

Selenium in critically ill patients

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There is increasing evidence that particular nutritional substrates may be important in critically ill patients and in recent years there has been growing interest in selenium. This review aims to outline the incidence of selenium deficiency in critically ill patients, the consequences of such a deficiency and present the evidence for, and effect of, selenium supplementation in these patients. Selenium levels fall during periods of oxidative stress as occurs in critically ill patients with conditions such as severe sepsis, burns, and following trauma. Data from individual studies and meta-analyses suggests that selenium is an important adjuvant therapy in certain critically ill patients and supplementation of selenium may offer a mortality benefit.

Keywords: *selenium; sepsis; septic shock; intensive care; antioxidants*

What is selenium?

Selenium is a trace mineral with important structural and enzymatic roles, found in minute quantities within the body. The main dietary sources of selenium are from bread, cereals, fish, and meat; brazil nuts contain the highest quantity of selenium per gram.¹ The Recommended Daily Allowance (RDA) of selenium is 60 µg for women and 75 µg for men.² The World Health Organisation suggests 40 µg/day of selenium is necessary to prevent disease, but in the UK, current intake is estimated at 34 µg/day;³ this value has fallen following changes in the wheat supply for bread manufacture from selenium-rich North America to the relatively selenium-depleted Europe. This reduced intake has been reflected in lower plasma levels in the general population.^{4,5} The mean plasma selenium level believed to be necessary for optimal selenoprotein activity is about 100 µg/L;⁶ the current EU average is 79 µg/L.⁷ At risk of selenium deficiency are people with poor quality diets, eg alcoholics, or those with reduced dietary intake, eg chronic illness, and patients receiving total parenteral nutrition (TPN).

What are the consequences of selenium deficiency?

Two selenium-deficient disease states have been described: Keshan disease (a cardiomyopathy) and Kashin-Bek disease (an osteoarthropathy). Patients on long-term TPN or with severe malnutrition can develop features similar to Keshan disease. Low plasma selenium levels without overt deficiency give rise to an impaired immune response and may increase susceptibility to disorders including cardiovascular disease, mood disorders, cancer, male infertility and spontaneous abortions. It is postulated that harmless viruses may become virulent by passing through a selenium-deficient host; Keshan disease may be secondary to coxsackie virus infection, and the emergence of HIV in Zaire and new strains of influenza in China may be related to these countries being relatively selenium deficient. Plasma selenium levels appear to be a

strong predictor of outcome in HIV disease and selenium supplementation appears to inhibit the progression of HIV disease to AIDS and prevents HIV replication.⁸

In critically ill patients, plasma selenium levels fall during periods of oxidative stress as occurs with severe sepsis and the systemic inflammatory response syndrome (SIRS) and there is increasing evidence that selenium may be an important adjuvant therapy possibly offering a mortality benefit to patients with severe sepsis.

What is the evidence that critically ill patients are selenium deficient?

Plasma selenium levels are reduced in the critically ill due to the chronic deficiency in the general population, reduced nutritional intake, haemodilution and biological fluid loss. However, it is difficult to interpret micronutrient plasma concentrations throughout the acute phase response due to reduced binding proteins, in particular albumin, through utilisation and redistribution. It was first established that selenium deficiency occurred in critically ill patients in 1990, where a 40% reduction in plasma selenium on admission to the intensive care unit (ICU) was demonstrated, not explained by an increase in urinary selenium excretion.⁹

Forceville and colleagues¹⁰ studied selenium kinetics in 134 consecutive admissions to the ICU with sepsis, SIRS or ischaemia-reperfusion injury. Mean plasma selenium levels on admission were low at 0.68 µmol/L (54 µg/L) with a difference in levels between patients with and without SIRS (0.62 µmol/L (49 µg/L) and 0.83 µmol/L (66 µg/L) respectively, $p < 0.001$). Non-survivors' plasma selenium levels fell despite modest supplementation (40 µg/day) and patients with a level below 0.7 µmol/L (55 µg/L) on admission had significantly more complications and an increased mortality.

