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Increased plasma selenium is associated with better outcomes in children with systemic inflammation

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ABSTRACT

Objective: The aim of this study was to assess the effects of changes in plasma selenium on the outcome of critically ill children.
Methods: Plasma selenium was prospectively measured in 99 children with acute systemic inflammation. The exposure variables were selenium level on admission and on day 5 of stay in the intensive care unit (ICU) and the difference in selenium concentrations between day 5 post-admission and the ICU admission (delta selenium). Selenium was given only as part of enteral diets. Age, malnutrition, red cell glutathione peroxidase-1 activity, serum C-reactive protein, Pediatric Index of Mortality 2, and Pediatric Logistic Organ Dysfunction scores were analyzed as covariates. The outcome variables were ventilator-free days, ICU-free days, and 28-d mortality.
Results: Plasma selenium concentrations increased from admission (median 23.4 μg/L, interquartile range 12.0–30.8) to day 5 (median 25.1 μg/L, interquartile range 16.0–39.0; $P = 0.018$). After adjustment for confounding factors, a delta selenium increase of 10 μg/L was associated with reductions in ventilator days (1.3 d; 95% confidence interval [CI], 0.2–2.3; $P = 0.017$) and ICU days (1.4 d; 95% CI, 0.5–2.3; $P < 0.01$). Delta selenium >0 was associated with decreased 28-d mortality on a univariate model (odds ratio, 0.67; 95% CI, 0.46–0.97; $P = 0.036$). The mean daily selenium intake (6.82 μg; range 0–48.66 μg) was correlated with the increase in selenium concentrations on day 5.
Conclusions: An increase in plasma selenium is independently associated with shorter times of ventilation and ICU stay in children with systemic inflammation. These findings raise the hypothesis that selenium supplementation could be beneficial in children with critical illnesses.

Introduction

Aerobic metabolism continuously produces free radicals or reactive oxygen species (superoxide and nitric oxide) and nitrogen (nitrogen peroxide), which are pro-oxidants and have the potential to harm the biological systems. Under normal conditions, these reactive species are removed by endogenous antioxidants as they are produced. The generation of reactive species becomes harmful when it exceeds the body's ability to eliminate them, thus characterizing oxidative stress [1]. In severe disease, in addition to aerobic metabolism, oxidative stress is a consequence to systemic inflammation and ischemia reperfusion [2].

Oxidative stress causes immunosuppression, necrosis, and apoptosis of cells, as well as other complications such as insulin resistance and organ dysfunction [1–3]. It has been related to carcinogenesis, progression of cardiovascular disease, aging-related neurologic disorders [1], retinopathy of prematurity, and bronchopulmonary dysplasia in premature infants [4].

Antioxidant defenses consist of molecules that prevent the uncontrolled production of reactive oxygen species or inhibit

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their reaction with biological components through enzymatic and nonenzymatic reactions. Selenium, an essential micronutrient in human health [5], is an integral part of endogenous antioxidant defense systems constituted by selenoenzymes glutathione peroxidases (GPx), thioredoxin reductase and selenoprotein P, which protect tissues from damage caused by oxidative stress [6]. Selenium deficiency has been associated with complications and unfavorable outcomes in various acute and chronic diseases. In intensive care, the growing interest in studying the effect of selenium supplementation in critically ill adults stems from the evidence of the association between its deficiency and poor clinical outcome [7,8] and also from the beneficial role of selenium in immune and antioxidant systems. The reduction in circulating and tissue concentrations of antioxidant enzymes observed in these patients has been associated with disease severity, progression of organ dysfunction and mortality [7–9], which have favored its supplementation in certain specific situations [9–11].

Despite the large amount of data from studies on adults, the link between plasma selenium and outcomes has not been well investigated in critically ill children. Low plasma selenium concentrations also have been reported in children admitted to intensive care units (ICUs); however, to date, it is unclear to what extent they are associated with disease severity and clinical outcomes [12–14]. This study was designed to assess the effects of changes in plasma selenium on the outcome in critically ill children. Our hypothesis is that an increase in selenium concentrations during the systemic inflammatory response is associated with an improved outcome for these patients.

Methods

This prospective observational study was conducted in a teaching hospital pediatric ICU with eight beds, between July 2009 and May 2011. This study was part of a larger project that investigated the role of malnutrition and inflammation on plasma selenium concentrations in critically ill children [15]. Ninety-nine patients who were admitted between July 2009 and May 2011 with systemic inflammatory responses, and stayed for ≥5 d in the ICU were eligible for inclusion in the study. Neonates, children with chronic liver or kidney diseases, patients who were expected to be admitted for <24 h, those with encephalic death, and readmissions to ICU did not participate in the study. Protocol and written informed consent was obtained from the parents of each child. The study was approved by the university's Research Ethics Committee and written informed consent was obtained from the parents of each patient.

Variables

The outcome variables were ventilator-free days, the ICU length of stay, and mortality within 28 d of admission. Ventilator-free days were defined as the number of days living and breathing without assistance from admission to day 28. Patients who did not survive to day 28 were assigned zero ventilator-free days [16]. ICU-free days were defined as days not needing ICU care in the first 28 d after admission.

