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Vitamin C and thiamine in critical illness

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Learning objectives

By reading this article, you should be able to:

- Name the causes of vitamin C and thiamine deficiencies in critically ill patients.
- Discuss the rationale for the use of vitamin C and thiamine in the critically ill.
- Evaluate the evidence for the benefits and potential harmful effects of giving vitamin C and thiamine.
- Describe the underlying mechanisms of the potential synergistic effects of vitamin C and thiamine.

Key points

- Vitamin C and thiamine deficiencies are common during critical illness because of increased requirements, decreased intake, reduced recycling and increased urinary excretion.
- Both vitamins have multiple key metabolic functions and act synergistically.
- Vitamin C has important antioxidant, anti-inflammatory, and immune-modulating effects, and is an essential cofactor for mono- and dioxygenase enzymes.
- Thiamine is crucial for cellular energy metabolism and cellular redox state, and also has antioxidant effects.
- Several small clinical studies show improvement of organ function or even a reduction in mortality with i.v. vitamin C and thiamine, but large clinical trials are required.

The very impressive beneficial effects of vitamin C and thiamine (vitamin B1) in severe sepsis, as reported in a recent study, gained widespread attention from both professional media and the lay press.[1] This has highlighted the importance of these well-known vitamins in critically ill patients. Both have several common characteristics: they are water soluble, cannot be synthesised by humans, and body stores are limited. Deficiency of both vitamins develops easily during critical illness as a result of increased oxidative stress and increased metabolism. As vitamin C and thiamine support crucial body functions, deficiency can increase the severity of illness and hamper recovery. Both vitamins are cheap, widely available, and can be administered safely.

However, deficiency is generally overlooked. Laboratory assessment is difficult and time consuming, so plasma concentrations are not available in daily practice. Furthermore, there is a widespread belief that standard nutrition is a sufficient source. An increasing number of clinical studies have sought to examine the potential therapeutic benefit of vitamin C and thiamine in supplemental or pharmacological doses, separately or in combination, because of a potential synergistic effect. In this review, we describe the rationale behind the supplemental and pharmacological administration of vitamin C and thiamine in the critically ill, report the main results of the relevant clinical studies, and discuss the potential synergistic effect of these vitamins.

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Vitamin C deficiency

Although vitamin C is the primary circulating antioxidant, humans, in contrast with many other mammals, have lost the ability to synthesise vitamin C. Because body stores are limited, insufficient intake for months leads to severe scurvy, as exemplified by the deaths of millions of healthy sailors during long sea journeys in previous centuries. Vitamin C concentrations can also be reduced by increased demands and insufficient intake. During episodes of oxidative stress, animals capable of synthesising vitamin C intensify its production. However, humans cannot synthesise vitamin C because of mutations in the L-gulono-γ-lactone oxidase gene encoding the enzyme responsible for the terminal step of vitamin C synthesis. The increased metabolic demands of critical illness combined with reduced recycling of vitamin C from dehydroascorbic acid (DHA) and glomerular hyperfiltration may contribute to acute vitamin C hypovitaminosis down to concentrations that can cause scurvy (Fig. 1). Giving a recommended amount of daily (par)enteral nutrition, even when enriched with vitamin C (up to 700 mg day^{-1}), does not prevent this.[2] In a recent study, around 70% of critically ill patients had hypovitaminosis C (plasma concentration <23 μmol L^{-1}) and ~30% had vitamin C deficiency (plasma concentration <11 μmol L^{-1}; scurvy concentrations) despite standard nutrition. These percentages were even higher in patients with sepsis (88% and 38%, respectively).[3] In addition, vitamin C concentrations decrease in several other conditions with high oxidative stress, such as intracerebral haemorrhage, cardiogenic shock, and cardiac arrest. The lowest concentrations (mean: 3.8 μmol L^{-1}) have been reported in patients with multiple organ failure (see Table 1).[4] Vitamin C concentrations in critical care patients have been reported to be inversely related to Sequential Organ Failure Assessment score, although this does not prove causality.[5]

