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The effect of Na-selenite treatment on the oxidative stress–antioxidants balance of multiple organ failure☆,☆☆

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ABSTRACT

Purpose: Our study tested the hypothesis that sodium (Na)-selenite expression treatment can reduce oxidative stress and increase plasma antioxidants, whereas modulating white blood cell antigen expression in severe sepsis. Selenite is a well known cofactor of glutathione peroxidases and other antioxidant enzymes; therefore, one may expect an antioxidant effect of treatment.
Materials: We randomized 40 severe septic patients into treatment and control groups. Treatment group (n = 21) received 1000-μg/2 hours Na-selenite load, followed by a 1000-μg/die medication. Oxidative stress markers, including malondialdehyde, maximal free radical production, and plasma antioxidants: free sulfhydryl groups, glutathione levels, and superoxide dismutase and catalase enzyme activity were measured.
Results: According to our results, the treatment regime successfully restored serum selenium levels. Treatment group developed a significant malondialdehyde increase by the fifth study day, whereas reactive oxygen species production decreased significantly. Reduced glutathione and plasma sulfhydryl groups showed no significant difference. Treatment group showed deteriorated expression of CD11a and slight increase of CD49d expression on monocytes throughout our study.
Conclusions: Although our Na-selenite treatment regime successfully restored the selenium deficiency of severe septic patients, antioxidant and white blood cell antigen expression modulating effect of the therapy was not observed in our patient group.

1. Introduction

Severe sepsis and septic shock became one of the leading causes of death in intensive care units (ICUs) worldwide, with the incidence of 50 to 95 cases per 100 000 and leading to more than 100 000 death each year [1], therefore a target of intense research [2]. During the development of sepsis, the recognition of not self-motifs is followed by cytokine release and cellular activation of the innate immune system [3]. Proinflammatory cytokines released will contribute to the development of oxidative stress by the increase of prooxidant effects (free radical production and inappropriate antioxidant effects) and further modulation of innate immune system [3]. Oxidative stress will result in lipid peroxidation, DNA damage and mitochondrial impairment on cellular level, and will develop the clinical picture of organ dysfunction [4]. Immunosupplementation including L-glutamine, L-arginine, or Na-selenite treatment is of high interest in severe sepsis, whereas the benefit of Na selenite for septic patients is still controversial [5,6]. Selenite is a trace mineral mostly found in cereals, fish, and edible nuts and in meats and poultry. Although normal human plasma levels are highly dependent on the method of measure severe sepsis is known to be accompanied by selenium (Se) deficiency [7]. As an important cofactor for glutathione peroxidases, mainly GPx6 selenoproteins are using the selenocystein amino acid as proton transporter for redox reactions [8]. The benefit of high-dose Se supplementation was formerly questionable as the prooxidant effect of hyperselenemia is well known. Manzanares et al [9] investigated the effect of high-dose treatment in critically ill patients and proved no negative effect.

We aimed our study to assess the effect of Na-selenite treatment according to the Selenium in Intensive Care study protocol on certain prooxidants and antioxidant markers in severe sepsis [5] and to follow the surface antigen properties of leukocytes during Na-selenite treatment.

2. Materials and methods

Severe septic patients from our multidisciplinary university ICU (Department of Anaesthesiology and Intensive Therapy, University of

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Table 1
Basic demographic and clinical characteristics of our patient groups. Data are expressed as median ± 25 to 75 interquartile

	Treatment group	Control group	
No. of patients	21	19	
Sex ratio (male/female)	11/10	12/7	ns
Age	62 (54-76)	66 (57-78)	ns
Survivial (S/NS)	12/9	8/11	ns
Clinical data (inclusion)			
SOFA score	8 (6-12)	9 (6-11)	ns
MODS	7 (2-10)	7 (3-9)	ns
Procalcitonin (ng/mL)	26.65 (9.41-62.43)	18.76 (3.22-26.73)	ns
C-reactive protein (mg/L)	265.42 (211.10-351.61)	200.00 (147.19-307.39)	ns
SAPS II (24 h)	50 (20-86)	56 (24-97)	ns
Gram-negative infections	8	3	
Gram-positive infenctions	3	2	
Fungal infections	1	0	
Serum Se levels (mmol/L)	37.65 (36.3-46.87)	36.00 (32.93-44.60)	ns

ns indicates not significant difference; S, survivior; NS, nonsurvivor; SAPS II, Simplified Acute Physiology Score II.

Pécs, Pécs, Hungary) with developed multiple organ failure—based on currently accepted Sequential Organ Failure Assessment (SOFA) score more than 2 for each organ—and procalcitonin levels equals or above 2 ng/mL were enrolled. Systemic inflammation response syndrome, sepsis, severe sepsis, and septic shock were defined according to the current American College of Chest Physicians/Society of Critical Care Medicine criteria and the 2008 Surviving Sepsis Guidelines.

