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Selenium supplementation in critically ill patients: A systematic review and meta-analysis

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ABSTRACT

Purpose: The oxidative stress is recognized as a constant feature in critical illness. Nevertheless, the use of antioxidant therapy remains controversial. We tried to demonstrate that intravenous selenium supplementation could promote antioxidant status and help protect against infection and organ failure, improving outcome in critically ill patients.
Materials and Methods: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing the exogenous supplementation of selenium versus standard therapy without any adjuvant in critically ill adults.
Results: Nine RCTs met inclusion criteria. Selenium supplementation was associated with a reduction in 28-day mortality of borderline statistical significance (risk ratio = 0.84, 95% confidence interval 0.71–0.99, $P = .04$). The analysis of pre-defined subgroups detected no significant effects regarding the supplementation with doses of selenium ≤500 μg/d, administration of a load dose with a bolus and duration of treatment. Only 2 studies analyzed 6-month mortality and could not show a difference. No effects could be demonstrated on hospital length of stay, pulmonary infections, or renal failure.
Conclusions: The use of high-dose selenium might be associated with a beneficial effect on 28-day mortality in critically ill patients. Nevertheless, the use of selenium as adjuvant therapy needs further evaluations.

1. Introduction

It is known that critical illness is typically characterized by oxidative stress, an alteration of the normal intracellular balance between the constant formation of oxidants, including reactive oxygen species (ROS) and reactive nitrogen species, and biological system's ability to detoxify the reactive intermediates or to repair the resulting damage [1,2]. The increase of free radicals production, the inadequate response of the defense systems involved in the detoxification of the cell by ROS, or both of these conditions, can damage biologically relevant molecules, such as DNA, RNA, proteins, and unsaturated fatty acids of the cell membranes, which may ultimately lead to cell death [3,4]. In critically ill patients, oxidative stress plays an important role in pathophysiological events leading to mitochondrial dysfunction and to systemic inflammatory response syndrome (SIRS), which may be complicated and result in acute respiratory distress syndrome and multiple organ dysfunction syndrome [5]. The antioxidant endogenous defense systems are extremely effective at counteracting ROS and the other reactive species. These antioxidants systems include both enzymatic proteins (such as superoxide dismutase, glutathione peroxidase, and catalase) and secondary antioxidants (or non-enzymatic) [6,7].

Selenium is a trace mineral and it is essential to the function of glutathione peroxidase, since it is a structural component of the active site of this selenoenzyme [6]. Evidence suggests that in critically ill patients plasma selenium is significantly below the normal range; furthermore, it has been demonstrated that depletion of this micronutrient is associated with a worse clinical outcome: low selenium levels were associated with a greater number of infectious complications and a higher incidence of mortality [8].

Since it seems evident the theoretical rationale of the use of antioxidants, such as selenium, in the critically ill patient, in the last decades, several clinical trials attempted to demonstrate if selenium supplementation can determine some effective clinical benefit. Recently, Manzanares et al has published a comprehensive meta-analysis of the use of antioxidants in critically ill patients [9]. Selenium is universally recognized as one of the most promising antioxidants [10].

The aim of this study is to systematically review the efficacy of intravenous selenium supplementation as monotherapy in critically ill patients. Furthermore, we wished to assess the robustness of the conclusions by predicting the potential impact of a new study on the statistical significance and heterogeneity of our meta-analysis, which explores the need and potential impact of further research in this field.

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2. Materials and methods

2.1. Objectives

The primary aim of this review was to investigate the effect of intravenous selenium supplementation on 28-day mortality in critically ill patients.

The secondary objective was to evaluate the effects of selenium supplementation on other outcomes, such as mortality at 6 months, length of intensive care unit stay, number of nosocomial respiratory infections, incidence of renal failure and/or need for a renal replacement therapy (RRT).

2.2. Criteria for considering studies for this review

2.2.1. Types of studies

We included all randomized (RCTs) and quasi-randomized controlled clinical trials of intravenous selenium supplementation in critically ill patients, given in addition to their routine care but not combined with other antioxidant agents (such as glutamine, zinc, copper, vitamins A, C, and E). Studies were included despite lack of double- or single-blinding, in consideration of the primary outcome evaluated, mortality, which hardly could be distorted by detection bias.