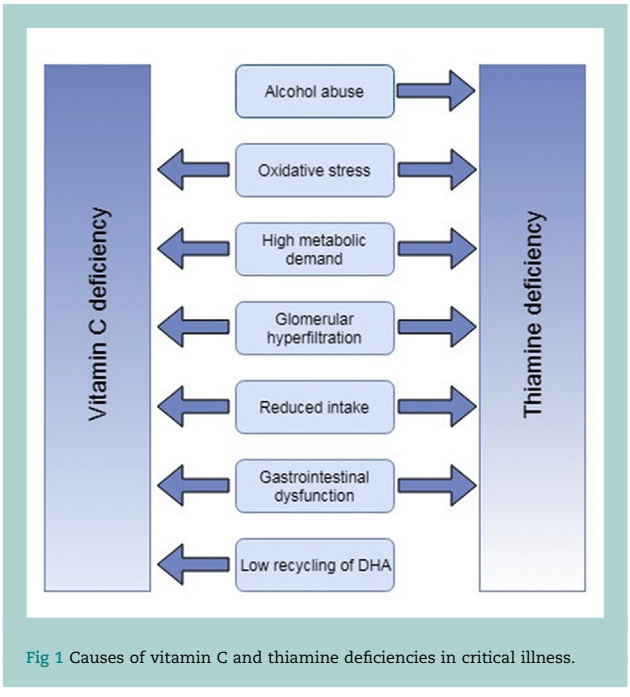

Fig 1 Causes of vitamin C and thiamine deficiencies in critical illness.

Pharmacokinetics of vitamin C

Because we cannot synthesise vitamin C, plasma concentrations in humans depend on exogenous intake. Importantly, the enteral absorption of vitamin C via the intestinal sodium-dependent vitamin C transporter 1 (SCVC1) is limited and potentially decreased during critical illness. Vitamin C is subsequently actively transported into most cells via the sodium-dependent vitamin C transporter 2, whereas in the brain vitamin C is mainly transported as dehydroascorbate (DHA) via glucose transporters where it is reduced back to vitamin C. Intracellular concentrations are high, especially in leucocytes and brain cells, to protect these cells against the oxidative stress associated with their function. Being a small water-soluble molecule, vitamin C is filtered by the glomerulus and actively reabsorbed via SCVC1. Whilst the urinary excretion of vitamin C is minimal if plasma concentrations are low, urinary excretion may be high in the presence of glomerular hyperfiltration, as seen in hyper-dynamic sepsis and trauma, or when tubular function is diminished. Thus, apart from increased metabolic demands and decreased recycling, critical illness may be associated with low plasma concentrations because of diminished intake and increased renal loss (Fig. 1).

Mechanisms of action of high-dose i.v. vitamin C

Beyond the prevention of the symptoms of scurvy, vitamin C is crucial in critically ill patients because of its multiple effects (Fig. 2). Some of these effects are stronger at supraphysiological concentrations and are all based on electron donation. Vitamin C is a direct free radical scavenger, but can also reduce the production of reactive oxygen species (ROS) and recover other antioxidants, such as vitamin E and glutathione. Furthermore, it can attenuate the pro-inflammatory response by inhibition of nuclear factor-kappa light chain enhancer of activated B cells, therefore decreasing cytokine release. It has important immune-modulating effects by promoting bacterial killing by neutrophils, lymphocyte proliferation, and interferon production. It can restrain bacterial growth and promotes wound healing. Additionally, vitamin C is a fundamental cofactor for the biosynthesis of vasopressin and catecholamines. Moreover, it augments catecholamine sensitivity by binding to adrenergic receptors. Vitamin C is also essential for microcirculation, as it protects the endothelial barrier and enhances microcirculatory patency.

