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MINI-REVIEW

Therapeutic potential of megadose vitamin C to reverse organ dysfunction in sepsis and COVID-19

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Sepsis induced by bacteria or viruses can result in multiorgan dysfunction, which is a major cause of death in intensive care units. Current treatments are only supportive, and there are no treatments that reverse the pathophysiological effects of sepsis. Vitamin C has antioxidant, anti-inflammatory, anticoagulant and immune modulatory actions, so it is a rational treatment for sepsis. Here, we summarise data that support the use of megadose vitamin C as a treatment for sepsis and COVID-19. Megadose intravenous sodium ascorbate (150 g per 40 kg over 7 h) dramatically improved the clinical state and cardiovascular, pulmonary, hepatic and renal function and decreased body temperature, in a clinically relevant ovine model of Gram-negative bacteria-induced sepsis. In a critically ill COVID-19 patient, intravenous sodium ascorbate (60 g) restored arterial pressure, improved renal function and increased arterial blood oxygen levels. These findings suggest that megadose vitamin C should be trialled as a treatment for sepsis and COVID-19.

KEYWORDS
acute kidney injury, COVID-19, hypotension, hypoxia, inflammation, oxidative stress, sepsis, sodium ascorbate, vitamin C

1 | INTRODUCTION

Sepsis is a pathophysiological syndrome characterised by an overwhelming immune response to a bacterial, viral or fungal infection that can lead to multiorgan dysfunction and death (Singer et al., 2016). Sepsis is the leading cause of mortality in intensive care units with an annual global incidence of 49 million cases and 11 million deaths (Rudd et al., 2020). Standard of care treatment for sepsis consists of antibiotics, fluid resuscitation and vasopressors (Rhodes et al., 2017), with continuous renal replacement therapy being increasingly used in critically ill patients (Bellomo et al., 2021). These interventions are mostly aimed towards keeping the patient alive in the expectation that organ function should recover following resolution of the infection. However, patients who recover from severe sepsis frequently exhibit a degree of chronic organ dysfunction. Currently, there are no treatments that reverse sepsis-induced organ dysfunction.

2 | PATHOPHYSIOLOGY OF SEPSIS-INDUCED CARDIOVASCULAR AND RENAL DYSFUNCTION

The factors causing sepsis-induced organ dysfunction remain unclear due to the complex pathophysiology of sepsis that changes as the response to the infection progresses. There is evidence that redox homeostasis is disrupted in sepsis resulting in oxidative stress, which together with excessive inflammation is thought to cause mitochondrial, endothelial and microvascular dysfunction, resulting in vasoplegia, inflammation-mediated tissue injury, tissue hypoxia and multi-organ dysfunction (Joffre & Hellman, 2021; Lankadeva et al., 2019) (Figure 1).

Hypotension secondary to peripheral vasodilatation is a hallmark of sepsis that is treated with aggressive fluid resuscitation and vasopressor therapy to restore target mean arterial pressure (Rhodes et al., 2017). Reduced vascular responsiveness to

Abbreviations: AKI, acute kidney injury; COVID-19, Coronovirus disease 2019; eNOS, endothelial nitric oxide synthase; RCTs, randomised clinical trials; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SOFA, sequential organ failure assessment.