See Appendix E1 for specifications relating to the blindness of the individual studies.

2.2.2. Types of participants

We included trials on adults with critical illness (including patients with SIRS, sepsis, septic shock, but also burns, trauma, patients undergoing major elective surgery, etc). We excluded studies on neonates, patients aged under 16 years and pregnant women.

2.2.3. Types of interventions

We examined RCTs that evaluated the effects of intravenous selenium supplementation in critical illness, compared to a control group in whom this supplementation was not performed. We did not include studies in which selenium was combined with other antioxidants, unless the trace element was administered as monotherapy in a subgroup, whose results were then reported separately. All administered doses and duration of supplementation reported in the studies were included in this review, without any selection.

2.2.4. Types of outcome measures

- Primary outcomes: all-cause mortality at 28 days.

When it was not reported we (1) contacted the authors, and (2) if they didn't respond, or told us that the required data were not available, we took into account, when reported, the mortality during the length of hospitalization.

- Secondary outcomes:
  - mortality at 6 months;
  - length of stay in an intensive care unit (ICU);
  - incidence of nosocomial pneumonia;
  - incidence of renal failure and/or need to RRT.

2.2.5. Safety

We examined the frequency and severity of local and systemic adverse events in each study arm.

2.3. Search methods for identification of studies

2.3.1. Electronic searches

We conducted a systematic search in the main electronic databases (PubMed, Embase and Cochrane Database of Systematic Reviews) to identify all published studies of our interest. We used the search terms "selenium", "critical", "patient", "illness" and "mortality" in all their variants (PATIENT-PATIENTS, CRITIC*-CRITICALLY-etc., ILL*-ILLNESSES-etc., DEAD-MORTALITY-MORTAL*-etc.). Similar search strategies were performed for Clinical Queries (specifically on Clinical Study Therapy and Systematic Review). There were no language or date restrictions in the search for trials. The electronic databases were last searched on January 8, 2013.

See supplemental material for details of search strategies, available on line.

2.3.2. Searching other resources

We hand-searched the reference lists of the studies resulting for other possible trials. A very recent and comprehensive meta-analysis [11], which evaluated intravenous selenium supplementation in septic patients, included an interesting randomized study [12] that had not emerged with our electronic searches. Data of this study have been included in our analysis.

2.4. Data collection and analysis

2.4.1. Selection of studies

Two review authors independently selected the studies for inclusion. The titles and abstracts of all reports identified by the electronic searches and hand-searching were examined by the authors. We classified the abstracts as (*a*) definitely include, (*b*) unsure and (*c*) definitely exclude. We obtained and re-assessed full-text copies of those classified as (*a*) definitely include and (*b*) unsure. After having reviewed the full-text copies, we classified the studies as (1) included, (2) awaiting assessment and (3) excluded. Studies identified by both review authors as (3) excluded were excluded and documented in the review. Studies identified as (1) included were included and assessed for methodological quality. The review authors were unmasked to the report authors, institutions and trial results during this assessment. Disagreements between the 2 review authors were resolved by a third review author.

2.4.2. Data extraction and management

Two review authors independently extracted the data for the primary and secondary outcomes from the studies identified as included. We resolved discrepancies by discussion. One review author extracted data, which were checked by a second author.

2.4.3. Assessment of risk of bias in included studies

Two review authors independently assessed the included trials for bias according to the methods described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins) [13]. The following parameters were assessed: sequence generation; allocation concealment; masking (blinding) of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting. We evaluated these parameters for each outcome measure or class of outcome measure as specified in the latest version of the Cochrane Handbook [13]. As reported in the Handbook, other sources of bias were risk of bias related to the specific study design used, or trial stopped early due to some data-dependent process, or an extreme baseline imbalance in patients selected.

If the information available in the published trial reports was inadequate to assess methodological quality, we contacted the trial authors for clarification. If they did not respond within 2 months, we classified the trial based on the available information.

We classified each parameter as low risk of bias, high risk of bias or unclear.

2.4.4. Measures of treatment effect

Data analysis followed guidelines set out in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions [13].