Dosing: vitamin C

In critically ill patients, enteral intake appears to be insufficient to normalise plasma concentrations. Standard enteral or parenteral nutrition contains a mean of 100–200 mg day^{-1} vitamin C. In healthy persons, a dietary intake of 200 mg day^{-1} is satisfactory to maintain normal plasma concentrations (40–80 μmol L^{-1}), and enteral supplementation can attain plasma concentrations of at most 220 μmol L^{-1}. High amounts of oral vitamin C can induce diarrhoea, and during critical illness, enteral uptake may be impaired further by gastrointestinal dysfunction. Intravenous administration is necessary to avoid the saturable enteral uptake, and a minimum dose of 2–3 g i.v. ('repletion dose') is required to normalise plasma concentrations.[6,7] To reach supraphysiological concentrations, even higher ('pharmacological') doses are necessary, especially as urine excretion increases at higher plasma concentrations. The

Table 1 Vitamin C and thiamine concentrations in critically ill patients. Supplementary references [S1–S6] are available as Supplementary materials. SD, standard deviation; SE, standard error; SIRS, systemic inflammatory response syndrome; MOF, multiple organ failure

Author, journal, and year published	Patients studied	Numbers of patients (*n*)	
Vitamin C			Plasma vitamin C concentration (μmol L^{-1}) on Day 1; expressed as mean (SD) unless stated
Borrelli and colleagues, *Crit Care Med*, 1996[4]	Surgical ICU	10 (MOF); 6 (no MOF)	3.8 (1); 12.0 (3.2)
Long and colleagues, *J Surg Res*, 2003[6]	Trauma/sepsis	12	Mean: 6.3 (SE: 17.1)
Senthil and colleagues, *Clin Chim Acta*, 2004[S1]	Cardiogenic shock after myocardial infarction	25 (healthy); 25 (cardiogenic shock)	59.1 (9.1); 26.7 (6.8)
Polidori and colleagues, *Stroke*, 2001[S2]	Intracerebral haemorrhage	13	29.0 (8.1)
	Head trauma	15	31.3 (9.1)
de Grooth and colleagues, *Intensive Care Med*, 2014[5]	Healthy volunteers	42	Median: 61 (IQR: 49–75)
	SIRS	28	Median: 20 (IQR: 13–32)
	Cardiac arrest	23	Median: 28 (IQR: 18–38)
Fowler and colleagues, *J Transl Med*, 2014[9]	Septic shock	24	Mean: 17.9 (SE: 2.4)
Carr and colleagues, *Crit Care*, 2017[3]	Sepsis	24	14.6 (8.7)
	Critically ill; no sepsis	17	19.7 (9.3)
Thiamine			
Cruickshank and colleagues, *Intensive Care Med*, 1988[22]	Critically ill		Thiamine deficiency (erythrocyte transketolase activity >25% 11%
	Survivors	79	29%
	Non-survivors	79	
Corcoran and colleagues, *Anaesth Intensive Care*, 2009[S3]	Critically ill		Red-cell thiamine concentration (nmol L^{-1}) (normal: 190–400) 268
	Survivors	111	264
	Non-survivors	18	
Donnino and colleagues, *J Crit Care*, 2010[S4]	Severe sepsis and septic shock	30	Prevalence of thiamine deficiency (plasma concentration: <9 nmol L^{-1}); admission: 10%; within 72 h: 20%
Donnino and colleagues, *Nutrition*, 2010[S5]	Cardiac surgery	14	Plasma thiamine concentrations; mean difference: 10.14 nmol L^{-1} before-and-after surgery
Costa and colleagues, *J Crit Care*, 2014[S6]	Septic shock	108	Prevalence of thiamine deficiency (serum thiamine: <16 nmol L^{-1}); within 72 h: 71.3%
Donnino and colleagues, *Crit Care Med*, 2016[26]	Septic shock and lactate >3 mmol L^{-1}	79	Prevalence of thiamine deficiency (plasma concentration: ≤7 nmol L^{-1}); on admission: 35%