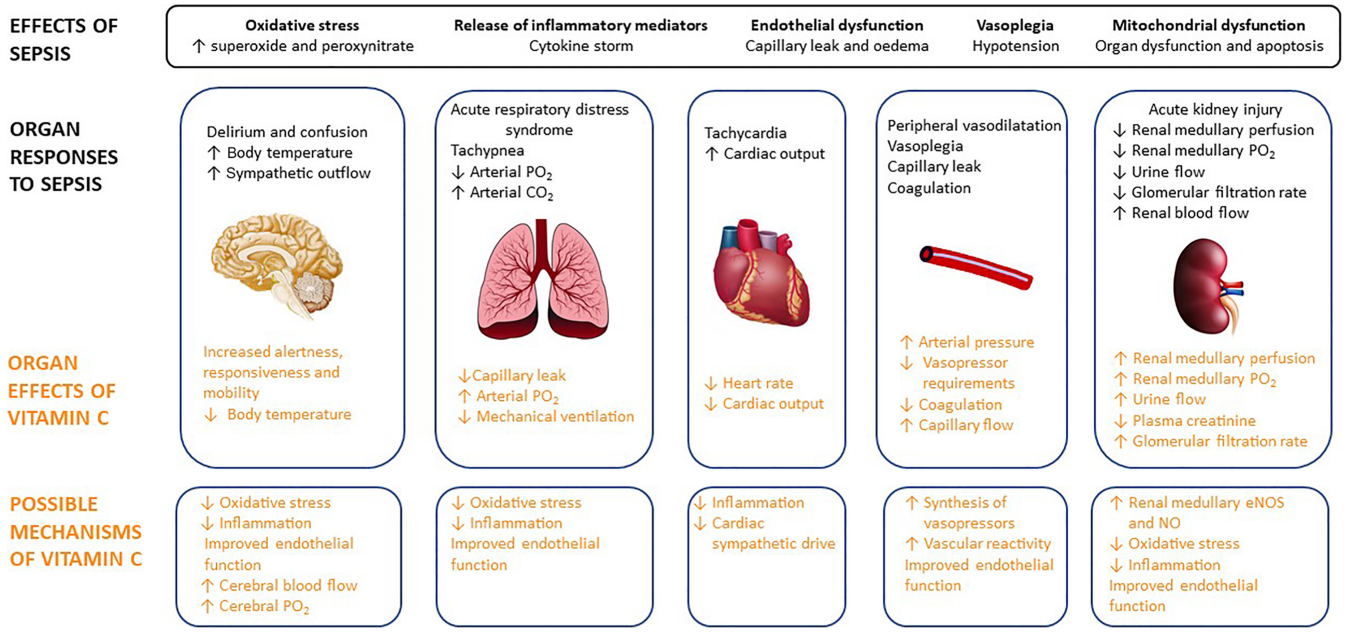

FIGURE 1 Overview of the systemic and organ specific effects of ovine sepsis, the effects of treatment we have observed with intravenous megadose vitamin C and the possible mechanisms of action that require investigation

noradrenaline, the primary vasopressor used clinically, is common in sepsis resulting in persistent and sometimes refractory hypotension (Annane et al., 1998), which, in itself, can result in tissue hypoperfusion and hypoxia, mitochondrial dysfunction and multi-organ failure.

Indeed, tissue hypoperfusion and hypoxia in the renal medulla are critical pathophysiological features of ovine hyperdynamic sepsis that precede the development of acute kidney injury (AKI) by 8 to 12 h (Calzavacca et al., 2015). Renal medullary hypoxia can lead to mitochondrial dysfunction, initiating a progressive loss of renal function culminating in AKI (Lankadeva et al., 2019; Nourbakhsh & Singh, 2014). Therapies that target these sepsis-induced pathophysiological processes may confer better circulatory management and mitigate AKI.

3 | ANTIOXIDANTS AS A THERAPY FOR SEPSIS-INDUCED ORGAN DYSFUNCTION

In view of the damaging effects of tissue hypoxia and oxidative stress, there has been interest over many decades in the use of antioxidants as a treatment for sepsis. The antioxidant N-acetylcysteine, which has both antioxidant and anti-inflammatory properties, showed some promise in experimental studies, but clinical studies have yielded largely disappointing findings (Chertoff, 2018). The antioxidant tempol has been shown to reduce the level of AKI in a porcine model of sepsis (Matejovic et al., 2005), but its effects have not been examined clinically. Recently, however, there has been increasing interest in the effects of vitamin C as a treatment for sepsis.