Our study protocol was accepted by the Regional Research Ethical Committee of the University of Pécs (2010/3614) and was carried out according to the ethical guidelines of the 2003 Declaration of Helsinki. A written informed consent has been acquired after detailed information regarding the study design and blood sampling from every patient included in the study. In case of consciousness disorder, the consent was provided by the next of kin according to national law. Patients with any type of known hematologic malignancy, cytostatic treatment in the last 30 days, high-dose prolonged steroid medication, disseminated intravascular coagulation score at least 5, and moribund state were excluded. We defined our end points as the withdrawal of consent or death during the research period. In case of death, patient data collected until the last experimental measurement was assessed. The diagnostic and treatment procedures of sepsis were conducted by strictly following the recent sepsis guidelines in both study and nonstudy patients. Laboratory parameters including C-reactive protein, procalcitonin, lactate levels, blood cell count, electrolyte levels, blood gas parameters, and organ function specific parameters were registered. To follow up the clinical status of severe septic patients, Multiple Organ Dysfunction Score (MODS) and SOFA scores were calculated for every day during the whole study period, and Simplified Acute Physiology Score II was calculated after 24 hours of admission.

Patients were randomized into treatment and control groups based on the envelope method. Treatment group received a 1000-μg/30 minutes loading dose of Na selenite and 1000-μg/die treatment for a maximum of 14 days. In case of hypernatremia (>150 mmol/L), we aimed for dose reduction (half amount), followed by immediate termination if serum Na levels remained elevated.

2.1. Blood sampling

Additional blood samples for oxidative stress, surface antigen flow cytometry, and serum selenite measurements were drawn on admission (day 1) and on the third, fifth, and seventh days with a 21-gauge cannula into a closed system blood sampling tubes. Samples were processed within maximum of 2 hours after collection. Cytometry measurements were carried out following sample processing, oxidative stress, and antioxidant measurements were carried out in one batch. Serum Se levels were measured in all time points in treatment group, whereas control group samples were assessed on day 1 and 5. Samples were stored on −70°C until further measurement.

2.2. Oxidative stress measurements

The measurements of oxidative stress and leukocyte activation markers were analyzed at the Department of Surgical Research and Techniques, University of Pécs using the methods as described earlier [10]. Malondialdehyde, a marker of lipid peroxidation, was determined with Ohkawa method. Free radical (reactive oxygen species [ROS]) generating capacity in whole blood was measured with a Whole Blood Lumi-aggregometer (Model 560; Chrono-log Corporation, Havertown, PA). This chemiluminescense method is based upon the reaction of luminol with free radicals. Phorbol-12-myristate-13-acetate was used to induce free radical production, and the resulting light output was recorded on a chart recorder (Model 707; Chrono-Log). The peak value of free radical production was calculated from the recorded curve, and the results were related to the white blood cell (WBC) counts. The slope of steep elevation in radical production was also determined. Plasma myeloperoxidase level,

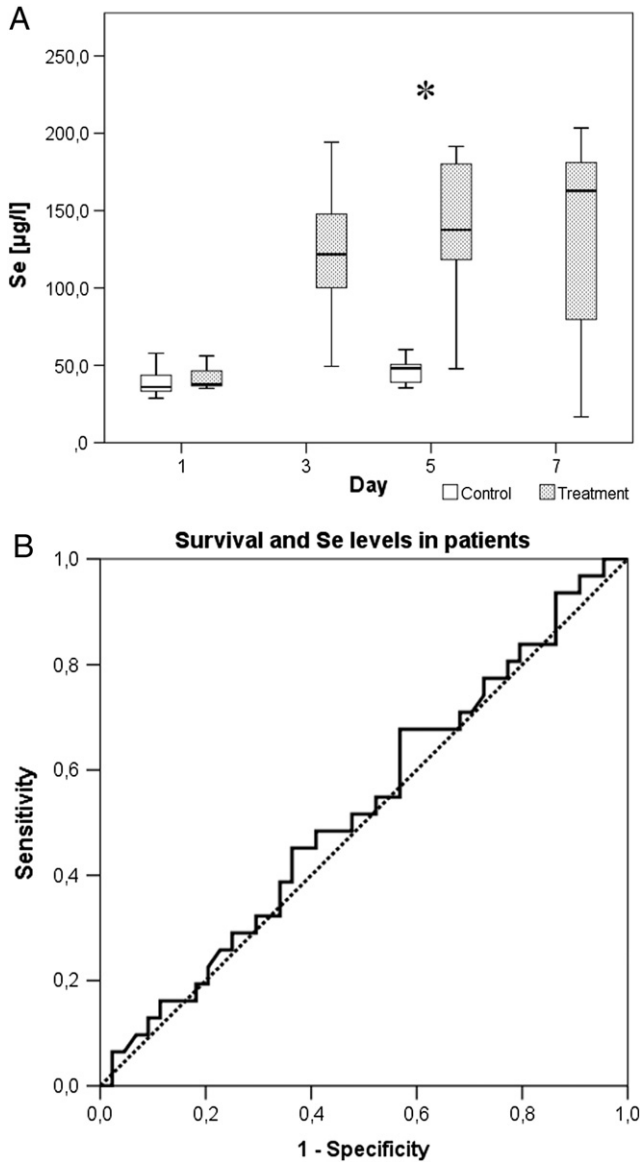

Fig. 1. A, Serum Se levels of severe septic patients (shaded boxes) and controls (white boxes). *$P < .05$. B, Receiver operating characteristic curve analysis of serum Se levels and patient 7-day survival in treatment of septic patients.