dose–response relationship between i.v. vitamin C administration and the attained plasma concentrations is linear. With the frequently used dosing protocol of 1.5 g 6-hourly, peak concentrations of 480 μmol L^{-1} (inter-quartile range [IQR] 325–680) are achieved.[8] In a recent pharmacokinetic study of vitamin C in critically ill patients with multiple organ dysfunction, 1 h concentrations of more than 1,000 μmol L^{-1} were reached. In patients with sepsis, a dose of 200 mg kg^{-1} day^{-1} for 4 days produced plasma concentrations of 5,700 μmol L^{-1} on Day 4.[9] It is not yet established whether supraphysiological concentrations are better, or what the optimal plasma concentrations and duration of therapy are in critically ill patients.

Clinical studies: vitamin C

Several clinical studies have investigated the potential beneficial effects of supplemental or pharmacological doses of vitamin C in critical conditions. However, doses, timing, and route of vitamin C, and combination with other drugs or vitamins have differed considerably between studies. We discuss the most relevant studies investigating patients with trauma, burns, ischaemia/reperfusion injury, or sepsis.

Patients after surgery or trauma

Two relevant studies using supplemental doses in patients after surgery or trauma have been performed. In an RCT of 595 critically ill surgical patients, i.v. vitamin C (1 g total dissolved solids t.d.s.) in combination with vitamin E reduced the development of new organ failure and decreased the length of ICU stay.[10] In a before-and-after study of 4,294 trauma patients, vitamin C (i.v. or enteral 1 g t.d.s.) combined with vitamin E and selenium reduced the length of ICU stay and mortality (6.1% compared with 8.5%; P=0.001).[11]

Sepsis

Most recent studies have focused on patients with sepsis. Two small RCTs showed impressive results. In a pilot RCT of 24 patients with severe sepsis and septic shock, i.v. vitamin C at