4 | RATIONALE FOR VITAMIN C THERAPY IN SEPSIS

Vitamin C, ascorbic acid, is an essential vitamin in humans that must be obtained in the diet, as it cannot be synthesised because of mutations in the gene for gluconolactone oxidase, the final biosynthetic enzyme in its synthesis. Vitamin C is essential for collagen synthesis, accounting for the symptoms of scurvy caused by its deficiency. Vitamin C also has numerous pleiotropic effects that would be predicted to be of benefit in sepsis, including as an anti-oxidant, anti-inflammatory, anticoagulant, immune modulator and stimulant of noradrenaline and vasopressin synthesis (Holford et al., 2020) (Figure 1). Furthermore, critically ill patients have low plasma vitamin C levels (11 vs. 62 $\mu mol \cdot L^{-1}$ in healthy subjects) (Schorah et al., 1996), most likely due to increased metabolic turnover and downregulation of cellular sodium-dependent vitamin C transporters (Subramanian et al., 2018), which is compounded by the inability of humans to synthesise vitamin C. Importantly, intravenous administration is required to produce high plasma levels of vitamin C, as there is a limit on its absorption from the intestine (Padayatty et al., 2004). These observations provided the impetus for clinical trials examining the effects of intravenous vitamin C in sepsis.

5 | CONTROVERSIES WITH HIGH-DOSE VITAMIN C THERAPY IN HUMAN SEPSIS

Single-centre controlled randomised clinical trials (RCTs) showed that intravenous vitamin C reduced inflammatory biomarkers and reduced

sequential organ failure assessment (SOFA) scores (50, 100 and 200 mg·kg^{-1}·day^{-1}, $n = 24$) (Fowler et al., 2014) and improved vasopressor sensitivity (2 g four times per day, $n = 28$) (Zabet et al., 2016). A widely publicised single-centre before and after study ($n = 47$), using a combination therapy of vitamin C (1.5 g four times per day) with hydrocortisone and thiamine, reduced organ failure and mortality from 40.4% to 8.5% (Marik et al., 2017). However, subsequent multicentre RCTs, VITAMINS (Fujii et al., 2020), ACTS (Moskowitz et al., 2020) and ATESS (Hwang et al., 2020) that trialled a maximum dose of vitamin C of 6 g·day^{-1} for up to 10 days with thiamine ± corticosteroid, had no significant benefit above placebo treatment. The CITRIS-ALI trial, that used 200 mg·kg^{-1}·day^{-1} (16 g·day^{-1} in an 80-kg patient) of intravenous vitamin C for 4 days, found no improvement in the primary end point of change in mean modified SOFA score. However, 28-day mortality was reduced from 46% to 30% (Fowler et al., 2019).

We hypothesised that the lack of consistent benefit in the clinical trials of vitamin C in sepsis might be due to the use of inadequate doses. In view of these findings, and the fact that very high doses of intravenous vitamin C have been shown to be safe in burns and cancer patients (Yanase et al., 2020), we recently investigated the safety and efficacy of a much larger dose (megadose) of vitamin C in a clinically relevant large animal model of sepsis. Such a preclinical safety study was essential as the very high plasma levels of vitamin C can have pro-oxidant effects (Chen et al., 2008), which may be detrimental in critical illness.

6 | A PRECLINICAL RANDOMISED CONTROLLED TRIAL OF MEGADOSE VITAMIN C IN OVINE SEPSIS

Intravenous administration of a megadose of sodium ascorbate (150 g per ~40 kg, 7 h) in established ovine hyperdynamic sepsis, induced by infusion of live *Escherichia coli*, caused a remarkable improvement in the clinical state from malaise, lethargy and somnolence to an alert, responsive, mobile state (Lankadeva et al., 2021). MAP was restored to pre-septic levels with reduced noradrenaline requirements, which decreased to zero in four of five cases. Megadose vitamin C increased arterial blood oxygen levels, indicative of improvements in lung function, restored body temperature from febrile to normal levels and reduced arterial blood lactate indicating improved metabolic function. The treatment also reversed renal medullary hypoperfusion and hypoxia, accompanied by a reversal in septic AKI, as shown by dramatic increases in urine flow and creatinine clearance leading to a normalisation of plasma creatinine levels (Figure 1).

