EDITORIAL

Vitamin C and thiamine for sepsis: time to go back to fundamental principles

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Vitamin C plays a vital role in human physiology. For decades, intriguing research has highlighted the possibility of acute effects of vitamin C deficiency in patients with sepsis [1]. Vitamin C is a mediator of endothelial function through its co-factor role with many enzymes (including one that catalyses the conversion of dopamine to noradrenaline). Vitamin C also works as an antioxidant by scavenging free radicals (Fig. 1). In animal models of sepsis, exogenous vitamin C increases perfused capillary density and arteriolar vasoconstrictor responsiveness, implying its possible role in treating vasoplegic status in sepsis [2].

The synergistic effect of hydrocortisone and vitamin C has also been suggested as vitamin C helps to reduce oxidised glucocorticoid receptors, and glucocorticoids induce the expression of a vitamin C transporter [2]. Thiamine, which is a coenzyme for the oxidation of pyruvate to acetyl-CoA in the Krebs cycle, is also depleted in some patients with sepsis [3]. Thus, thiamine has been suggested as another treatment option for sepsis.

The combination of vitamin C, thiamine, and hydrocortisone has recently been advocated as a treatment for patients with septic shock, largely based upon a single-centre before-after study [4]. This suggestion has provoked substantial global debate on incorporation into clinical practice ahead of assessing the balance of benefits and harms in valid clinical trials that comprise a contemporaneous control group with potentially confounding factors balanced between study arms.

In this issue of *Intensive Care Medicine*, results from the ATESS trial, a double-blind RCT of vitamin C and

thiamine for septic shock are reported [5]. The trial was conducted in four emergency departments in South Korea. The trial was designed to assess the effect of intravenous vitamin C (50 mg/kg, max 3 g/dose, every 12 h) and thiamine (200 mg, every 12 h) for 48 h compared with placebo on organ dysfunction. A sample size of 116 was calculated to have 80% power to detect a difference of 1.5 points in the change of SOFA score at 72 h of enrolment.

Subsequently, 111 of 116 randomised patients were included in the analysis. There was no difference in delta SOFA score [median of differences, 0 (−2–1), $p=0.96$]. None of the secondary outcomes, including mortality, vasopressor dependency, need for mechanical ventilation or renal replacement therapy, and inflammatory biomarkers, indicated a beneficial effect of the intervention.

The allocation sequence and randomisation were concealed appropriately, and the major co-intervention with hydrocortisone was well-balanced between the groups, indicating likely minimal risk of bias due to confounding. The intervention was provided to patients at around 3 h after meeting the standard criteria of septic shock, and plasma levels of vitamin C and thiamine at 72 h of enrolment showed clear separation of the two groups.

The trial was well-designed from several perspectives. First, early administration of the intervention at emergency departments, along with early administration of antibiotics and vasopressors, strengthened the potential for this trial to detect early treatment-specific effects while minimising variability in outcomes due to variations in the standard of care for septic shock.

While an intervention of vitamin C, thiamine and hydrocortisone has been advocated as a triple-cocktail therapy [4], this trial tested the combination of vitamin C and thiamine, alongside clinician-determined appropriate treatment with hydrocortisone—balanced between

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study arms, allowing attribution of effects to vitamin C and thiamine.

Several limitations should be noted. First, the duration of the intervention was 48 h, and the primary follow-up period was 72 h, which might be short for the effects to be detected. The pharmacokinetics of intravenous vitamin C in critically ill patients have been tested with 1 g/dose or 5 g/dose every 12 h for 48 h achieving normal or supranormal trough concentrations; however, a few patients in both groups still had hypovitaminosis at 96 h [6].

In another RCT, 1.5 g of intravenous vitamin C was administered every six hours [7]. The nested cohort study found that the plasma concentration of vitamin C was kept in the supranormal range at 6 h, and the half-life of the first dose was 4.3 h [8]. This raises the possibility that vitamin C levels could have been sub-optimal between dosing in the ATESS trial, and could fall beyond the initial treatment period, both leading to a risk of missing a treatment effect.

The measurement of thiamine is more difficult. There is no universal method to measure thiamine as it can exist in various forms, i.e., free-thiamine, thiamine monophosphate, thiamine pyrophosphate, thiamine triphosphate, each requiring somewhat unique methods [9]. In this trial, thiamine deficiency was defined as serum levels <66.1 nmol/L [5], a higher threshold than

in some previous studies [3, 10]. Finding an optimal therapeutic range and the optimal method of monitoring thiamine concentration would benefit from additional research.

Since the first report of a large effect size with triple therapy [4], more than 20 trials have been planned or are underway. So far, two trials assessing the effect of vitamin C and thiamine while controlling the use of hydrocortisone as a mandated co-intervention, or balanced by randomisation, have shown no significant effect [5, 7]. Three trials evaluating vitamin C, thiamine and hydrocortisone, including the recently published ACTS trial, have demonstrated an inconsistent effect upon the vasopressor requirement and SOFA score [11, 12]. Nevertheless, increasing literature has better defined the role of corticosteroids for septic shock [13, 14], highlighting that treatment with vitamin C and/or thiamine, should likely be independently investigated.

Furthermore, the sample size of the ATESS trial and recent ones are relatively small [5, 11], which often produce fragile results. However, fragile results still influence opinions, in this case, on a contemporary controversy. The numerous ongoing trials would likely better serve patients and practitioners if there were attempts to define common interventions and outcomes, to allow meta-analytic combination of trials; and/or if larger collaborative trials could occur from the outset.

Until larger sample sizes improve the precision of an effect size across populations and sub-populations of septic patients, the results of the ATESS trial and others counsel us to remain focused on the fundamental principles in treating sepsis—prompt and measured resuscitation that includes early appropriate empiric antibiotics and source control—while subjecting new therapies to methodologically rigorous clinical trials [15].

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Author contributions

All authors contributed substantially to the conception of the editorial and drafted or provided critical revision of the article and provided final approval of the version submitted for publication.

Compliance with ethical standards

Conflicts of interest

TF was an investigator of VITAMINS trial. All authors declare no COI.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 10 August 2020 Accepted: 4 September 2020

Published online: 18 September 2020

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