Sakr and co-workers¹¹ also examined selenium levels in relation to sepsis and SIRS. On ICU admission, 92% of patients had plasma selenium levels below 74 µg/L – their reference

level for healthy subjects. Plasma selenium levels subsequently decreased in all patients with SIRS, especially when associated with sepsis, despite 100 µg/day of selenium. The degree of organ dysfunction appeared to be a major determinant of the decline in selenium concentration, and the levels were again inversely related to the APACHE and SOFA scores. A minimum plasma selenium level of 36 µg/L predicted ICU mortality with a high sensitivity and specificity.

These landmark studies on selenium kinetics in the critically ill demonstrated that the magnitude of the plasma selenium level negatively correlates with the degree of oxidative stress and may be predictive of outcome. Patients with severe sepsis and SIRS have the greatest reduction in selenium levels, which correlates with the higher mortality rates associated with these conditions. Since low plasma levels do not necessarily equate with deficiency, selenium levels have been measured in conjunction with selenoprotein activity; reduced selenium levels are associated with reduced glutathione peroxidase activity and therefore impairment of the enzyme systems for which selenium is required is demonstrated.¹²⁻¹⁴ This suggests there is a deficiency of selenium in critically ill patients, especially in conditions of high oxidative stress.

What happens during renal replacement therapy?

Story and colleagues¹⁵ measured trace element elimination by continuous veno-venous haemofiltration, finding ultrafiltrate losses of vitamin C, copper and chromium but not selenium. However, animal studies have detected selenium in ultrafiltrate¹⁶ and some human studies have found significant trace element losses in ICU patients undergoing renal replacement therapy¹⁷ in quantities suggesting selenium losses are greater than standard supplementation.

Why might selenium supplementation be beneficial in sepsis?

The pathophysiology of sepsis involves severe oxidative stress and endothelial damage. Oxidant production is normally balanced by antioxidant systems (enzyme scavengers and non-enzymatic dietary antioxidants) – termed redox balance. When the antioxidant system is unbalanced by either overproduction of reactive oxygen species and free radicals or the underproduction of antioxidants and destruction of scavengers, the situation is defined as oxidative stress. Inflammatory conditions such as sepsis promote periods of oxidative stress which leads to the development of complications of sepsis such as the acute respiratory distress syndrome (ARDS) and multi-organ failure. The level of oxidative stress is associated with the severity of critical illness.¹⁸

Glutathione peroxidases (GPx)

Selenium limits oxidative stress predominantly through the actions of glutathione peroxidase, probably the most important antioxidant enzyme system preventing injury to cells, including the endothelium. GPx are part of the scavenger system responsible for the cleavage of free radicals and are selenium-dependent, with their activity regulated by the availability of selenium. In critical illness, selenium

requirements are initially increased as it is redistributed to the endothelium and organs for metabolic use (eg GPx synthesis) giving rise to low blood selenium levels – despite which plasma GPx activity is normal. GPx activity then decreases as mismatching of supply and demand of selenium occurs.

Glutathione (GSH)

GSH functions as an antioxidant, both as a component of the GPx enzyme system and independently.¹⁹ It contains glutamine, cysteine and glycine. Supplementation with n-acetylcysteine and glutamine are strategies that have been employed to enhance this aspect of the antioxidant defence system in critically ill patients.

Other selenoproteins

There are approximately 25 known selenoproteins whose antioxidant/immune functions result from regulation of intracellular pathways, eg NF-κB transcription activation, arachidonic acid cascade, and mitochondrial functions.

How can supplementation be achieved?

Selenium is inexpensive, safe and can be supplemented orally or intravenously as sodium selenite, eg Selenase®.²⁰ There are no clear recommendations regarding routine supplementation of selenium in TPN (compared with other trace elements such as zinc, iron, copper, chromium, manganese, and iodine). It should be administered as a continuous infusion since bolus dosing leads to rapid urinary excretion.

Is there any evidence that selenium supplementation in ICU patients is beneficial?

A number of small studies on selenium supplementation from Europe (as sodium selenite) and Japan (as ebselen, an oral synthetic seleno-organic compound which mimics GPx) have been published following the demonstration of reduced plasma selenium levels on admission to ICU.

In sepsis

There have been five studies to date looking at selenium supplementation in critically ill patients with severe sepsis, septic shock and SIRS, investigating a total of 431 patients. In 1997, Zimmermann and colleagues²¹ published the first study of selenium administration in patients with SIRS and multi-organ failure (APACHE II >15). They administered a bolus of 1,000 µg parenteral sodium selenite followed by an infusion of 1,000 µg/day to 20 patients for 28 days and compared the results with 20 controls. They demonstrated a non-significant mortality benefit from selenium supplementation (supplemented group 3/20 patients versus control group 8/20 patients).