The redistribution of intrarenal perfusion in ovine septic AKI (Calzavacca et al., 2015) is accompanied by reduced gene expression of renal medullary **endothelial nitric oxide synthase (eNOS)** (Langenberg et al., 2008). It is important to determine if the reversal of renal medullary microcirculatory dysfunction by vitamin C results from its ability to increase eNOS activity and thus nitric oxide bioavailability (Ladurner et al., 2012).

7 | TREATMENT OF COVID-19 WITH VITAMIN C

Critically ill COVID-19 patients develop an excessive inflammatory response, disseminated intravascular coagulation and multiorgan dysfunction. Immunosuppressive agents such as **tocilizumab** (a humanised monoclonal antibody against the **IL-6 receptor**) (Salama et al., 2021) and **dexamethasone** (RECOVERY Collaborative Group, 2021) have been shown to be beneficial treatments for such patients. The known actions of vitamin C indicate that it would also be a possible adjunct treatment for COVID-19. The findings that plasma vitamin C levels are low in COVID-19 patients (Chiscano-Camon et al., 2020), and that vitamin C lowers expression of **angiotensin converting enzyme 2**, the entry point for SARS-CoV-2 into cells (Ivanov et al., 2021), further indicate that it may have beneficial actions in COVID-19. Intravenous vitamin C (1.5–14.0 g) has been investigated in COVID-19 patients with mild beneficial effects (Jamalimoghadamsiahkali et al., 2021; Zhao et al., 2021), but the effects of megadoses have not been studied.

Following our finding of beneficial effects of megadose vitamin C in ovine sepsis, a critically ill patient with COVID-19-induced acute respiratory distress syndrome, hypotension and AKI was treated with intravenous sodium ascorbate (60 g over 7 h) (Lankadeva et al., 2021). As in septic sheep, sodium ascorbate restored arterial pressure in the face of complete withdrawal of noradrenaline. Plasma creatinine decreased from 118 to 84 μmol·L^{-1}, whereas urine flow increased from 10 to 400 ml·h^{-1}. There were decreases in heart rate from 130–105 beats per minute and in blood lactate, from 2.6 to 1.9 mmol·L^{-1}. Arterial blood oxygen levels improved while fractional inspired oxygen was reduced. The patient was subsequently extubated on intensive care Day 15 and discharged from hospital 22 days after megadose vitamin C treatment.

8 | CLINICAL TRIALS OF MEGADOSE VITAMIN C

Two pilot placebo controlled RCTs are currently underway examining the effects of intravenous megadose vitamin C treatment (sodium ascorbate, 60 and 120 g) in septic patients across three tertiary hospitals in Australia (ACTRN12620000651987p; NCT04796636).

9 | CONCLUSIONS

Our findings demonstrate that intravenous megadose intravenous vitamin C reversed organ dysfunction and improved the clinical state in a clinically relevant ovine model of sepsis. We also demonstrated the safety and benefit of this treatment in one critically ill COVID-19 patient. It is now critical to complete dose–response studies in which the plasma levels of vitamin C are measured to determine the optimum dosing regimen. Further studies are necessary to determine the mechanisms by which megadose intravenous vitamin C improves the

clinical state and reverses multi-organ dysfunction in sepsis. Such studies are essential to provide the scientific rationale for the design of large double-blinded multicentre RCTs.

10 | NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander, Fabbro et al., 2019a, 2019b; Alexander, Kelly et al., 2019).

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CONFLICT OF INTEREST

YRL, RB and CNM have a provisional patent on vitamin C use in sepsis (2020901120).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

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