Selenium in Intensive Care (SIC) study: Results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock*

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Objective: Sepsis is associated with an increase in reactive oxygen species and low endogenous antioxidative capacity. We postulated that high-dose supplementation of sodium-selenite would improve the outcome of patients with severe sepsis and septic shock.

Design: Prospective randomized, placebo-controlled, multiple-center trial.

Setting: Eleven intensive care units in Germany.

Patients: Patients were 249 patients with severe systemic inflammatory response syndrome, sepsis, and septic shock and an Acute Physiology and Chronic Health Evaluation (APACHE) III score >70.

Interventions: Patients received 1000 μg of sodium-selenite as a 30-min bolus injection, followed by 14 daily continuous infusions of 1000 μg intravenously, or placebo.

Measurements and Main Results: The primary end point was 28-day mortality; secondary end points were survival time and clinical course of APACHE III and logistic organ dysfunction system scores. In addition, selenium levels in serum, whole blood, and urine as well as serum glutathione-peroxidase-3 activity were measured. From 249 patients included, 11 patients had to be excluded. The intention-to-treat analysis of the remaining 238 patients revealed a mortality rate of 50.0% in the placebo group and 39.7% in the selenium-treated group (p = .109; odds ratio, 0.66; confidence interval, 0.39–1.1). A further 49 patients had to be excluded before the final analysis because of severe violations of the study protocol. In the remaining 92 patients of the study group, the 28-day mortality rate was significantly reduced to 42.4% compared with 56.7% in 97 patients of the placebo group (p = .049, odds ratio, 0.56; confidence interval, 0.32–1.00). In predefined subgroup analyses, the mortality rate was significantly reduced in patients with septic shock with disseminated intravascular coagulation (n = 82, p = .018) as well as in the most critically ill patients with an APACHE III score ≥102 (>75% quartile, n = 54, p = .040) or in patients with more than three organ dysfunctions (n = 83, p = .039). Whole blood selenium concentrations and glutathione peroxidase-3 activity were within the upper normal range during selenium treatment, whereas they remained significantly low in the placebo group. There were no side effects observed due to high-dose sodium-selenite treatment.

Conclusions: The adjunct treatment of patients with high-dose sodium-selenite reduces mortality rate in patients with severe sepsis or septic shock. (Crit Care Med 2007; 35:●●●●●●)

Key Words: selenium; antioxidants; systemic inflammatory response syndrome; sepsis; septic shock; organ failure

The mortality rate in patients with sepsis and septic shock is still between 28% and 50% (1), and efforts to reduce mortality are a great challenge in intensive care medicine (2, 3). Although intensive insulin treatment (4), substitution of activated protein C (5), and supplementation of hydrocortisone in patients with reduced adrenal reserve in septic shock (6, 7) have been shown to reduce the mortality rate in severe sepsis and septic shock, it is still unsatisfying.

Besides cytokine activation, oxidative stress and free oxygen species might con-
tribute to the development of multiple organ failure in septic shock (8). Reactive oxygen species and reactive nitrogen spe-
cies have been shown to modulate cell signaling, proliferation, apoptosis, and
cell protection (9, 10). The selenium-
dependent glutathione-peroxidases (GPx)
as well as thioredoxin reductases are im-
portant compounds responsible for the
maintenance of the redox system in all
cells including the immune-competent
cells. According to present knowledge,
the activity of these enzymes is mainly
regulated by the availability of selenium
(11–14). During severe oxidative stress
like sepsis or septic shock, the require-
ment of selenium might be increased, as
patients with systemic inflammatory ac-
tivity (SIRS), sepsis, and septic shock ex-
hibit low selenium and GPx activities.
The GPx-3 activity, which is the main
GPx activity in serum, is negatively cor-
related with the severity of the diseases
(15, 16). In preterm infants, a selenium
supplementation decreased morbidity
(17, 18).

