


SEPSIS

Restrictive fluid therapy and high-dose vitamin C in sepsis

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Two recent randomized trials provide evidence to guide the management of sepsis. The CLASSIC trial reports that restrictive fluid therapy has no mortality benefit compared to a standard regimen in patients with septic shock, whereas the LOVIT trial reports that high-dose intravenous vitamin C might be harmful in patients with severe sepsis.

Refers to Meyhoff, T. S. et al. Restriction of intravenous fluid in ICU patients with septic shock. *N. Engl. J. Med.* **386**, 2459–2470 (2022) | Lamontagne, F. et al. Intravenous vitamin C in adults with sepsis in the intensive care unit. *N. Engl. J. Med.* **386**, 2387–2398 (2022).

in the restrictive group and 13% in the standard therapy group) and lower volumes of fluid administered in the standard therapy group than in other similar studies. Nevertheless, given the absence of any discernible between-group differences in outcomes, use of restrictive fluid therapy is unlikely to have a substantial effect on mortality, even in centres that employ more liberal fluid regimens.

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To date, no treatments have been demonstrated to reverse sepsis-induced organ dysfunction. Disrupted redox homeostasis and systemic oxidative stress, along with hyperinflammation, are pathophysiological hallmarks of sepsis that result in microvascular, endothelial and mitochondrial dysfunction, which cause tissue hypoxia and vasoplegia and seem to contribute to organ failure⁷. Vitamin C is a major anti-oxidant with additional pleiotropic anti-inflammatory, anticoagulant and immunomodulatory effects that becomes depleted in response to oxidative stress, providing a rationale for examining the effects of vitamin C in sepsis⁷. Randomized trials evaluating the effectiveness of intravenous vitamin C for sepsis, either alone or in combination with other therapies such as glucocorticoids and thiamine, an approach known as ‘metabolic resuscitation’, have yielded varying results⁸.

Approximately one in five people worldwide die due to sepsis when infection causes an overwhelming immune response that results in progressive organ failure^{1,2}. Usual care treatment consists of antibiotics, infection source control, fluid resuscitation and vasopressors, with the aim of reducing the microbial burden and supporting organ function³. The recent Conservative versus Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC)⁴ and Lessening Organ Dysfunction with Vitamin C (LOVIT)⁵ trials provide incremental evidence on fluid volume for resuscitation and treatment with high-dose intravenous vitamin C, respectively, in patients with sepsis (TABLE 1).

Fluid therapy is a cornerstone of the management of severe sepsis; however, insufficient evidence exists to guide recommendations on the appropriate volume for managing haemodynamic instability after initial resuscitation³. Liberal fluid therapy is common, despite concerns about the potentially harmful effects of high fluid volumes⁴. For example, in the Australian Resuscitation In Sepsis Evaluation (ARISE) trial, which included 1,600 adults with septic shock, patients in the usual care group received an average of >80 ml/kg of intravenous fluid in the first 72 h after enrollment⁶.

The CLASSIC trial is a European, parallel-group, open-label randomized study that compared a restrictive versus standard fluid therapy regimen in 1,550 adults with septic shock⁴. The primary outcome was 90-day mortality

and the secondary outcomes included serious adverse events, defined as a composite of ischaemic events and acute kidney injury (AKI). The median cumulative volume of intravenous fluids received in the ICU was 1,798 ml in the restrictive group and 3,811 ml in the standard therapy group. Outcomes in the two groups were strikingly similar, including 90-day mortality (adjusted relative risk, 1.00; 95% CI, 0.89–1.13), serious adverse events (adjusted relative risk, 0.95; 95% CI 0.77–1.15) and subsequent use of kidney replacement therapy (KRT, 22% in both groups).

The study was limited by its open-label design, high rates of protocol violations (21.5%

Table 1 | Key data from the CLASSIC and LOVIT trials

	CLASSIC ⁴	LOVIT ⁵
Sites	Europe	Canada, France, New Zealand
Design	Open-label RCT	Blinded RCT
No. of patients	1,554	863
Intervention	Restrictive fluid regimen	IV ascorbic acid (200 mg/kg per day for 96 h)
Control	Standard fluid regimen	Placebo
Primary outcome	90 day mortality: adjusted RR 1.00 (95% CI 0.89–1.13)	Death or persistent organ dysfunction: adjusted RR 1.15 (95% CI 0.90–1.47)
Primary outcome: AKI subgroup analysis	Absolute % point difference –0.8 (–8.0 to 6.7)	Not available
Secondary outcome: incidence of stage III AKI	Risk ratio 0.94 (95% CI 0.79–1.13)	Risk ratio 1.00 (95% CI 0.85–1.19)

RCT, randomized controlled trial; RR, relative risk.

