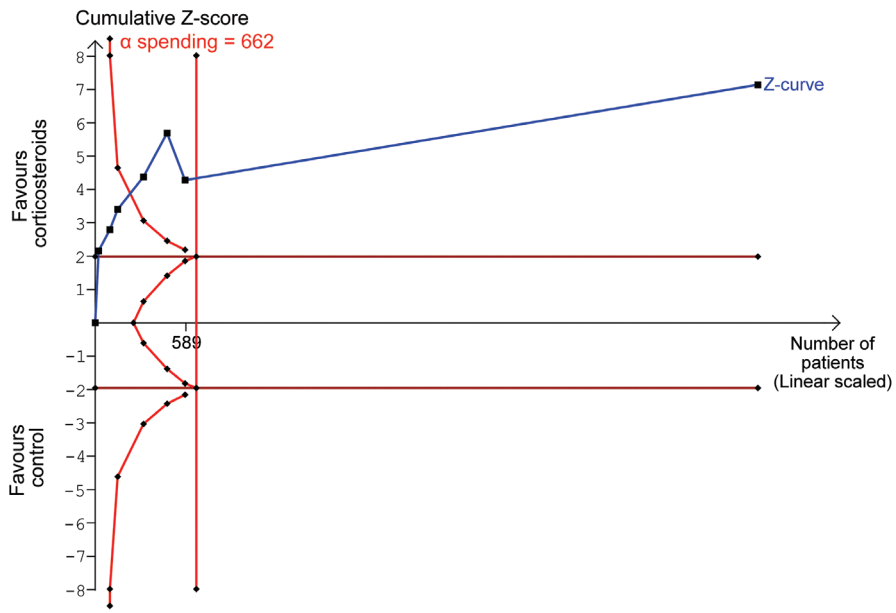
Comparing apples and oranges: the vasoactive effects of hydrocortisone and studies investigating high dose vitamin C combination therapy in septic shock

Tomoko Fujii, Andrew A Udy and Balasubramanian Venkatesh

Vitamin C is an essential water-soluble vitamin with antioxidant and anti-inflammatory properties, in addition to being a cofactor in the synthesis of catecholamines in the human body.[1-3] As vitamin C enhances the endogenous synthesis of noradrenaline and vasopressin,[3] and is depleted in patients with septic shock,[4] it is certainly not implausible that vitamin C administration in this setting may improve haemodynamic instability and promote more rapid shock reversal. Indeed, an early phase randomised controlled trial in 24 patients with severe sepsis found a statistically significant reduction in sepsis-related Sequential Organ Failure Assessment (SOFA) scores in patients receiving vitamin C (50 mg/kg or 200 mg/kg per day) compared with placebo.[5]

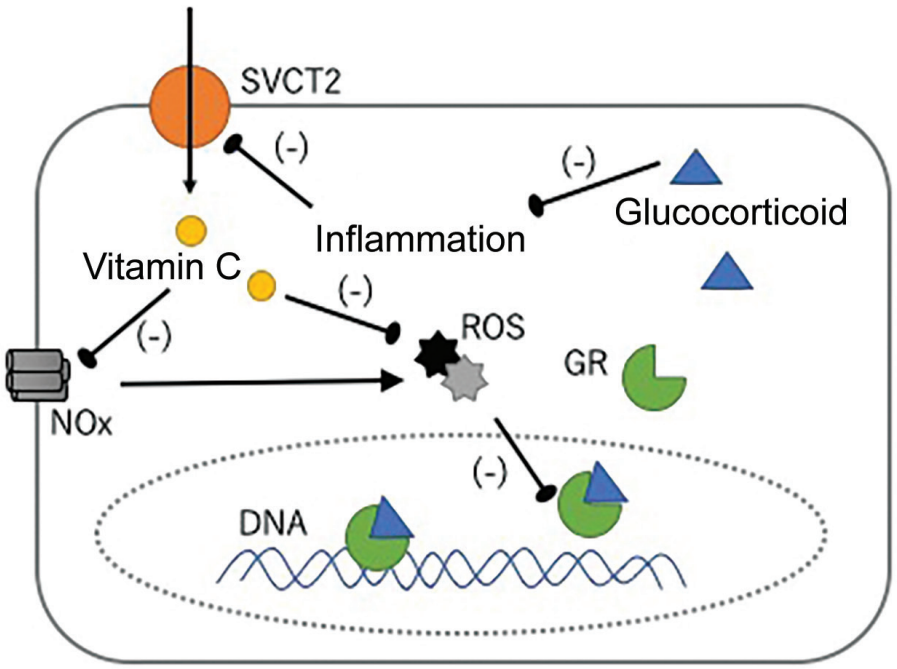
Many clinical trials have also assessed the efficacy of corticosteroids in the management of septic shock.[6] In this fashion, glucocorticoids inhibit the arachidonic acid cascade, NF-κB transcription, and nitric oxide production, all of which are thought to contribute to the low vascular resistance state characteristic of sepsis.[7] Moreover, the ADRENAL (Adjunctive Glucocorticoid Therapy in Patients with Septic Shock) trial demonstrated that low dose hydrocortisone (200 mg/day for a maximum of 7 days or until death or discharge from the ICU) resulted in a significant decrease in time to resolution of septic shock (median, 3 days; interquartile range [IQR], 2–5 days) compared with placebo (median, 4 days; IQR, 2–9 days; $P < 0.001$),[8] a finding that has also been confirmed in a recent systematic review with meta-analysis.[6] In this systematic review, seven studies (4302 patients) assessed time to resolution of shock, with the mean difference between the corticosteroid (< 500 mg/day) and control groups being –1.52 days (95% CI, –1.71 to –1.32; $P < 0.0001$). Extending this finding to consider the risk of random errors, trial sequential analysis suggests a mandatory information size of 662 participants (Figure 1), which has clearly been