The exposure variables were defined in two ways: First, as plasma selenium concentration on admission and on day 5 post-admission and second, as the difference between plasma selenium concentrations between day 5 post-admission and admission to the ICU (delta selenium). The following factors were considered as covariates that could potentially affect the outcomes: age, sex, malnutrition, severe sepsis or septic shock, C-reactive protein (CRP), red cell GPx-1 activity, serum albumin and lactate, and clinical severity as measured by Revised Pediatric Index of Mortality (PIM 2) [17] and Pediatric logistic organ dysfunction (PELOD) [18]. Systemic inflammatory response syndrome, severe sepsis, and septic shock were defined according to pediatric consensus terminology [19]. Blood samples for plasma selenium, CRP, albumin, and serum lactate analysis were obtained at baseline and on day 5, with 48 h of tolerance for collection. Plasma selenium concentration was determined using graphite furnace atomic absorption spectrophotometry with Zeeman background correction. The reference range recommended by the laboratory (46–143 μg/L) was adopted [20] as there are no reference values for plasma selenium in normal Brazilian children. These values correspond approximately to the overall mean values reported for healthy children [21]. CRP concentrations were performed by turbidimetry and serum albumin and lactate were analyzed by colorimetric method, with reference values for lactate <2 mMol/L.

Nutritional assessment

For nutritional status classification, the anthropometric indicators weight for age (W/A), height for age (H/A), and body mass index (BMI) were compared with the World Health Organization 2006 growth standards [22]. For children <2 y, we used the W/A or H/A, whereas the BMI was used for children >2 y. old. Patients with an anthropometric index *z* score <−2 were considered malnourished. Calculations were performed using the Anthroplus software (version 1.0.2; World Health Organization, Geneva, Switzerland).

Nutrition therapy was performed according to the ICU protocol [23] and was initiated after nutrition assessment in the setting of hemodynamic stability. Patients were considered hemodynamically stable if they were not hypotensive and did not require significant hemodynamic support including high-dose catecholamine agents, alone or in combination with a large volume of fluid or blood product resuscitation to maintain cellular perfusion [24]. Feeding was preferably done by the enteral route. Selenium was given only as part of the enteral diets and the dietitian calculated daily intake. Selenium contents of cow's milk formula and enteral formula used in the ICU were 13 to 24 and 30 to 48 μg/L, respectively. An exception occurred with children ages 6 to 12 mo who were fed with infant formula not fortified with selenium.

Statistical analysis

Categorical data were summarized using frequencies and percentages, and normally distributed or non-normal quantitative data were summarized using means and SDs or median and interquartile range (IQR) depending on the type of variables distribution. Selenium concentrations and delta selenium, PIM 2 and PELOD scores, red cell GPx-1 activity, CRP, lactate and albumin serum concentrations, and age were analyzed as continuous, quantitative variables. Laboratory parameters on admission and on day 5 of ICU stay were compared using a paired *t* test and the Wilcoxon test.

The effect of the explanatory variables on both ventilator-free and ICU-free days was analyzed by multivariable linear regression. Univariate and multivariable analyses were performed in all approaches and variables with a $P < 0.20$ in the univariate analysis were selected for the multivariable model. The effect of delta selenium on mortality was explored with a univariate logistic regression model and all tests were bicaudal assuming a cutoff of 5% ($\alpha < 0.05$) to reject the null hypothesis. Intercooled Stata 12.1 (StataCorp LP, College Station, TX, USA) software was used for statistical calculations.

Results

The main characteristics of the patients are shown in Table 1. Plasma selenium individual values below the lower limit of the reference interval (46 μg/L) were found in 90.9% and 82.8% of patients on admission and day 5, respectively. Median values increased from admission (23.4 μg/L; IQR 12–30.8) to day 5 (25.1 μg/L; IQR 16–39; $P = 0.018$). Box plots for plasma selenium on admission and day 5 are shown in Figure 1.

The median delta selenium was 4 μg/L (IQR −4 to 15 μg/L). Comparative analysis between the other laboratory parameters on admission and on day 5 of ICU stay were as follows: CRP 49.3 mg/L (IQR 18.8–112.9) and 29.4 (IQR 7.0–73.5), $P < 0.001$; lactate 1.0 mMol/L (IQR 0.8–1.5) and 1.0 mMol/L (IQR 0.7–1.4), $P = 0.21$; serum albumin 3.0 g/dL ± 0.61 and 3.29 g/L ± 0.53 ($P < 0.001$); and red cell GPx-1 activity 12.39 ± 2.33 and 12.66 ± 1.8 ($P = 0.09$), respectively.

Variables that were associated with ventilator-free and with ICU-free days in the univariate analysis with $P < 0.20$ were included in a multivariable linear regression model, as shown in Tables 2 and 3, respectively. After adjustment for confounding factors, the increase of 10 μg/L in selenium concentration (delta selenium) was associated with an increase of 1.3 d in ventilator-free days and of 1.4 d in ICU-free days. Plasma selenium on admission was not associated with the outcomes. Plasma selenium on day 5 was associated with ventilator-free days (β coefficient = 0.10; 95%, confidence interval [CI],