The LOVIT trial is the largest clinical trial to date to test the hypothesis that vitamin C is beneficial in sepsis⁵. In this phase 3 multi-centre, placebo-controlled trial, 863 adults with sepsis who were receiving vasopressor therapy were randomly assigned to intravenous vitamin C at a dose of 200 mg/kg per day for four days or to placebo. The primary outcome was a composite of death or persistent organ dysfunction (defined as receipt of vasopressors, invasive mechanical ventilation or new KRT) at day 28. Unexpectedly, the primary outcome was increased in the vitamin C group in the unadjusted analysis (risk ratio, 1.21; 95% CI, 1.04 to 1.40; $P=0.01$), but no difference between the groups was found after adjusting for age, sex, severity of illness, steroid use and time to randomization (risk ratio, 1.15; 95% CI, 0.90–1.47). Secondary analyses, including serial evaluation of biomarkers of tissue dysoxia, inflammation and endothelial injury, did not provide insights into potential mechanisms of action of vitamin C⁵.

“ the role of intravenous vitamin C in sepsis remains uncertain ”


The findings of the LOVIT trial are tempered by those of a concurrently published meta-analysis of 41 randomized controlled trials of intravenous vitamin C in adults with severe infection ($n=4,915$), including the LOVIT trial, which reported low certainty evidence that vitamin C might reduce mortality (risk ratio, 0.88; 95% CI, 0.73–1.06 for in-hospital mortality)⁸. Disparate results were reported in sensitivity analyses that were limited to blinded trials deemed at low risk of bias⁸. The heterogeneity in treatment effect and lack of biological evidence of harm with intravenous vitamin C are confounding. Moreover, potential explanations for the differences are purely speculative.

The LOVIT trial design was robust, with blinding of the intervention, high protocol adherence, a short median enrolment time after ICU admission (12 h) and measurement of baseline vitamin C levels (which did not differ between the groups)⁵. However, unintentional differences might have disadvantaged the vitamin C group, including higher proportions of patients with COVID-19, emergency surgery, septic shock, mechanical ventilation, KRT and intra-abdominal sepsis, and fewer patients with urinary tract sepsis. Key secondary outcomes, including 6-month mortality, days without organ failure and 28-day mortality, were not significantly different, and the incidence of stage 3 AKI was identical, in the vitamin C and placebo groups.

Putative biochemical mechanisms for possible harm of intravenous vitamin C include the composition of the treatment. In LOVIT, vitamin C was administered as ascorbic acid with a pH as low as 5.0 and delivered at a dose 3–4 fold higher than in previous randomized trials⁸. Whether administering this volume of titratable acid is harmful in the setting of sepsis and in the presence of a compromised buffering system is unclear. Notably, pre-clinical studies in large animal models using the base salt of vitamin C, sodium ascorbate (pH 7.2), at a substantially higher dose than that of the ascorbic acid used in the LOVIT trial (3 g/kg versus 0.2 g/kg), have shown rapid reversal of sepsis-induced organ dysfunction⁹.

In summary, the CLASSIC and LOVIT randomized controlled trials provide incremental evidence to guide the management of septic shock in patients in the ICU. A restrictive fluid resuscitation regimen is not superior or inferior to more liberal fluid resuscitation therapy, and future studies are likely to focus on the possible impact of using 20% albumin solutions in septic shock, which is already being investigated (NCT03654001 and NCT03869385). As the role of intravenous

vitamin C in sepsis remains uncertain, its use can only be justified within the context of randomized controlled trials. Such trials are currently under way in patients with COVID-19 (NCT04401150) and septic acute respiratory distress syndrome (EudraCT 2020-003923-40).

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Competing interests

M.P.P. is conducting a trial of mega-dose vitamin C in septic shock. R.B. is conducting a trial of the physiological effect of mega-dose vitamin C in septic shock and holds intellectual property for mega-dose vitamin C therapy in sepsis.

RELATED LINKS

NCT03654001: <https://clinicaltrials.gov/ct2/show/NCT03654001>

NCT03869385: <https://clinicaltrials.gov/ct2/show/NCT03869385>

NCT04401150: <https://clinicaltrials.gov/ct2/show/NCT04401150>

EudraCT 2020-003923-40: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-003923-40/FR>