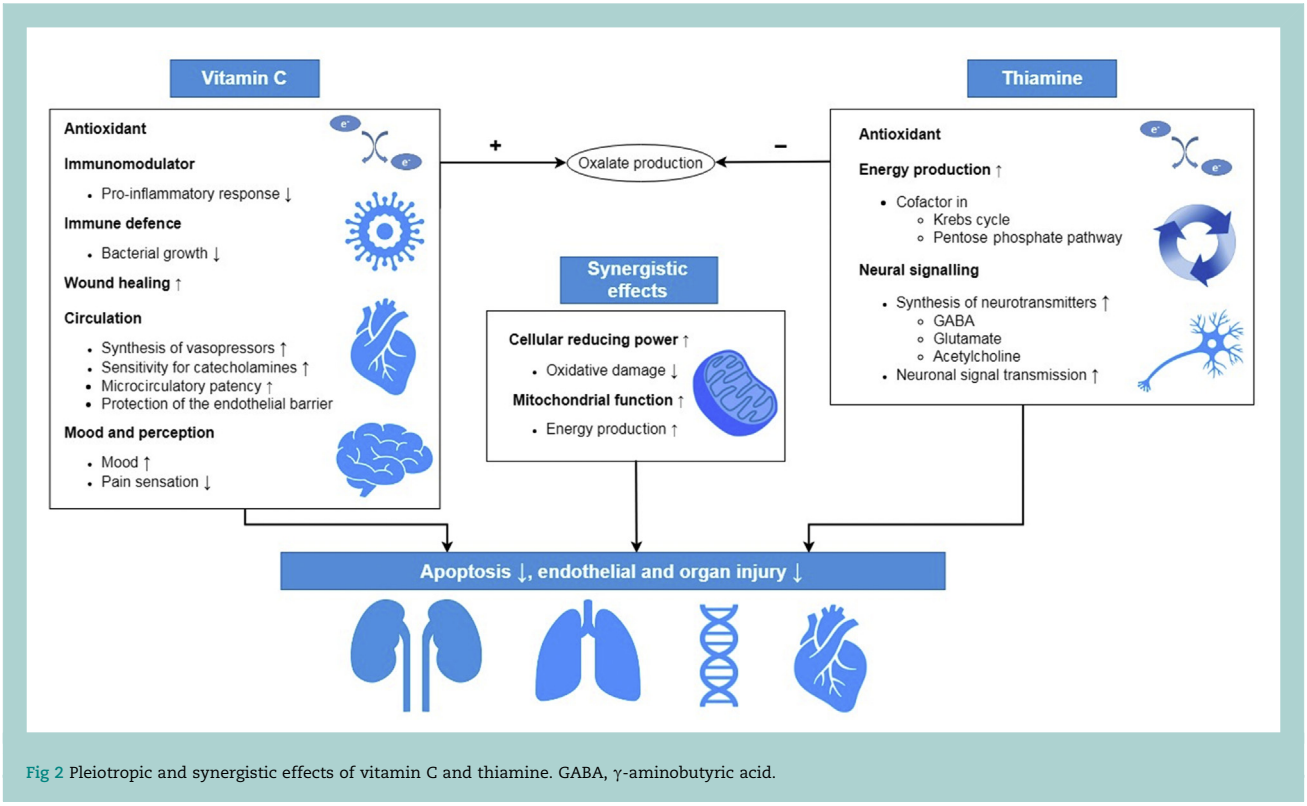

Fig 2 Pleiotropic and synergistic effects of vitamin C and thiamine. GABA, γ-aminobutyric acid.

doses of 50 and 200 mg kg^{-1} day^{-1} for 4 days reduced the concentrations of inflammatory markers and organ dysfunction.[9] This effect seemed to be dose-dependent. In another small RCT of 28 patients with septic shock, i.v. vitamin C 100 mg kg^{-1} day^{-1} reduced the need for vasopressors and improved survival.[12]

Burns

In patients with severe burns, two small studies have been performed. In an RCT of 37 patients and a retrospective study of 33 patients, very-high-dose vitamin C (66 mg kg^{-1} h^{-1}) for 24 h was associated with reduced fluid requirements and time on mechanical ventilation and increased urine output.[13,14]

Ischaemia/reperfusion injury

Two clinical studies investigated the effect of i.v. vitamin C in myocardial injury and gave vitamin C i.v. before a percutaneous coronary intervention (PCI). In the first study, in patients with acute ST-elevation myocardial infarction, higher plasma concentrations of vitamin C (>1,000 μmol L^{-1}) were associated with improved myocardial and microcirculatory function.[15] The results of a randomised trial of 532 patients with coronary artery disease admitted for elective PCI suggested that myocardial injury (estimated by troponin I and creatine kinase MB) and oxidative stress were attenuated by a single dose of vitamin C 3 g i.v. within 6 h before PCI.[16]

Adverse effects of vitamin C

Pharmacological doses of vitamin C could theoretically induce adverse effects, such as oxalate nephropathy, pro-oxidative effects, and factitious hyperglycaemia.

Oxalate is a breakdown product of vitamin C. High doses of i.v. vitamin C substantially increase urinary oxalate excretion (median: 150 mg day^{-1} at a dose of 5 g b.d.).[7] However, oxalate nephropathy in patients with primary hyperoxaluria takes at least several months to develop. There are case reports describing oxalate nephropathy after high-dose vitamin C, but only at extreme doses or after prolonged intake. In a recent study of 157 adult patients receiving i.v. vitamin C two to three times a week at a dosage up to 100 g per infusion, no renal stones were reported.[17] In most studies of critically ill patients using high-dose i.v. vitamin C, the substance was administered for a limited period of time (mostly 4 days), and adverse renal events were not reported. Furthermore, vitamin C (6 g day^{-1}) in combination with thiamine and hydrocortisone was found to be associated with improved kidney function in a recent before-and-after study in patients with sepsis.[1]