At the same time, Angstwurm *et al*¹² studied 42 critically ill patients (APACHE II >15) with SIRS secondary to sepsis, and supplemented one group with a reducing regimen of parenteral sodium selenite (535 µg/day for three days, 285 µg/day for three days and 155 µg/day for three days); the control group received 35 µg/day. Plasma selenium and GPx levels were normalised within three days by the supplementation regimen compared with the controls whose levels remained low.

A non-significant mortality benefit of selenium supplementation was seen (supplemented group 33% versus control group 52%, $p=0.135$). There was a significant reduction in APACHE III score and requirement for haemofiltration. *Post hoc* subgroup analysis of 20 patients with an APACHE III score >53 (the median score) suggested there might be a mortality benefit in those most deficient.

In 2007, Mishra and co-workers¹³ published a randomised controlled trial of 40 critically ill patients with severe sepsis (APACHE II >15). Eighteen patients received a reducing course of parenteral selenium for nine days using a regimen similar to Angstwurm's study; the control group received 32 $\mu\text{g}/\text{day}$. Plasma selenium levels and GPx activity were again reduced on admission but increased significantly by day three in the high-dose supplementation group. The SOFA score decreased significantly in the selenium-supplemented group, but there was no difference in renal replacement therapy requirements and no mortality benefit seen (control group 50% versus supplemented group 44%, $p=0.94$).

Forceville's group²² published a randomised controlled study of 60 patients, on the effects of selenium supplementation in septic shock (SAPS score >25). The selenium group was given a 4,000 μg loading dose of parenteral sodium selenite in an attempt to use the pro-oxidant properties of seleno-compounds to inhibit NF- κB binding to DNA and prevent the subsequent initiation of the inflammatory cascade, followed by 1,000 $\mu\text{g}/\text{day}$ as an intravenous infusion for nine days. There was no significant difference in the primary endpoint of time to vasopressor withdrawal, nor was there a significant difference in survival (45% versus 45%, $p=0.59$ at 28 days).

The largest selenium supplementation trial to date is the Selenium in Intensive Care (SIC) study.¹⁴ This was a multi-centre, randomised controlled trial involving 249 patients with severe SIRS, sepsis and septic shock (APACHE III >70). The regimen involved a 1,000 μg selenium bolus followed by 1,000 $\mu\text{g}/\text{day}$ for two weeks. Patients were either enterally or parenterally fed, and glutamine and other trace elements were not specifically given but were not disallowed or documented. A trend towards the primary end-point of mortality benefit in the selenium supplementation group was again seen, supplemented group 40% (46/116) versus control group 50% (61/122), but was not significant despite flaws in the intention-to-treat analysis. The predefined sub-group analysis of the patients with APACHE III scores >102 (the highest quartile) gave rise to a significant difference in mortality ($p=0.04$) but were for a small proportion of the study population (supplemented group 15/27 versus controls 22/27); this concurred with the analysis of those patients with more than three organ failures.

In burns

Patients with greater than 20% body surface area burns incur significant trace element losses, with selenium lost in quantities of up to 600 $\mu\text{g}/\text{day}$.²³ Oxidative stress is also high, resulting in decreased antioxidant capacity, depressed immunity, and a propensity for developing infection. Infection remains the leading cause of death after major burns, but the mortality remains relatively low. Berger and colleagues have

published a number of studies on trace element substitution in burned patients including some of the first selenium supplementation studies.²⁴⁻²⁶ In these studies, supplemental selenium normalised plasma selenium levels resulting in fewer infections compared with the control groups whose levels remained low.

In trauma

Porter *et al*²⁷ in 1999 studied 18 adult trauma victims with principally gunshot wounds, supplementing the treatment group with selenium, vitamin C, vitamin E and n-acetylcysteine. The treated group had fewer infections compared with the placebo group and a significantly decreased ICU and hospital length of stay. In 2001, Berger and colleagues studied the impact of antioxidant supplementation on blood antioxidant status²⁸ and thyroid hormone metabolism²⁹ in 32 adult trauma patients. The patients were divided into three groups:

- a selenium-supplemented group
- an antioxidant-supplemented group (selenium, copper, zinc and vitamin E)
- a placebo group, who received no supplemental selenium.

