Nutrition 29 (2013) 158–165

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Selenium blood concentrations in patients undergoing elective cardiac surgery and receiving perioperative sodium selenite

Christian Stoppe M.D. [a,b,*], Jan Spillner M.D. [c], Rolf Rossaint M.D. [a], Mark Coburn M.D. [a], Gereon Schälte M.D. [a], Anika Wildenhues M.D. [a], Gernot Marx M.D. [d], Steffen Rex M.D. [a,e]

[a] Department of Anesthesiology, University Hospital, RWTH Aachen, Germany
[b] Institute of Biochemistry and Molecular Cell Biology, University Hospital of the RWTH Aachen, Germany
[c] Department of Thoracic, Cardiac, and Vascular Surgery, University Hospital, RWTH Aachen, Germany
[d] Department of Intensive Care, University Hospital, RWTH Aachen, Germany
[e] Department of Anesthesiology, University Hospitals Gasthuisberg, KU Leuven, Belgium

ARTICLE INFO

Article history:
Received 2 March 2012
Accepted 24 May 2012

Keywords:
Cardiopulmonary bypass
Systemic inflammatory response syndrome
Inflammation
Multiple organ failure
Selenium
Antioxidants
Glutathione peroxidase

ABSTRACT

Objectives: We recently reported that cardiac surgical patients in our institution exhibited low selenium blood levels preoperatively, which were further aggravated during surgery and independently associated with the development of postoperative multiorgan failure. Low circulating selenium levels result in a decreased antioxidant capacity. Both can be treated effectively by sodium-selenite administration. Little is known about the kinetics of exogenously administered sodium-selenite during acute perioperative oxidative stress. The aim of this study was to assess the effects of perioperative high-dose sodium-selenite administration on selenium blood concentrations in cardiac surgical patients.

Methods: One hundred four cardiac surgical patients were enrolled in this prospective observational trial. Patients received an intravenous bolus of 2000 μg selenium after an induction of anesthesia and 1000 μg selenium every day further during their intensive care unit (ICU) stay. Selenium blood levels were measured at regular intervals.

Results: Preoperative sodium-selenite administration increased selenium blood concentrations to normal values on ICU admission, but failed to prevent a significant decrease of circulating selenium on the first postoperative day. During the further ICU stay, selenium blood levels were normalized by the administration strategy and did not exceed the German reference range. No acute selenium-specific side effects occurred. When matching the participating patients to a historical control group without sodium-selenite administration, the chosen strategy was associated with a decrease in SAPS II (23 ± 7 versus 29 ± 8, $P = 0.005$) and SOFA scores (4 ± 3 versus 7 ± 2, $P = 0.007$) on the first postoperative day, but was unable to improve the postoperative outcome in patients staying >1 d in ICU.

Conclusions: Despite preemptive high-dose sodium-selenite administration, cardiac surgical patients experienced a significant decrease in circulating selenium levels on the first postoperative day.

Introduction

Cardiac surgery with the use of extracorporeal circulation and cardioplegic arrest elicits a systemic inflammatory response [1,2] and provokes ischemia-reperfusion–related oxidative stress with the release of cytotoxic reactive oxygen and nitrogen species. Oxidative stress results in cellular injury, activates inflammatory pathways [3], and is increasingly being recognized as a major factor contributing to the development of organ failure in critically ill patients [4].

Several endogenous defense mechanisms specifically protect tissues from oxidative stress. In a variety of antioxidant (AOX) enzymes such as glutathione peroxidase (GPx), the trace element selenium is incorporated in the form of selenocysteine and therefore is involved in multiple steps of intracellular antioxidant

Christian Stoppe and Jan Spillner contributed equally to the article.

Presented in part on the ESICM 23nd Annual Congress, Barcelona, Spain, 9-13 October 2010.

The Department of Anesthesiology (University Hospital, RWTH Aachen, Germany) received a research grant from Biosyn Company.

