

## What is the Optimal Dose of Selenium and Other Antioxidants in Critically Ill Patients?

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### Dear Editor,

Sepsis is an uncontrolled systemic host response to invasive infection that leads to multiple organ failure and is characterized by unacceptably high mortality and morbidity due to organ failure. Despite advances in medical science and care, unfortunately, sepsis has remained the principle cause of death in critically ill patients. It is caused by excessive secretion of proinflammatory mediators such as tumor necrosis factor alpha (TNF- $\alpha$ ) as well as reactive oxygen species (ROS) and low endogenous antioxidative capacity (1).

Sepsis is associated with the generation of oxygen free radicals and decrease in plasma selenium concentration. Forceville et al. (2) investigated 134 consecutive admitted patients to intensive care unit (ICU) and showed that plasma selenium levels were decreased by up to 40%, especially in those with septic shock. Furthermore, selenium concentrations of less than 0.7  $\mu\text{mol/L}$  (0.1  $\mu\text{mol/L}$ ) were associated with a fourfold increase in mortality and threefold increase in new organ failure and ventilator-associated pneumonia. Selenium is an essential trace mineral that plays an important role in host defense (3, 4). Selenium has two modes of action that may be dose dependent: antioxidant action via incorporation into selenoenzymes, and pro-oxidant action through the direct effects of seleno-compounds (5). As an antioxidant, selenium may limit free radical damage to host cells. As a pro-oxidant, it may provide a transient anti-inflammatory effect by inducing apoptosis of reactive inflammatory cells and potentially damage invading microorganisms. Although the optimum safe dose and method of administration remains controversial, the greatest efficacy in critically ill patients with systemic inflammatory response syndrome (SIRS) has been reported from very high selenium doses, administered by bolus and

followed by continuous infusion. A loading dose given as a bolus in early phase of septic shock and SIRS could have the following effects: a) direct reversible inhibition of NF- $\kappa$ B binding to DNA through a rupture of the disulfide bridging bond controlling gene expression and thus, down regulating the synthesis of proinflammatory cytokines (at selenium concentrations > 5  $\mu\text{mol/L}$ ) (6, 7); b) induction of apoptosis and cytotoxicity in activated proinflammatory circulating cells at the microcirculation level; and c) a direct virucidal and bactericidal effect (8). In patients with septic shock, the combined effect of intravenous bolus followed by continuous infusion is thought to stimulate the synthesis of selenoprotein P, which protects against endothelial dysfunction and leads to decreased organ failure (9).

Current evidence suggest that in critically ill patients, low selenium levels are associated with higher risk of death, multiple organ failure, and higher markers of oxidative stress (10). On the other hand in a prospective cohort study enrolling critically ill patient, those with SIRS and sever sepsis were found to have 40% lower selenium levels than patient without SIRS did. Increasing levels of selenium are correlated with increased glutathione peroxidase, a key endogenous antioxidant defense mechanism (11).

The recommended daily dietary requirement for healthy adult patients ranges from 60 to 100 mcg/day (12). However, the ideal dose, duration, and route of selenium supplementation in patients in ICU have not been established yet. In the last two decades, several clinical trials have evaluated the role of seleno-compounds (especially sodium selenite) as part of an antioxidant strategy for critically ill patients with SIRS and multiple organ dysfunction syndrome. Nonetheless, sometimes the results

have been contradictory and inconclusive and the optimal dose, the best mode of administration, and duration of this intervention for patients in ICU are still unknown.

The toxicity of selenium is clearly dose dependent and varies depending on the type of selenium compound, and route of administration (13). The toxicity involves a pro-oxidant effect from replacement of sulfur with a selenium atom in key molecules, leading to neurotoxicity, anemia, liver dysfunction, and pancreatic changes (9). In a clinical trial, a continuous infusion of high doses of sodium selenite, 4 mg of selenium during the first day and 1 mg/day for the following nine days, led to no obvious toxicity (5). In our study, we gave 2000 µg of selenium as bolus dose during an hour, followed by 24-hour infusion of 1500 µg in 50 mL of normal saline for 14 days, and we did not observe any obvious toxicity. Daily doses of sodium selenite providing between 1000 to 1600 µg or even more for 10 to 14 days after an initial intravenous bolus appear to be safe without any adverse effects (9). Further studies should aim to confirm the benefit of high dose intravenous selenite, alone or in combination, on antioxidant capacity and mortality of the critically ill patients. Due to many changes in hemodynamics such as severe reduction of glutathione reserves in patients with sepsis, high amounts of selenium can be given to treat this disorder. In our study, blood samples were collected in order to obtain more information about the effect of selenium in the human body, and further information will be published in the near future.

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## Authors' Contributions

Study concept and design, acquisition of data, analysis and interpretation of data: Reza Mosaed, Mohammad Hosein Ghadimi; Drafting of the manuscript and administrative, technical, and material support: Reza Mosaed;

Critical revision of the manuscript for important intellectual content: Mojtaba Mojtahedzadeh, Arezoo Ahmadi; and Study supervision: Mojtaba Mojtahedzade.

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## References

1. Victor VM, Rocha M, Esplugues JV, De la Fuente M. Role of free radicals in sepsis: antioxidant therapy. *Curr Pharm Des.* 2005;**11**(24):3141-58.
2. Forceville X, Vitoux D, Gauzit R, Combes A, Lahilaire P, Chappuis P. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. *Crit Care Med.* 1998;**26**(9):1536-44.
3. Sakr Y, Reinhart K, Bloos F, Marx G, Russwurm S, Bauer M, et al. Time course and relationship between plasma selenium concentrations, systemic inflammatory response, sepsis, and multiorgan failure. *Br J Anaesth.* 2007;**98**(6):775-84.
4. Avenell A, Noble DW, Barr J, Engelhardt T. Selenium supplementation for critically ill adults. *Cochrane Database Syst Rev.* 2004(4):CD003703.
5. Forceville X, Laviolle B, Annane D, Vitoux D, Bleichner G, Korach JM, et al. Effects of high doses of selenium, as sodium selenite, in septic shock: a placebo-controlled, randomized, double-blind, phase II study. *Crit Care.* 2007;**11**(4):R73.
6. Jeong DW, Yoo MH, Kim TS, Kim JH, Kim IY. Protection of mice from allergen-induced asthma by selenite: prevention of eosinophil infiltration by inhibition of NF-kappa B activation. *J Biol Chem.* 2002;**277**(20):17871-6.
7. Stewart MS, Spallholz JE, Neldner KH, Pence BC. Selenium compounds have disparate abilities to impose oxidative stress and induce apoptosis. *Free Radic Biol Med.* 1999;**26**(1-2):42-8.
8. Vincent JL, Forceville X. Critically elucidating the role of selenium. *Curr Opin Anaesthesiol.* 2008;**21**(2):148-54.
9. Hardy G, Hardy I, Manzanares W. Selenium supplementation in the critically ill. *Nutr Clin Pract.* 2012;**27**(1):21-33.
10. Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. *Intensive Care Med.* 2005;**31**(3):327-37.
11. Berger MM, Baines M, Chioléro RL, Wardle CA, Cayeux C, Shenkin A. Influence of early trace element and vitamin E supplements on antioxidant status after major trauma: a controlled trial. *Nut Res.* 2001;**21**(1-2):41-54.
12. Rayman MP. The importance of selenium to human health. *Lancet.* 2000;**356**(9225):233-41.
13. Spallholz JE. On the nature of selenium toxicity and carcinostatic activity. *Free Radic Biol Med.* 1994;**17**(1):45-64.