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The Anti-inflammatory and Antioxidative Effects of Selenium Supplementation on Critical Post-surgical Pediatric Patients

Fatemeh Roudi[1,2], Mohsen Zakerian[3], Golnaz Ranjbar[1*]

1. Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
2. Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Department of Persian Medicine, School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

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ABSTRACT

Oxidative stress after major surgeries is associated with poor clinical outcomes, such as delayed wound healing and increased length of stay in the pediatric intensive care unit. Due to the growth and development phase in childhood, changes in the levels of oxidative stress and inflammation are of paramount importance in pediatric patients. Acute metabolic stress is correlated with the rate of oxidative stress and is believed to increase after major surgeries in pediatric patients. Therefore, it has been suggested that the presence of selenium in various selenoenzymes and selenoproteins may be largely involved in the antioxidative defense system in surgical inflammation through the regulation of glycolysis, gluconeogenesis, insulin transport pathways, gene expression of inflammatory mediators, and other functions of lymphocytes B and T, natural killer, and lymphokine activated killer cells. In acute metabolic stress, selenium requirement following major surgeries is considered essential in pediatric patients, and selenium supplementation in these patients may be helpful and cost-effective in the long run. Further clinical studies are required to clarify the potential beneficial effects of selenium supplementation, as well as its dose safety and efficacy rate.

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Introduction

Major surgeries may cause acute damages that could stimulate the immune system, thereby increasing the inflammatory mediators and reactive oxygen species (ROS) mainly at the surgical site (1, 2). Surgery-induced metabolic and hormonal alterations, inflammation, and oxidative stress may lead to the intensive care unit (ICU) admission of the children undergoing major surgeries (1). Given the importance of the growth and development phase in childhood, the interventions that might reduce the rates of inflammation and oxidative stress in pediatric patients could effectively decrease the length of ICU stay and mortality rate (3).

Selenium is an essential micronutrient, which modulates the antioxidative defense system of the body. Several studies have reported the beneficial effects of selenium on inflammation (4-6).

This review study aimed to determine the possible beneficial effects of selenium supplementation on the reduction of inflammation and oxidative stress in critical post-surgical pediatric patients.

Systemic Inflammatory Response to Post-surgical Oxidative Stress

Major surgeries are considered to be controlled traumas, which induce acute-phase response and lead to local and systemic inflammatory responses (14). Inflammation is known as a protective process, which is induced due to cell and tissue damage against acute stress (14). Although it is believed that the presence of ROS is essential to the activation of the signaling pathways of the antioxidant defense mechanisms, multiple complications are expected in case of their excessive production; such examples are increased lipid peroxidation, delayed wound healing, and damage to the DNA and protein content of the cells. Furthermore, this process could deteriorate the clinical condition of patients postoperatively (11, 15). Postoperative oxidative stress and inflammatory responses may lead to insulin resistance, cell

* *Corresponding author:* Golnaz Ranjbar, Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: 00985138002411. Email: Ranjbarg1@mums.ac.ir.

necrosis and apoptosis, immunosuppression, organ failure, and increased length of ICU and hospital stay (16). Figure 1 depicts the pathophysiology of oxidative stress and inflammation after surgical traumas.