Figure 1. Trial sequential analysis of time to resolution of shock*



* Large Z-value means that the observed difference between the effect of hydrocortisone group and placebo group cannot be solely explained by the chance, and the value is calculated every time a new trial is added to meta-analysis with respect to the accumulated information. The α-spending boundary provides the required number of patients to detect 1.4 days reduction in the random effects model meta-analysis, with the total α of 0.05 (two-sided) overall and a power of 80%.

Figure 2. A diagram of potential synergy of vitamin C and hydrocortisone*



GR = glucocorticoid receptor; NOx = NOx family NADPH oxidase; ROS = reactive oxygen species; SVCT2 = sodium–vitamin C cotransporter 2. * Vitamin C is taken up into cells via SVCT2, which is downregulated in inflammation. Glucocorticoids increase the expression of SVCT2 by its anti-inflammatory property. The DNA binding site of glucocorticoid-GR complex is oxidised by ROS in sepsis. Vitamin C reverses oxidation of the glucocorticoid receptor by scavenging ROS and downregulating NOx.

far exceeded, and results in adjusted 95% confidence intervals (CIs) that remain highly significant (adjusted 95% CI, –1.82 to –0.97). Therefore, these findings consistently demonstrate that corticosteroid therapy shortens the time to resolution of septic shock.

High dose intravenous (IV) vitamin C as an adjunct therapy in the setting of septic shock has seen increasing interest recently. This follows the publication of a single centre before and after study that implied that the use of IV vitamin C (1.5 g every 6 h) together with IV hydrocortisone (50 mg every 6 h) and IV thiamine (200 mg every 12 h) as metabolic resuscitation might decrease hospital mortality and the duration of vasopressor therapy.[9] The rationale for this combination includes the potential synergistic effects of vitamin C and hydrocortisone in sepsis. Specifically, vitamin C is taken up into cells via the sodium–vitamin C cotransporter, which is downregulated in sepsis. Glucocorticoids have been shown to increase the expression of this transporter,[10,11] while conversely, vitamin C reverses oxidation of the glucocorticoid receptor, thereby increasing the activity of glucocorticoids[12] (Figure 2). These appealing mechanisms should be further explored and updated using new approaches, such as proteomics or metabolomics.[13]

As of the 20 June 2019, there are 11 randomised controlled trials (one terminated and ten ongoing or unpublished) listed in ClinicalTrials.gov (https://clinicaltrials.gov) assessing the effect of combination IV vitamin C and hydrocortisone in patients with septic shock (Table 1). All current trials combine IV vitamin C (~ 6 g/day) and low dose hydrocortisone (< 500 mg/day) with or without thiamine (400 mg/day) as the intervention. And all but two trials are looking into the cardiovascular effects as an outcome. Notably, only two trials compare this combination intervention with low dose hydrocortisone, while the remainder use placebo or 0.9% sodium chloride. Moreover, the largest of these placebo-controlled studies (VICTAS [ClinicalTrials.gov Identification No. NCT03509350]; *n* = 2000) utilises vasopressor and ventilator-free days as the primary outcome.