* Corresponding author. Tel.: +49-241-8088179; fax: +49-241-8082406.
E-mail address: christian.stoppe@gmail.com (C. Stoppe).

0899-9007/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nut.2012.05.013

defense mechanisms [5–7]. A depression and redistribution of selenium and hence an insufficient endogenous AOX capacity have been repeatedly observed in critically ill patients with a systemic inflammatory response and/or multiorgan dysfunction and shown to be associated with the development of inflammatory and infectious complications, severity of illness, a progression of organ failure, and ultimately mortality [4,8–10]. These observations have driven various clinical trials in which the efficacy of selenium supplementation was analyzed in critically ill patients with manifest systemic inflammation [11–17]. However, these studies yielded controversial results, mainly due to different supplementation protocols, varying doses and preparations of selenium, and the inclusion of heterogeneous patient populations.

We have previously observed that the majority of cardiac surgical patients exhibit whole blood levels of selenium below the German reference range already before surgery that was further aggravated intraoperatively [18]. Moreover, in our patient population, the observed intraoperative lowering of circulating selenium levels was associated with the later development of postoperative multiorgan dysfunction. Recently, it has been demonstrated that selenium deficiency before the onset of oxidative stress is associated with a worsening of oxidative damage when compared to a normal preinjury selenium status [19]. Hence, an adequate preoperative micronutrient status should theoretically be of paramount importance to curtail perioperative oxidative stress [20,21]. Therefore, a preemptive selenium administration prior to oxidative injury seems reasonable. However, little is known about the kinetics of exogenously administered selenium in situations of acute perioperative oxidative stress in cardiac surgical patients.

The aim of the present observational study was therefore to describe blood selenium concentrations in cardiac surgical patients with preoperative low selenium levels who are treated with *pre*operative and daily continued high-dose sodium-selenite administration. Moreover, we assessed postoperative organ dysfunction in sodium-selenite–substituted patients by means of established scores and compared the values with those obtained from a historical control group.

Materials and methods

Patients

After approval by the institutional review board committee, information from the responsible authorities (Federal Institute for Drugs and Medical Devices), and obtainment of written informed consent, 104 patients undergoing elective cardiac surgery with the use of cardiopulmonary bypass (CPB) and cardioplegic arrest were enrolled in this trial. The study is registered at ClinicalTrials.gov (no. 01394068).

In Germany, the use of sodium-selenite is licensed as a medicine for all patients with selenium deficiency as assessed by low selenium blood levels. In a previous study at our institution we recently observed that the majority of cardiac surgical patients exhibit whole blood levels of selenium below the German reference range (100–140 μg/L) already *before* surgery. This hyposelenemia was further aggravated in *all* patients by the surgical procedure involving CPB, irrespective of whether systemic inflammation occurred or not. [18]. Therefore, all patients scheduled for elective cardiac surgery with the use of CPB at our institution were consecutively included in this open-label trial. Exclusion criteria were emergency operations, pregnancy, age less than 18 y, and failure to obtain informed consent. In four patients, the surgical technique was switched intraoperatively and performed without CPB. In these patients, sodium-selenite substitution was not continued and they were excluded from further analysis.

Study medication and administration

After induction of anesthesia (52 ± 12 min before initiation of CPB), all patients received an intravenous bolus of 2000 μg selenium within 30 min that was administered as a bolus infusion via the central venous catheter. On every further morning (8:00 AM) during the intensive care unit (ICU) stay, patients received an intravenous bolus of 1000 μg selenium in the same manner. This dosing regimen was chosen according to the prescription information and on the basis of efficacy and safety in previous supplementation trials in patients with systemic inflammation [12,15].

Selenium was administered in the form of sodium-selenite (selenase T pro injection ampoules; Biosyn Arzneimittel GmbH, Fellbach, Germany). Each ampoule (10 mL) contains 3.33 mg sodium selenite pentahydrate, corresponding to 1000 μg selenium.

