the biological rationale, preclinical and clinical data including one published in this edition of *IJA*,[1] and applying rigors of evidence-based medicine as opposed to emotion-based medicine to decide on the current scope of its use.

BIOLOGICAL RATIONALE

Vitamin C (ascorbic acid) has a pleiotropic effect on various metabolic functions.[2] It is an antioxidant, improves endothelial function, improves microcirculation, decreases excessive endothelial permeability and acts as a cofactor in norepinephrine and vasopressin synthesis. It is not synthesised in the body and has to be replaced from external sources in deficiency states. The normal plasma vitamin C level is ≥23 μmol/L. In sepsis and other related conditions such as trauma and ischaemia/reperfusion injury, the serum levels (and presumably tissue levels) are decreased substantially. A recent study has shown that 88% of the septic patients have hypovitaminosis C (i.e., <23 μmol/L), whereas 38% have severe deficiency as seen in scurvy (i.e., <11 μmol/L). This deficiency is probably caused by reduced recycling of oxidised vitamin C. Low vitamin C level is associated with increased organ dysfunction and mortality, although this association does not imply causality; it may just reflect an epiphenomenon of critical illness similar to other physiological derangements such as hyperglycaemia, anaemia and hypovitaminosis, corrections of which do not convert into mortality benefit. In general, use of vitamin C both in replacement and pharmacological doses is safe, although precipitation of oxalate crystallopathy has been noted with high-dose vitamin C. Vitamin C can also interfere with glucose reading in point-of-care glucometer and can mask hypoglycaemia. Many of the clinical studies have used vitamin C with other antioxidants such as vitamin E and selenium. The rationale of its use with glucocorticoids is its facilitative property on steroid receptors by reversing their oxidation. Thiamine is used with high-dose vitamin C to prevent hyperoxaluria. Combination of deficiency state in septic patient with a reasonably safety profile has led to its use in critically ill patients.

Preclinical data

In animal model of traumatic shock, vitamin C was found to attenuate proinflammatory and procoagulant pathways.[3] In a cardiac arrest model, it was found to have a beneficial effect on neuronal and myocardial recovery when combined with hypothermia. In an ischaemia/reperfusion kidney model, vitamin C used in combination with vitamin E and hydrocortisone attenuated oxidative injury.

CLINICAL DATA

The current clinical data on the use of vitamin C on critically ill patient usually address improvement of surrogate markers like organ failure, length of stay, resuscitative fluid requirement, improved myocardial function and decrease in vasopressor requirement, in diverse patient populations with sepsis, trauma, burns, post angioplasty and so on, using large doses of vitamin C.[4] The renewed interest in this molecule came after the publication of a case–control, before–after study published in *Chest* by Marik *et al.* in 2017 on 80 patients (40 cases and 40 control) with septic shock. The study demonstrated not only

significant improvement in surrogate markers but also a dramatic reduction in hospital mortality with treatment of a cocktail of vitamin C, thiamine and hydrocortisone (8.4%) compared with a propensity-matched historical control (40.4%).[4]

In this issue of *IJA*, Marik *et al*.'s protocol was replicated in a small group of post cardiac surgery patients with septic shock, with reduction in vasopressor dose as the primary outcome, but they could not demonstrate any reduction in organ dysfunction or mortality.[1] The strength of the study was randomisation, but it was underpowered for mortality outcome. The results from this study need to be replicated in a larger trial.

KNOWLEDGE GAP

At present, there are substantial knowledge gaps in our understanding of vitamin C efficacy in critically ill patients. The following gaps in our understanding need to be studied before widespread use of Marik *et al*.'s cocktail is implemented in clinical practice:

1. In most of the clinical studies, vitamin C has been used with hydrocortisone with reduction in vasopressor requirement as the primary endpoint. There is a strong evidence now of vasopressor-sparing effects of hydrocortisone alone, hence the additional benefit of vitamin C needs to be studied separately
2. As we are entering an era of personalised medicine, vitamin C should be given to patients who have subnormal levels of the molecule and the dose should be targeted to achieve therapeutic levels rather than a fixed dose as practiced now
3. The optimal timing and duration need to be addressed, probably depending on a marker of ongoing oxidative injury
4. Additional role of thiamine needs to be studied.
5. The specific patient subgroup of trauma, burn, surgical and medical patients in whom this therapy will be helpful need to be identified
6. Pharmacokinetic/pharmacodynamic data which will address bolus versus continuous infusion of this molecule need to be determined
7. Safety profile in patients with renal failure need to be studied.

Around eight randomised clinical studies including a couple from India are underway to confirm the data by Marik *et al*. and to address the knowledge gaps in this area (CITRIS-ALI: NCT02106975) has been completed, hydrocortisone, vitamin C and thiamine for the Treatment of Sepsis and Septic Shock (HYVCTTSSS: (HYVCTTSSS)) is recruiting at present. Amrita institute in Kochi has undertaken a randomised study of Marik *et al*.'s protocol in septic shock patients in a medical/surgical ICU.

The key question that is often asked by the practicing physician is "given the present data and pending future studies, whether vitamin C, thiamine and hydrocortisone should be used in critically ill patients?" It is natural that in conditions with high mortality like sepsis with only supportive therapy and infection control being the present treatment armamentarium, physicians will be inclined to use molecules with insufficient data but with no substantial harm and available at an affordable cost. Although this approach may not be scientifically desirable, it will be equally difficult to go against this trend. A compromise approach would be to document the use of this regimen in a standardised way along with patient specifics and have a big data bank for analysis, which might even be more informative than small randomised studies or meta-analyses.

Finally, similar to Vanden Bergh's trial on glucose control and Rivers' study on early goal directed therapy, both of which were contradicted in subsequent trials, but were practice changing by increasing awareness of blood sugar control and early protocolised care in critically ill, studies on vitamin C use will increase awareness of vitamin deficiency states in these patients and some benefits can be expected by replacing it with simple inexpensive molecules.

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