

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

Clive May¹, Rinaldo Bellomo², and Yugeesh Lankadeva¹

¹The Florey Institute of Neuroscience and Mental Health

²The University of Melbourne

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Abstract

Sepsis causes multi-organ dysfunction and is a major cause of death in intensive care units, but there are no treatments that reverse the pathophysiological effects of sepsis. Vitamin C has antioxidant, anti-inflammatory, anticoagulant and immune modulatory actions, so is a potential treatment for sepsis. Recent clinical trials of high-doses of intravenous vitamin C (6-16 g/day) had variable effects. Since much higher doses are without side-effects in cancer and burns patients, we studied the effects of a mega-dose of intravenous sodium ascorbate (150 g/40 kg) in a clinically relevant ovine model of sepsis. This treatment dramatically improved the clinical state and over 3-7-h improved cardiovascular, pulmonary, hepatic and renal function and reduced body temperature. In a critically ill COVID-19 patient, intravenous sodium ascorbate (60 g) restored arterial pressure, improved renal function and increased arterial blood oxygen levels. Clinical trials are testing the effectiveness of mega-dose vitamin C in septic patients.

Introduction

Sepsis is a pathophysiological syndrome characterised by an overwhelming inflammatory and immune response to a bacterial, viral or fungal infection that can lead to multi-organ 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, Baldwin, Ronco & Kellum, 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.

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 (Joffe & Hellman, 2021) (Lankadeva, Okazaki, Evans, Bellomo & May, 2019).

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 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, Evans, Bailey, Bellomo & May, 2015). Renal medullary hypoxia can lead to mitochondrial dysfunction, initiating a progressive loss of renal function culminating in AKI (Lankadeva, Okazaki, Evans, Bellomo & May, 2019; Nourbakhsh & Singh, 2014). Therapies that target these sepsis-induced pathophysiological processes may confer better circulatory management and mitigate AKI.

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.

Rational for vitamin C therapy in sepsis

Vitamin C, ascorbic acid, is an essential vitamin in humans that must be obtained in the diet; 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). Furthermore, septic patients have abnormally low plasma vitamin C levels, likely due to increased metabolic turnover (de Grooth et al., 2018) and downregulation of cellular sodium-dependent vitamin C transporters (SVCTs) (Subramanian, Sabui, Moradi, Marchant & Said, 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 the intestinal absorption (Padayatty et al., 2004). These observations provided the impetus for clinical trials examining the effects of intravenous vitamin C in sepsis.

Controversies with high-dose vitamin C therapy in human sepsis

Single-centre controlled randomised clinical trials (RCT) showed that intravenous vitamin C reduced inflammatory biomarkers and reduced sequential organ failure assessment (SOFA) scores (50, 100, 200 mg/kg/day, n=24) (Fowler et al., 2014) and improved vasopressor sensitivity (2 g 4 times/day, n=28) (Zabet, Mohammadi, Ramezani & Khalili, 2016). A widely publicised single-centre before and after study (n=47), using a combination therapy of vitamin C (1.5 g 4 times/day) with hydrocortisone and thiamine, reduced organ failure and mortality from 40.4% to 8.5% (Marik, Khangoora, Rivera, Hooper & Catravas, 2017). However, subsequent multi-centre 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 for up to 10 days with thiamine \pm corticosteroid, had no significant benefit above placebo (Fujii et al., 2020) (Moskowitz et al., 2020) (Hwang et al., 2020). The CITRUS-ALI trial, that used 200 mg/kg/day (16 g/day in an 80 kg patient) of vitamin C for 4 days, however, reduced 28-day mortality from 46% to 30% (Fowler et al., 2019).

We hypothesized 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 (mega-dose) of vitamin C in experimental sepsis.

Rationale for mega-dose vitamin C treatment in sepsis

Intravenous administration of a mega-dose of sodium ascorbate (150 g/~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 4 of 5 cases. Mega-dose 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.

The re-distribution of intra-renal perfusion in ovine septic AKI (Calzavacca, Evans, Bailey, Bellomo & May, 2015) is accompanied by reduced gene expression of renal medullary endothelial nitric oxide synthase (eNOS) (Langenberg, Bagshaw, May & Bellomo, 2008). The reversal of renal medullary microcirculatory dysfunction by vitamin C may result from its ability to increase eNOS activity and thus nitric oxide bioavailability (Ladurner et al., 2012). Furthermore, the antioxidant effects of vitamin C are likely to reduce mitochondrial dysfunction and cellular injury.

Treatment of COVID-19 with vitamin C

Critically ill COVID-19 patients develop an excessive inflammatory response, disseminated intravascular coagulation and multi-organ dysfunction. Immunosuppressive agents like tocilizumab (a humanized monoclonal antibody against the interleukin-6 receptor) (Salama et al., 2021) and dexamethasone (Group et al., 2021) have been shown to be beneficial treatments for such patients. The known actions of vitamin C indicate that it would also be a plausible adjunct treatment for COVID-19. The findings that plasma vitamin C levels are low in COVID-19 patients (Chiscano-Camon, Ruiz-Rodriguez, Ruiz-Sanmartin, Roca & Ferrer, 2020), and that vitamin C lowers expression of angiotensin converting enzyme 2, the entry point for SARS-CoV-2 into cells (Ivanov, Goc, Ivanova, Niedzwiecki & Rath, 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, but the effects of mega-doses have not been studied.

Following our finding of potent beneficial effects of mega-dose 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 hours) (Lankadeva et al., 2021). As in septic sheep, sodium ascorbate restored arterial pressure in the face of withdrawal of noradrenaline, accompanied by reduced plasma creatinine, increased urine flow and reduced heart rate. Arterial blood oxygen levels improved while fractional inspired oxygen was reduced. The patient was subsequently extubated and discharged from hospital 22 days after mega-dose vitamin C treatment.

Clinical trials of mega-dose vitamin C

A pilot placebo-controlled RCT is currently underway examining the effects of intravenous mega-dose vitamin C treatment (sodium ascorbate, 60 g) in 30 septic patients (ACTRN12620000651987p) in Australia with an additional RCT in COVID-19 patients scheduled to commence in Columbia.

Conclusions

Our findings demonstrate a potent ability of mega-dose intravenous vitamin C to reverse organ dysfunction and improve the clinical state in a clinically relevant ovine model of sepsis. We also demonstrated the safety of this treatment and its benefit in a 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 vitamin C reverses multi-organ dysfunction in sepsis, with a focus on its anti-oxidant and anti-inflammatory actions. Such studies are essential to provide the scientific rationale for the design of large double-blinded multi-centre RCTs.

Figure legend

Overview of the systemic and organ specific effects of sepsis, the effects of treatment we have observed with intravenous mega-dose vitamin C in ovine sepsis and the possible mechanisms of action.

Conflicts of Interest: YRL, RB and CNM have a provisional patent on Vitamin C use in sepsis (2020901120).

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