Given that the best available evidence[6,8] consistently demonstrates that hydrocortisone shortens the duration of vasopressor dependency in septic shock, when a trial primarily aims to assess the positive cardiovascular effects of IV vitamin C in combination with hydrocortisone (as assessed by change in SOFA score, time to vasopressor independence, or otherwise), it would seem clear that IV hydrocortisone monotherapy should be provided to participants in the control group as well.[14]

This raises an important consideration in clinical trial design, namely whether the control population should receive "wild type" or more protocolised care. While standardising care in the control groups risks alienating

Table 1. Ongoing or unpublished trials investigating the effect of the combination therapy of intravenous vitamin C and hydrocortisone in septic shock

NCT Number	Interventions	Control	Outcome measures	Sample size	Country
NCT03258684 (HYVCTTSSS)	Vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), thiamine (200 mg every 12 h)	0.9% sodium chloride	▪ Hospital survival ▪ Duration of vasopressor therapy, requirement for renal replacement therapy, ICU LOS, change in serum PCT, SOFA score	80	China
NCT03380507 (HYVITS)	Vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), thiamine (200 mg every 12 h)	Usual care	▪ Hospital mortality by Day 60 ▪ Time to death, change in SOFA scores, ICU LOS, hospital LOS, duration of vasopressor therapy, lactate clearance, RRT, need for ECMO	212	Qatar
NCT03333278 (VITAMINS)	Vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), thiamine (200 mg every 12 h)	Hydrocortisone (50 mg every 6 h)	▪ 7-day vasopressor-free time ▪ ICU mortality, ICU-free days at Day 28, hospital mortality, 28-day mortality, 90-day mortality, changes in SOFA score, hospital LOS, 28-day cumulative vasopressor-free hours, 28-day cumulative invasive mechanical ventilation-free hours, RRT duration	216	Australia New Zealand Brazil
NCT03335124 [Terminated]	Vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), thiamine (200 mg every 12 h)	0.9% sodium chloride	▪ Hospital mortality ▪ 60-day mortality, 28-day mortality, time to vasopressor independence, PCT clearance, delta SOFA score, ICU LOS and ICU-free days, hospital LOS	5 (actual)	Slovenia
NCT03389555 (ACTS)	Vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), thiamine (100 mg every 6 h)	0.9% sodium chloride	▪ SOFA score change ▪ Renal failure, 30-day mortality	200	United States
NCT03422159 (ORANGES)	Vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), thiamine (200 mg every 12 h)	0.9% sodium chloride	▪ Time to vasopressor independence, change in SOFA score ▪ 28-day mortality, PCT clearance, ICU mortality, ICU LOS, ICU-free days, hospital LOS, hospital mortality	140	United States
NCT03509350 (VICTAS)	Vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), thiamine (100 mg every 6 h)	Placebo	▪ Vasopressor and ventilator-free days (30 days) ▪ Mortality at 30 days, delirium-free and coma-free days	2000	United States
NCT03592693 (CORVICTES)	Vitamin C (1.5 g every 6 h), hydrocortisone (200–250 mg infusion)	Placebo	▪ Hospital mortality ▪ 60-day mortality, 28-day mortality, PCT clearance, delta SOFA score, 28-day neurological failure-free days, ICU mortality, 28-day ICU-free days, ICU LOS, hospital LOS	400	Greece
NCT03649633 (CORVICTES-YM)	Vitamin C (1.5 g every 6 h), hydrocortisone (200–250 mg infusion)	Placebo	▪ Cerebral autoregulation, cerebral blood flow ▪ Neurological failure-free days, ventilator-free days, favourable in-hospital neurological outcome, patient-reported health-related quality of life, biomarkers	100	Greece
NCT03821714	Vitamin C (1.5 g every 6 h), hydrocortisone (200 mg infusion), thiamine (200 mg every 12 h)	Hydrocortisone (200 mg infusion)	▪ Perfused vessel density	40	China
NCT03872011	Vitamin C (2 g every 6 h), hydrocortisone (200 mg infusion), thiamine (200 mg every 12 h)	0.9% sodium chloride	▪ 90-day mortality ▪ ICU mortality, hospital mortality, 28-day mortality	406	China

ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; LOS = length of stay; PCT = procalcitonin; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment.

clinicians, or may be perceived as engineering a particular result, in the case of a combination intervention (where one component has established efficacy in terms of the primary outcome), the latter would seem clearly required.

In summary, many of the ongoing and unpublished trials of vitamin C therapy in combination with hydrocortisone do not consider the vasoactive effects of hydrocortisone in trial design and will assess the impact of this combination on shock resolution in comparison to placebo. This may significantly overestimate the effects of IV vitamin C and is, perhaps, more a case of comparing apples and oranges.

Competing interests

Tomoko Fujii and Andrew Udy are investigators of the VITAMINS trial (NCT03333278). Balasubramanian Venkatesh is an investigator of the ADRENAL Trial.

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