A recently published meta-analysis of
all available small intervention studies
with selenium in critically ill patients re-
vealed a tendency toward mortality re-
duction (Z = 1.70; p = .09), with the best
results obtained with high doses of s Od-
ium-selenium (19).

We present the results of a first mul-
tiple-center, prospective, double-blind,
placebo-controlled study, the Selenium
in Intensive Care (SIC) study, where the
efficacy and safety of a high-dose sele-
num supplementation in patients with
severe SIRS, sepsis, and septic shock are
shown.

METHODS

Study Design

The study was designed as a phase III,
multiple-center, double-blind, randomized
placebo-controlled trial. All patients fulfilling
the inclusion criteria were enrolled in the
study. Eleven independent German intensive
care units (medical, surgical, and anesthetic)
participated in the trial. The study design was
approved by the local ethic committee of each
single center and conformed with ethical
guidelines (Declaration of Helsinki) and the
International Conference on Harmonization
(ICD), and all patient files were monitored by
an external institute (GRM, Gesellschaft für
Therapieforschung mbH Munich, Germany).
Data were collected by independent data man-
gers and compared with the case report form.

Patients were randomly assigned to treat-
ment (Se1) or placebo (Se0). The study group
(Se1) received 1000 µg of sodium-selenite
within 30 mins intravenously followed by 1000
µg of sodium-selenite during 24 hrs continu-
ously for 14 days; thus, the total amount of
selenium was 15 mg within 14 days. This dos-
age was chosen on the basis of efficacy in
previous pilot studies (20, 21) and later was
shown to be effective in a meta-analysis (17).
The placebo group (Se0) received sodium
chloride 0.9% in the same regimen. Additional
selenium supplementation up to 100 µg of
selenium per day, together with other trace
elements during parenteral nutrition, was
allowed in all patients.

The inclusion criteria were as follows:
Males and females ≥18 yrs with an Acute
Physiology and Chronic Health Evaluation
(APACHE) III score (22) ≥70 and at least
two of the following criteria (23):
Rectal body temperature >38°C or hypo-
thermia <36°C
Heart rate >90 beats/min
Respiratory frequency >20’ and Paco2 <32
mm Hg (<4.3 kPa)
Leukocytes >12,000/µL or <4,000/µL or
>10% immature leukocytes
Decrease of platelet count >50% within the
first 24 hrs or platelets <150,000/µL at
admission
Admission into the study after diagnosis
within 24 hrs
Beginning of treatment within 1 hr after
inclusion
Informed consent either from the patient or
the relative/close friend
The exclusion criteria were as follows:
Pregnancy
Missing informed consent of the patient or
the relative/intimate friend of the patient
Withdrawal of informed consent by patient
or next of kin after inclusion into the study
Participation in any other clinical trial cur-
rently or within the last 30 days
Prior participation in this clinical trial
Cerebral injury due to hypoxia after cardio-
pulmonary resuscitation
Primary concomitant disease with an ex-
pected high mortality within 2 months
Do-not-resuscitate code
Malignant primary disease as the cause of
SIRS or sepsis, for example, agranulocytosis
as a result of chemotherapy or idiopathic
bone marrow aplasia
Hemorrhagic-necrotizing pancreatitis with-
out infectious complications

Treatment Assignments

Patients were randomly assigned in a one-
to-one ratio to receive vials containing 48 mL
of study medication intravenously. The study
medication had to be started within 1 hr after
inclusion, with a bolus injection of one vial
during 30 mins, followed by a continuous in-
fusion (2 mL/hr) for 14 days. Patients oth-
wise were treated according to the best prac-
tice, including parenteral or enteral nutrition
together with vitamins and trace elements as
necessary. No further specific directives for
medical treatment, mechanical ventilation, or
dialysis procedures were provided to the study
centers.

Predefined severe protocol violations were
as follows: study drug administration delay of
>6 hrs after inclusion, interruption of study
drug administration for >6 hrs, missing bolus
administration, number of vial administra-
tions lower than defined, or administration of
selenium containing solutions >100 µg/day.