Monitoring of selenium concentrations and acute deleterious effects or toxicity

Whole blood and serum samples were obtained from the arterial line and stored at room temperature (whole blood) and at −80°C (serum) before transport to the laboratory. The samples were obtained prior to induction of anesthesia (before administration of the first sodium-selenite bolus), after admission to the ICU, 4 h later, and on each morning during the ICU stay at 8:00 AM before the administration of 1000 μg selenium.

Selenium concentrations were determined with electrothermal atomic absorption spectroscopy by using a graphite furnace absorption spectrometer equipped with a Zeeman effect background correction to eliminate unspecific absorption (5100 PC; Perkin-Elmer, Paris, France) [22].

In all patients with an ICU stay >1 d ($n = 44$), serum GPx-activity was determined using a method coupling the peroxidase reaction with the reduction of oxidized glutathione [23]. One unit of GPx activity is defined as that which oxidizes 1 mol of NADPH/min in the assay system [24].

The determination of selenium and GPx activity was performed by investigators in the laboratories of Biosyn Arzneimittel GmbH and in the Institute of Clinical Chemistry, Friedrich-Schiller University Jena, Germany (GPx activity).

The reference values for selenium in Germany for the normal population are 100–140 μg/L in whole blood and 80–120 μg/L in serum as indicated in the legally approved prescription information. The normal reference value for serum GPx activity in our laboratory has been recently redetermined to be 138-233 units/L.

According to the prescription information of sodium-selenite, the following safety measures were an integral part of our observation plan: 1) In the case of a whole-blood selenium concentration exceeding 170 μg/L: information of the principal investigator by the laboratory, discontinuation of study medication only in case that control measurements would reveal a whole-blood selenium concentration exceeding 230 μg/L; 2) In the case of a whole-blood selenium concentration exceeding 230 μg/L: immediate discontinuation of study medication and control measurements of selenium levels; 3) In the case of clinical signs of selenium overdose (e.g., garlic-like smell of exhaled air, somnolence, nausea, diarrhea): immediate discontinuation of study medication, control measurements of selenium levels, and symptomatic therapy.

CPB

Included patients were operated with a conventional CPB circuit (Stockert s5; Sorin Group Germany, München, Germany). CPB was performed in moderate hypothermia (28°C–32°C). Immediately after cross-clamping, cardiac arrest was induced by the antegrade infusion of cold crystalloid cardioplegic solution (Custodiol; Köhler Chemie, Alsbach-Hähnlein, Germany). The CPB circuit was prefilled with 1500 mL crystalloid priming solution and 250 mL mannitol and 100 mL 8.4% sodium-bicarbonate.

Intensive care unit and nutritional support

After completion of the surgery, all patients were transferred to the ICU and received balanced fluid substitution without any additional supplements for the first 12–24 h. Tracheal extubation was performed when standard extubation criteria were fulfilled. Patients were discharged from the ICU after fulfillment of our standardized discharge criteria.

In patients unable to be fed orally, enteral nutrition was started according to our universal institutional procedures by increasing the standard solution (NUTRISON; Pfrimmer Nutricia GmbH, Erlangen, Germany) stepwise over 3 d using a continuous perfusion via gastric feeding tubes. The minimal infusion rate in the enteral-fed patients was 10 $mL \cdot h^{-1}$ (interquartile range: 240–720 mL per day accounting for 14.25–42.75 μg or enteral selenium intake per day). Additional micronutrient supplements containing 6.5 mg Zn, 1.3 mg Cu, 0.27 mg Mn, and 32 μg sodium selenite were given daily (Addel N; Baxter Deutschland GmbH, Unterschleißheim, Germany).

Data collection

Baseline preoperative status was assessed the evening before surgery. On postoperative day (POD) 1, the simplified acute physiology score (SAPS II) was determined [25]. Moreover, the sequential organ failure assessment (SOFA)