There were no significant differences in the clinical end-points measured. Plasma selenium levels and plasma GPx activity were increased by 500 $\mu\text{g}/\text{day}$ selenium and the thyroid hormones demonstrated only modest change.

In pancreatitis

Selenium has been routinely supplemented in several European centres for some time for patients with either acute or chronic pancreatitis as it was thought to offer a mortality advantage.³⁰⁻³² However, this assumption has recently been challenged. Lindner *et al*³³ in Germany studied 70 patients with acute pancreatitis and demonstrated no benefit from selenium supplementation. Siriwardena and colleagues³⁴ in the UK performed a randomised, double-blind, placebo-controlled trial of intravenous antioxidant supplementation in severe acute pancreatitis and found no statistical difference in the primary end-point of the presence of organ dysfunction at seven days.

Meta-analyses

Avenell and co-workers³⁵ performed a review of selenium supplementation for critically ill adults for the Cochrane Collaboration, updated in 2008 to include ten randomised trials of either selenium or ebselen supplementation. The study group included 1,172 patients from predominantly the Japanese, ebselen in neuro-intensive care studies; the meta-analysis population also included patients with burns, trauma, and post-major surgery. The data were analysed for mortality benefit and infection risk. The authors concluded that there was limited evidence to recommend selenium or ebselen supplementation in critically ill adults and commented on the poor quality of trials, the heterogeneous nature of the groups, and the small populations studied.

Heyland *et al*³⁶ included eight studies in the 2007 update of the meta-analysis of selenium supplementation in critical care from the Canadian Critical Care Nutrition Group. The study population consisted of 424 patients with pancreatitis, sepsis, SIRS, burns, major surgery and trauma. They concluded that

Author and year	Critical illness	No. of patients	Daily Se/ebsele	Mortality		Included in meta-analysis*
				Se+	Se-	
Kuklinski 1991 ³¹	Pancreatitis	17	Se 500 g 8 days	0/8	8/9	Avenell Heyland (+/-)
Zimmerman 1997 ²¹	SIRS	40	Se 1000 g bolus + 1000 g 28 days	3/20	8/20	Avenell Heyland
Berger 1998 ²⁴	Burns	20	Se 159 g 8 days	1/10	0/10	Heyland
Angstwurm 1999 ¹²	Sepsis/SIRS	42	Se 535 g for 3 days then reducing	7/21	11/21	Avenell Heyland
Porter 1999 ²⁷	Trauma	18	Se 200 g ? days	0/9	0/9	Heyland
Berger 2001 ^{28, 29**}	Trauma	32	Se 500 g 5 days	2/20	1/12	Heyland
Berger 2001 ^{28**}	Trauma	21	Se 500 g 5 days	2/9	1/11	Avenell
Berger 2004 ^{***26}	Burns	21	Se 380 g 14-21 days	1/11	1/10	Heyland
Lindner 2004 ³³	Pancreatitis	70	Se 2000 g bolus + 1000 g 7 days	5/35	3/35	Avenell
Mishra 2007 ¹³	Sepsis/SIRS	40	Se 474 g for 3 days then reducing	11/18	15/22	Avenell
Forceville 2007 ²²	Septic shock	60	Se 4000 g on first day, then 1000 g/day 9 days	14/31	13/29	No
Angstwurm 2007 ¹⁴	Sepsis/SIRS	249	Se 1000 g bolus then 1000 g/day 14 days	46/116	61/122	Avenell Heyland

* Avenell³⁵ analysed studies on selenium or ebselen alone, Heyland³⁶ analysed studies on selenium either alone or as one of a number of antioxidants.

** Berger published this study in two parts, Avenell comments upon *Nutrition Research* paper, "selenium only" patients. Heyland comments upon "selenium only" and "selenium plus copper, zinc and tocopherol" groups combined using data from both papers (*Nutrition Research* and *Intensive Care Medicine*).

*** updated figures from study (not meta-analysis). Se = selenium.

Table 1 Studies of selenium in the critically ill. Characteristics of included studies.

there was a beneficial mortality effect from supplementing selenium in the critically ill (risk ratio 0.69, 95% confidence interval 0.59-0.82) (**Table 1**).