End Points and Safety Criteria

The primary end point was 28-day mortal-
ity. Secondary end points were as follows:
1. Time of survival after enrolment
2. Variable part of the APACHE III score
   (22), percentage of change between day 1
   and last visit
3. Logistic organ dysfunction system score
   (24) at all visits or last available visit
4. Incidence of renal failure within the 28-
day survey
5. Days of dialysis or chronic veno-venous
   hemofiltration dialysis
6. Incidence of cardiovascular failure defined
   as the demand for vasoactive drugs des-
   pite volume substitution
7. Number of days with vasopressor therapy
to maintain adequate tissue perfusion
8. Days of mechanical ventilation
9. Incidence of nosocomial pneumonia
10. Incidence of acute respiratory distress
    syndrome
11. Incidence of reinflection
12. Duration of stay (days) in the intensive
care unit for all patients
13. Analyses of subgroups (age, gender, sever-
    ity of illness, number of organ failure,
    intensive insulin treatment, source of in-
    fection, surgical vs. internal) (Table 1)

The tertiary end points were the determi-
nation of selenium levels in whole blood, se-
rum, and 24-hr urine excretion and GPx-3
activity on days 1, 3, 7, 14, 21, and 28.

The safety criteria included all adverse
events like changes in vital parameters, acid-
base balance, liver and kidney function tests,
and hematologic variables, especially changes
in whole blood and serum selenium concen-
trations on days 1, 3, 7, 14, 21, and 28 as well
as selenium excretion in the urine until day 21. The safety collective included all randomized patients (n = 246).

**Evaluation of Patients and Laboratory Tests**

Patients were followed for 28 days after inclusion. Baseline characteristics including demographic information, preexisting health conditions, organ function, markers of disease severity, infection, and laboratory tests were assessed within 24 hrs before study drug administration and on days 3, 7, 14, 21, and 28.

Probes of EDTA blood, serum, and samples of a 24-hr urinary collection were obtained at baseline and on days 3, 7, 14, 21, and 28 for the blinded determination of sodium-selenite (25) as well as GPx-3 activities (26) in a central independent reference laboratory (Institute of Clinical Chemistry, Friedrich-Schiller University Jena, Germany). The reference values for selenium for the normal population are serum selenium 0.72–1.33 μmol/L, in whole blood 0.96–1.78 μmol/L, and in 24-hr urine samples 0.02–0.79 μmol/L. The normal reference GPx-3 activity is 96–150 units/L.

Microbial samples were analyzed in the local institutes of bacteriology at the day of inclusion and throughout day 28, if new infections were suspected. All other routine laboratory tests also were determined in local laboratories.

Sepsis was defined according to the established sepsis criteria (23). Septic shock was defined as hypotension, not sufficiently responding to volume replacement, requirement for vasopressors, and decrease in platelet counts >50% within the first 24 hrs.

**Statistical Analysis**

Randomization was done using the program BiAS for Windows (version 7.0) and the SAS procedure PROC PLAN. Before we broke the code, the monitoring of all files and case report forms, data management, and the complete statistical analysis were done by an independent external institute (GKV, Gesellschaft für Therapieforschung mbH Munich, Germany). The data management was performed using ACCESS 2000 and the statistical analysis was performed using SAS (version 9.1).

The null hypothesis (H0) and alternative hypothesis (H1) are as follows: H0, p1 = p0; and H1, p1 < p0, where p1 stands for the 28-day mortality rate under sodium-selenite and p0 for the 28-day mortality rate under placebo. The chi-square test was used, which is equivalent to the two-tailed Z-test (normal approximation). According to the one-tailed testing situation, a chi-square test at a significance level of α = .05 was used. This is equivalent to the one-tailed Z-test with α = .025.