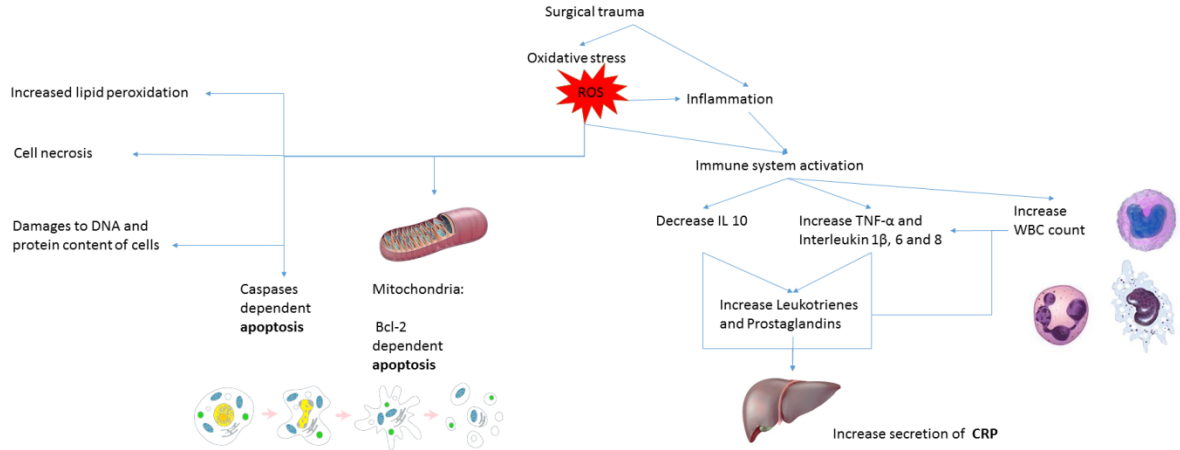


Figure 1. Pathophysiology of Oxidative Stress and Inflammatory Responses after Surgical Trauma

According to the literature, the metabolic responses to surgeries occur through insulin resistance and secretion of catabolic hormones (e.g., glucagon, catecholamines, and corticosteroids). Therefore, these factors may affect the metabolism through reducing cellular glucose uptake and increasing the breakdown of triglycerides to free fatty acids (17). However, the most significant influential factors in the mentioned processes are systemic and local inflammatory cytokines and oxygen free radicals. Additionally, amino acids are effective in the production of acute-phase proteins and wound healing (17). As such, regulation of balance between the inflammatory and oxidative stress status in critical post-surgical pediatric patients may improve their clinical outcomes at the pediatric intensive care unit (PICU).

Properties of Selenium

Selenium is an essential micronutrient, which induces the endogenous antioxidative defense system and is expressed as selenoproteins and selenoenzymes, especially glutathione peroxidase and selenoprotein S (5, 6). The recommended daily intake of selenium varies depending on age in preterm infants, infants, and children; in these age groups, the recommended values have been determine to be 2-3 and 1-3 µg/kg of the body weight (up to 100 µg/day) (7, 8). Selenium is involved in both the thioredoxin and glutathione antioxidative systems (9). Moreover, selenium plays a key role in the regulation of the glycolysis pathways, protection of the body against lipid peroxidation, DNA synthesis, metabolism of thyroid hormones, and activity of natural killer cells and lymphocytes B and T (6, 10). This micronutrient is metabolized by the liver to selenoproteins and selenium metabolites (mainly trimethyselenonium), which are excreted into the urine and slightly through feces (9).

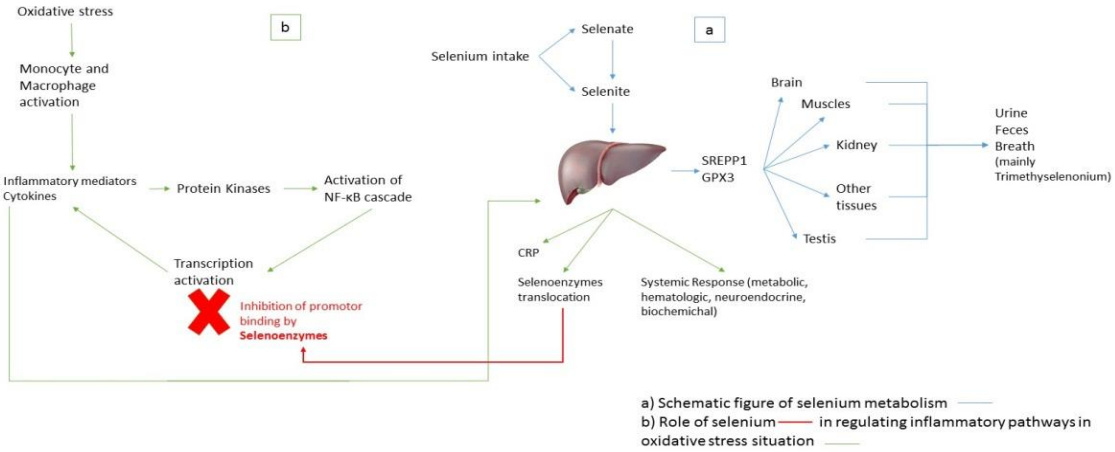
The most informative biomarkers used for the estimation of the selenium status in the body include extracellular glutathione peroxidase (10-25% of the plasma selenium) and selenoprotein P1 (40-60% of the plasma selenium) (9). The plasma concentrations of selenium and selenium-containing proteins are mainly amount-dependent, while factors such as age, smoking habits, malnutrition, obesity, race, and inflammation may also affect the plasma levels of selenium biomarkers (9). These selenoproteins show their plateau expression in conditions with adequate selenium intake (9).