Ongoing clinical trials

Two randomised controlled trials are currently ongoing: SIGNET³⁷ (Scottish Intensive Care Glutamine or seleNium Evaluative Trial) will examine the effects of 500 µg/day selenium and/or glutamine parenterally in 500 ICU patients who are being parenterally fed. The primary outcomes are length of ICU and hospital stay, mortality and episodes of sepsis. It is due to complete in 2009. The REDOX³⁸ (Reducing Deaths due to OXidative Stress)

study will examine the effects of glutamine and/or antioxidants in 1,200 mechanically-ventilated critically ill patients with evidence of acute organ failure. The antioxidant supplement will include 500 µg selenium parenterally and 300 µg enterally (in addition to zinc, vitamins A, C and E). The primary end point is 28-day mortality, and results are expected in 2010.

Single versus multiple antioxidants

The studies mentioned above differ in the approaches they take to antioxidant supplementation; some examine the effects of selenium alone, others examine combinations of antioxidants. Study of a single nutrient allows any consequence to be

attributed to that nutrient, but micronutrients function as a network, and providing a single component in order to generate clinically important outcomes may create an imbalance. Thus, the rationale for those studies combining antioxidants is that synergistic functions demand a multi-modal approach.

What is the optimal dose of selenium for supplementation on the ICU?

Sodium selenite has pro-oxidant effects and, in humans, symptoms of toxicity occur with whole blood selenium levels above 1,000 µg/L. Acute selenium intoxication is similar to arsenic poisoning and may lead to shock, ARDS and death. Chronic toxicity occurs with supplementation of 3-7 mg per day over weeks.^{20,39} The safe upper limit for short term supplementation is 1,000 µg/day²⁰ and for long-term supplementation is 400-550 µg/day.

The Forceville study attempted to use the pro-oxidant effects of sodium selenite to clinical advantage by using a large initial dose.²² They reported no improved clinical endpoints and no obvious acute toxicity but an increase in multi-organ failure in the supplemented group. Selenium excess is linked to oxidative stress⁴⁰ and the proposed beneficial pro-oxidant effect may not occur *in vivo*.⁴¹

Most studies have aimed only to normalise plasma selenium levels and optimise plasma GPx function, relying on the antioxidant properties of selenium due to its incorporation into selenoenzymes, with doses ranging from 300-1,000 µg/day enterally or parenterally for 9-28 days. In order to establish the optimal dose of antioxidants for the REDOXs trial Heyland's group performed a dosing study, finding a dose of 800 µg/day selenium to be optimal.⁴² There is no evidence to suggest that up to 1,000 µg/day of parenteral sodium selenite is detrimental to health.

Conclusions

Selenium is an important trace mineral, particularly essential for its antioxidant function in critically ill patients. There is good evidence that critically ill patients are selenium deficient, but patients with conditions of high oxidative stress, eg sepsis/SIRS, are especially at risk. Critically ill patients are also at risk of deficiency due to increased biological fluid losses, through conditions such as burns, trauma and pancreatitis and from interventions such as renal replacement therapy.

Supplementation is inexpensive and easy to achieve, with short periods of moderate doses quickly normalising plasma selenium levels and plasma glutathione peroxidase activity. NICE recommends measuring selenium levels on admission to the ICU;⁴³ this would allow meaningful supplementation to take place and is potentially prognostic. Selenium is only one of a number of micronutrients for which mechanisms to ensure adequate replacement are not in place, especially in patients fed through TPN. Purely achieving the UK RDA of selenium is likely to be insufficient for ICU patients, in whom the literature suggests it should be supplemented parenterally so absorption can be assured. A dose of 500 µg/day seems to be safe and effective at restoring plasma enzyme activity.

Original studies on selenium supplementation in the critical

care environment are from heterogeneous groups of patients and include selenium supplemented in various dosing regimes. On integrating the available data, the meta-analyses demonstrate a potential mortality benefit from supplementing selenium in general ICU patients.^{35,36} However, in order to answer the question of whether selenium supplementation in sepsis leads to an improvement in clinically relevant end points, an adequately powered, randomised, placebo-controlled trial of high methodological value is required.

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