Vitamin C can potentially be pro-oxidant by three different pathways. Firstly, all physiological effects are based on electron donation, thereby converting vitamin C to the ascorbate radical. Although potentially pro-oxidant, the ascorbate radical is a relatively stable molecule that mainly reacts with itself and is less damaging for other molecules than most radicals it has scavenged. Secondly, vitamin C can reduce the concentrations of free metals, such as copper and iron, and generate ROS by the Fenton reaction. However, in a meticulous review, the pro-oxidant effect appeared to be mostly an *in vitro* phenomenon (where free iron exists), whereas *in vivo* (where iron is bound to proteins) the antioxidant effect outweighed the pro-oxidant effect, as estimated by markers of DNA, protein, and lipid peroxidation.[18] Finally, super-high doses of vitamin C (achieving plasma concentrations of >5 mmol L^{-1}) can generate hydrogen peroxide, which seems to be toxic for some types of cancer,

but not for human cells, because of the large reducing capacity of circulating erythrocytes.[19]

Of note, high doses of i.v. vitamin C (>50 g day^{-1}) can cause falsely increased glucose measurements by some point-of-care devices (POC). Vitamin C is biosynthesised out of monosaccharides in animals and plants. Vitamin C and glucose are very similar six-carbon molecules. As a result, POC measurements based on glucose-dehydrogenase-pyrroloquinoline quinone amperometric method of testing may indicate spuriously increased glucose concentrations. This could lead to inappropriate insulin therapy and iatrogenic hypoglycaemia. Factitious hyperglycaemia does not occur with central laboratory-analysed blood glucose measurements. Therefore, blood glucose measurements should be determined by core laboratory assays while pharmacological dose of i.v. vitamin C is administered.

Thiamine deficiency

Thiamine can be produced by bacteria, fungi, and plants, but not by humans. The limited body stores of around thiamine 30 mg are predominantly located in muscles, liver, and kidneys.[20] Insufficient intake can lead to thiamine deficiency within 18 days.[20] However, analogous to vitamin C, the oxidative stress and systemic inflammation in critical illness (trauma, sepsis, cardiac arrest, and after cardiac surgery) can rapidly deplete thiamine reserves (Table 1). In addition, gastrointestinal dysfunction and increased urinary loss can further diminish thiamine concentrations, whereas at the same time the high glucose content of parenteral or enteral nutrition will increase normal requirements. Alcohol abuse may contribute to thiamine deficiency as a result of poor nutrition, decreased gastrointestinal absorption, and diminished liver stores. Altogether, the prevalence of thiamine deficiency in critically ill patients is about 20%.[21] This percentage can increase up to 70% during ICU stay and is associated with an increase in mortality rate of up to 50%.[22] Thiamine body stores are better reflected by direct thiamine pyrophosphate (TPP) measurement (using high-performance liquid chromatography) in whole blood and erythrocytes than in plasma.

Thiamine: pharmacokinetics

In contrast to vitamin C, enteral absorption occurs by passive diffusion when the thiamine concentration in the jejunum is high, and by active absorption via thiamine transporter proteins when jejunal concentrations are low. There are several different thiamine compounds in the body. Whereas free thiamine is non-phosphorylated, the other forms have one or more phosphate groups. Thiamine diphosphate (also called TPP) is the most important one. About 1% of TPP can be found in the blood, mainly in the erythrocytes. Thiamine and its metabolites are excreted predominantly by the kidneys, and diuretics increase urinary loss.