Approximately 90% of the general pediatric population have adequate serum concentrations of selenium. On the other hand, this rate decreases to almost 10% in critically ill children (1, 11, 12). According to a recent study by Safaralizadeh et al., the serum selenium reference range in Iranian children has been estimated at 63-106 µg/l (13).

Selenium and Inflammation

According to the literature, selenium supplementation in the diseases with inflammatory pathophysiology (e.g., rheumatoid

arthritis, asthma, and inflammatory bowel disease) may reduce the levels of inflammatory interleukins, NF-kB and TNF-α (6). Additionally, selenium supplementation may lead to oxidative stress reduction and regulation of glycolysis, gluconeogenesis, and insulin transport pathways (11, 16). Selenium may also play a pivotal role in the improvement of the immune function and inflammation reduction through the regulation of the eicosanoids synthesis pathways and increasing the synthesis of prostaglandins and thromboxanes (6, 18). In addition, selenium supplementation could lower the expression of cytokine genes and adhesive molecules, while increasing the expression of the interleukin-2 receptor. Therefore, the activity of lymphocytes B and T, natural killer cells, and lymphokine-activated killer cells is expected to increase in the body (6). Figure 2 shows selenium metabolism and its role in the regulation of inflammatory pathways in association with oxidative stress.



leukotrienes and prostacyclins as opposed to

Figure 2. Selenium Metabolism and Its Role in Regulation of Inflammatory Pathways

Role of Selenium in Post-surgical Inflammation and Oxidative Stress Levels

According to the previous studies conducted on adult populations, most critically ill surgical patients have low plasma/serum selenium levels (19). In addition, previous interventional studies have indicated that selenium supplementation (especially at high doses) may improve the oxidative stress and inflammation status in critically ill adults (19). Evidence suggests that the redistribution of selenium, endothelial injury, altered metabolic process, and insufficient intake of selenium are the main contributing factors for the low selenium concentrations in critically ill patients, particularly in pediatric cases (1, 11, 20). On the other hand, plasma/serum selenium levels have been reported to be directly correlated with organ failure and severity of oxidative stress, while low levels of serum selenium are associated with the increased duration of mechanical ventilation dependency, ICU length of stay, and 28-day mortality (11).

Previous pediatric observational studies have proposed inconsistent results regarding serum/plasma selenium levels in acute-phase stress response. According to the studies conducted by Browman and Leite, 90.7% and 90.9% of critically ill children had low serum selenium levels during ICU admission (1, 11). Moreover, a recent clinical trial investigating the levels of oxidative stress biomarkers after cardiac surgery demonstrated increased plasma selenium concentrations after surgical trauma, and the elevation was attributed to glutathione peroxidase activity in critical conditions. However, the results of analysis of variance indicated no significant increase in the mentioned variable (21).

According to the literature, acute metabolic stress after major surgeries is highly prevalent, and additional selenium intake is required as the dose administration of physiological selenium may be insufficient (19, 22). According to the Australian guidelines of enteral and parenteral nutrition, short-term increase in selenium requirement after surgeries may be

due to the need for metabolic and antioxidative maintenance, and such patients may substantially benefit from high-dose selenium supplementation (22).

To the best of our knowledge, no clinical trials have investigated the possible benefits of high-dose selenium supplementation for critically ill children postoperatively. Therefore, it is recommended that further clinical trials (especially randomized clinical trials) be performed in this regard on critically ill post-surgical pediatric patients admitted to the PICU.

Conclusion

It is believed that oxidative stress and inflammation after major surgeries are prominent causes of poor clinical outcomes. Few studies have demonstrated the benefits of high-dose selenium supplementation through the reduction of oxidative stress and inflammation levels in critically ill post-surgical children. Therefore, further clinical trials are required in order to confirm the safety and efficacy of selenium doses in critically ill pediatric patients admitted at the PICU.

Authors' Contributions

All the authors equally contributed to conducting this review study.

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Conflicts of interest

None declared.

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