The sample size was calculated at the base of 80% power to detect a 20% reduction in 28-day mortality rate in the study population according to the results of the pilot studies (20, 21). For the statistical analysis of the primary efficacy criterion, a one-tailed significance test at a significance level of α = .025 was performed. The trial was designed to enroll 196 eligible patients.

A planned interim analysis was carried out after 120 patients had been enrolled according to the method of O’Brian-Fleming with a significance level of α1 = .0027; the final statistical analysis was conducted with α2 = .0246. Thus, a global significance level of α = .025 was guaranteed. The one-tailed significance level α2 = .0246 corresponds to a significance level of α2 = .0492 for the chi-square test. The test statistical analysis of all secondary efficacy criteria and the tertiary efficacy criterion was conducted using two-tailed significance tests with α = .05.

For efficacy criteria, the length of stay in the intensive care unit as well as the incidence rate and number of days of acute renal failure, acute circulatory failure, development of pneumonia, and development of acute respiratory distress syndrome was assessed.

Comparisons of treatment groups with regard to incidence rates were done via statistical testing and by calculating the odds ratio (OR).

The statistical analysis of safety and tolerability criteria was performed descriptively.

**RESULTS**

**Study Population**

Between December 1999 and October 2004, 249 patients were randomized and enrolled in the study (Fig. 1). Before final analysis, three patients and the relatives of two patients withdrew consent after...
Severity of illness (2.0%), one patient committed suicide, two patients were lost for follow-up, in one patient treatment was terminated by the physicians because of a do-not-resuscitation decision, one patient was identified to suffer from acute leukemia, and one patient was incompitant. Thus, 11 patients were excluded, leaving 238 patients randomized to selenium (n = 116) or placebo (n = 122) for the intention-to-treat analysis (Table 2).

From these, 49 patients had to be excluded before breaking the code because of not fulfilling the inclusion criteria (n = 14) or severe violation of the study protocol (n = 35): study medication delayed or interrupted for >6 hrs (n = 13), no bolus administration (n = 6), number of vial administration lower than defined (n = 11), and administration of additional sodium-selenite >100 µg/day (n = 5). Therefore, the final per-protocol population consisted of 189 patients, 92 in the study group (Se1) and 97 in the placebo group (Se0).

**Characterization of Patients**

The characterization of patients is shown in Table 2 for all randomized patients and in Table 3 for the patients treated per protocol. Age distribution, body mass index, and severity of illness assessed by APACHE III score or organ dysfunction defined by logistic organ dysfunction system score were comparable between the groups. The SIRS criteria were fulfilled in 97.9% of patients treated per protocol.

Due to the lower number, women were not equally distributed between Se1 (18 of 92; 19.6%) and Se0 (33 of 97; 34%; p = .025, chi-square-test). In addition, the mean age of women (69 ± 14.2 yrs) was higher than in men (62 ± 13.3 yrs): in Se1 33.3% and in Se0 21.2% of women were older than 80 yrs, compared with 5.4% and 9.4% of men.

The mean body mass index (BMI) was similar in both groups, but in the Se1 group 10.3% of patients had a low (<20 kg/m²) BMI and 7.5% a high BMI (>40 kg/m²) compared with Se0 (5.1% low BMI, 1.5% high BMI).

The mean whole blood selenium concentrations (0.74 ± 0.22 µmol/L in Se1, 0.74 ± 0.16 µmol/L in Se0) as well as serum selenium concentrations (0.48 ± 0.23 µmol/L in Se1, 0.46 ± 0.16 µmol/L in Se0) were similarly low in both groups at admission. Also, the mean C-reactive protein and procalcitonin levels were similar in both groups.

Intensive insulin treatment was received by 54 patients (25 of Se1 and 29 of Se0), documented by blood glucose levels <120 mg/dl in more than ten determinations per day. Hydrocortisone (200 mg/day) was substituted in 56 Se1 and 67 Se0 patients. No patient was treated with activated protein C.