Mechanisms of action of TPP

Whilst non-phosphorylated thiamine mainly acts as an antioxidant, TPP is crucial for cellular energy production, especially from glucose. TPP is an obligatory cofactor for pyruvate dehydrogenase to convert pyruvate (derived from glucose) into acetyl coenzyme A (CoA), necessary for entering the mitochondrial Krebs cycle. Thiamine deficiency diverts glucose metabolism to the anaerobic pathway, and pyruvate will be converted to lactate instead of acetyl CoA, leading to lactic acidosis. Therefore, thiamine deficiency should be considered in patients with unexplained hyperlactataemia. In the Krebs cycle, TPP is also an essential cofactor for α-ketoglutarate dehydrogenase, which converts α-ketoglutarate to succinyl CoA, a necessary step before ensuing oxidative phosphorylation and production of ATP. In addition, TPP is an important cofactor for transketolase, a key enzyme in the pentose phosphate pathway that generates reduced nicotinamide adenine dinucleotide phosphate (NADPH) and ribose-5-phosphate. NADPH is required for reductive biosynthetic reactions, especially fatty acid and steroid synthesis. In addition, NADPH is also used for the reduction of glutathione, and therefore, is essential for the cellular redox capacity. Ribose-5-phosphate is a precursor for the synthesis of nucleotides and nucleic acids, vital in critical illness. Because of these important functions of TPP, thiamine deficiency can affect the cardiovascular, muscular, gastrointestinal, and both central and peripheral nervous systems. This can lead to severe clinical syndromes, such as cardiac beriberi (congestive heart failure with oedema) and Wernicke's encephalopathy (ophthalmoplegia, ataxia, and confusion). The brain appears to be particularly vulnerable to thiamine deficiency. Thiamine concentrations in the brain are lower than in other organs, but at the same time, the brain is highly dependent on TPP because of its important role in mitochondrial energy production, synthesis of glucose-derived neurotransmitters, generation of acetylcholine, neuronal signal transmission, and production of myelin.[23] Thiamine deficiency, therefore, can impair oxidative metabolism and may lead to brain damage.[24] Because of its many effects on multiple vital organs, thiamine deficiency in critically ill patients can be devastating.

Dosing

The recommended daily intake of thiamine during health is 1.1–1.2 mg day^{-1} for adults. Standard enteral nutrition formulations contain 2–3 mg day^{-1} and parenteral nutrition contains 3–4 mg day^{-1}. The doses recommended for refeeding syndrome are 200–300 mg day^{-1} i.v., and in Wernicke's encephalopathy, 200–500 mg t.d.s. i.v. can restore thiamine concentrations in critically ill patients within hours. In clinical studies including critically ill patients, thiamine doses similar to those administered for refeeding and Wernicke's encephalopathy were used.

Clinical studies: thiamine

Because of the high prevalence of thiamine deficiency in critically ill patients, several clinical studies have been performed to investigate the potential benefit of thiamine administration. These studies do not show uniform results. Doses and timing differed substantially between studies.

Cardiac surgery

In two studies, preventive administration of thiamine to patients undergoing cardiac surgery did not affect the postoperative lactate concentrations or clinical outcomes. However, cellular oxygen consumption was higher in those receiving thiamine.[25]

Sepsis

In a small study of patients with septic shock, thiamine did not reduce lactate concentrations or overall mortality.[26]

However, in a subgroup of patients with thiamine deficiency at baseline, thiamine replacement was associated with decreased lactate concentrations and reduced mortality. The secondary analysis of this study showed lower creatinine concentrations and less progression to renal function requiring renal replacement therapy in the overall group of patients who received thiamine.

Burns

In a very small study of critically ill patients with burn injuries, thiamine administration was associated with significantly reduced pyruvate and lactate concentrations.[27]

Adverse effects

The enteral and i.v. administration of thiamine has minimal adverse effects, as supported by toxicological data in animals. Intravenous use has occasionally led to anaphylaxis, whilst doses of more than 400 mg may induce nausea, anorexia, and mild ataxia.

Synergism between vitamin C and thiamine

The addition of thiamine to vitamin C can reduce the risk of oxalate nephropathy via the reduction of oxalate production. The two drugs may also act synergistically to attenuate oxidative damage and cellular apoptosis, and restore organ function.

However, evidence of clinically significant benefit from a well-designed adequately powered trial is awaited.

Furthermore, thiamine and vitamin C can act in concert to reduce organ injury in critical illness by affecting different pathways. Vitamin C is the primary circulating antioxidant, acts as a direct radical scavenger, reduces ROS production, and regenerates other antioxidants (vitamin E and glutathione); whereas TPP generates NADPH, which also contributes to the recovery of the reduced form of glutathione. Together, they substantially improve the cellular reducing power. In addition, thiamine is essential for mitochondrial energy production, whereas vitamin C attenuates mitochondrial dysfunction and protects the endothelial barrier. Therefore, both vitamins may jointly attenuate apoptosis, reduce endothelial damage, and decrease organ injury.

Finally, both vitamins may contribute to reversal of shock: thiamine by improving myocardial mitochondrial energy status, and thus treating a component of high-output heart failure; and vitamin C by recovering catecholamine and vasopressin synthesis and sensitivity, and protecting the capillary barrier.

Clinical studies: thiamine, vitamin C, and hydrocortisone

Because of their potentially synergistic effects, several clinical studies have investigated the combination of vitamin C and thiamine. In patients admitted to the ICU after complicated cardiac surgery, subarachnoid haemorrhage, or major trauma, i.v. administration of a mixture of selenium, zinc, vitamin C, and thiamine (100 mg day^{-1}) did not improve organ function, but attenuated the inflammatory response and decreased hospital length of stay in patients after cardiac surgery or trauma.[28] Recently, a well-known before-and-after study investigated the effect of the 'Marik cocktail' consisting of i.v. vitamin C (1.5 g q.d.s.), i.v. thiamine (200 mg b.d.), and i.v. hydrocortisone (50 mg q.d.s.) in patients with severe sepsis or septic shock. Hydrocortisone was added because glucocorticoids may increase the expression of the sodium/vitamin C transporters, whereas vitamin C may increase glucocorticoid sensitivity. This study reported reduced mortality (from 40% to 8%), reduced mean duration of vasopressor use (from 55 to 18 h), and reduced organ dysfunction, including renal impairment in the treatment group. The latter is an important result with regard to the small risk of vitamin C-induced oxalate nephropathy in susceptible patients.[1] Another before-and-after study using the same combination of vitamin C, thiamine, and hydrocortisone in patients with severe pneumonia showed a substantial reduction of hospital mortality and an improved radiological score on day 7. Kidney function was not different between groups.[29] Although these results are very encouraging, significant limitations of these two studies were size, single-centre design, and the use of historical controls. Therefore, it is too early for a wide-scale implementation of this protocol, and large, prospective clinical trials are needed to validate these results.

Conclusions

Vitamin C and thiamine deficiencies are common in critically ill patients. This is mainly caused by the unfavourable combination of increased needs resulting from oxidative stress and inflammation, and diminished intake. Both vitamins exert multiple effects and support key metabolic functions. Vitamin C is the primary antioxidant in humans, an important cofactor for mono- and dioxygenase enzymes, and additionally has anti-inflammatory and immune-modulating effects. Thiamine also acts as an antioxidant, and is in its phosphorylated form crucial for cellular energy metabolism and cellular redox state. Thiamine specifically protects the brain. Deficiency of these vitamins in critically ill patients may worsen organ injury and hamper recovery. Several clinical studies have suggested earlier recovery from shock and organ failure using repletion doses (vitamin C 2–3 g i.v. and thiamine 100 mg day^{-1}), or even a reduction in mortality when using pharmacological doses (vitamin C >2 g i.v. day^{-1} and thiamine 200–400 mg day^{-1}). However, these studies are small and differ substantially with regard to dose, timing, and duration of therapy. Vitamin C and thiamine may act synergistically. Large clinical trials, required to validate these results, are already underway (see www.clinicaltrials.gov: NCT03389555, NCT03509350, NCT03258684, NCT03422159, NCT03333278, and NCT03380507). It is hoped that these trials and others will also determine the optimal treatment regimen with regard to dose, timing, and duration of therapy with vitamin C and thiamine, and whether combining these two vitamins yields better outcomes for patients.

Declaration of interest

The authors received a grant from the Netherlands Organisation for Health Research and Development to perform a multicentre trial to investigate the effect of high-dose i.v. vitamin C in post-cardiac arrest syndrome.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjae.2019.05.005.

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