**Efficacy**

28-Day Mortality. The interim analysis after inclusion of 120 patients revealed a reduction in mortality rate from 48.4% in the placebo group (n = 62) to 37.9% in the treatment group (n = 58; p = .25; OR, 0.65, 95% confidence interval [CI], 0.31–1.35).

In the intention-to-treat analysis (n = 238), 46 of 116 patients in the Se1 group and 61 of 122 Se0 patients died (p = .109; OR, 0.66; 95% CI, 0.39–1.10). The estimated mean survival time was 20.3 days in group Se1 and 17.6 days in group Se0 (p = .098).

In the per-protocol analysis (n = 189), 39 of 92 (42.4%) patients in the Se1 group compared with 55 of 97 (56.7%) in the Se0 group died within 28 days.
Biochemical markers

Table 3. Characterisation of the per-protocol population at study entry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Se1</th>
<th>Se0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs, n (mean ± SD)</td>
<td>92 (64.1 ± 13.1)</td>
<td>97 (65.9 ± 14.0)</td>
<td>189 (65.0 ± 13.5)</td>
</tr>
<tr>
<td>&lt;50, n (%)</td>
<td>16 (17.4)</td>
<td>12 (12.4)</td>
<td>28 (14.8)</td>
</tr>
<tr>
<td>50–65, n (%)</td>
<td>26 (28.3)</td>
<td>27 (27.8)</td>
<td>53 (28.0)</td>
</tr>
<tr>
<td>65–80, n (%)</td>
<td>40 (43.5)</td>
<td>45 (46.4)</td>
<td>85 (45.0)</td>
</tr>
<tr>
<td>&gt;80, n (%)</td>
<td>10 (10.9)</td>
<td>13 (13.4)</td>
<td>23 (12.2)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>74 (80.4)</td>
<td>64 (66.0)</td>
<td>138 (73.0)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>18 (19.6)</td>
<td>33 (34.0)</td>
<td>51 (27.0)</td>
</tr>
<tr>
<td>Males &gt;80 yrs, n (%)</td>
<td>4 (5.4)</td>
<td>6 (9.4)</td>
<td>10 (7.2)</td>
</tr>
<tr>
<td>Females &gt;80 yrs, n (%)</td>
<td>6 (33.3)</td>
<td>7 (21.2)</td>
<td>13 (25.5)</td>
</tr>
<tr>
<td>Body mass index, kg/m², n (mean ± SD)</td>
<td>84 (27.5 ± 7.1)</td>
<td>94 (26.7 ± 5.2)</td>
<td>178 (27.1 ± 6.2)</td>
</tr>
</tbody>
</table>

Severity of illness

Number of organs failing, n (%)                   1–2    | 11 (12.0) | 20 (20.6) | 31 (16.4) |
|                                                  | 3       | 41 (44.6) | 34 (35.1) | 75 (39.7) |
|                                                  | 4       | 26 (28.3) | 30 (30.9) | 56 (29.6) |
|                                                  | 5–6     | 14 (15.2) | 13 (13.4) | 27 (14.3) |

Biochemical markers

Procalcitonin (normal <0.5 μg/L), n (mean ± SD)       61 (35.0 ± 106.1) | 67 (34.9 ± 76.5) | 128 |
| CRP (normal <5 mg/L), n (mean ± SD)                 91 (200.3 ± 119.1) | 97 (193.9 ± 124.9) | 188 |
| Serum selenium (0.72–1.33 μM/L), n (median)         91 (0.48) | 97 (0.45) | 188 |

Pathogen, n

Gram positive                                    26 | 19 | 45 |
Gram negative                                    12 | 12 | 24 |

Se1, treatment group; Se2, placebo group; SIRS, systemic inflammatory response syndrome; APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein.

Figure 2. Survival time. Survival curves in patients of the intention-to-treat analysis were generated by the Kaplan-Meier curve. Difference between groups was calculated by the log rank test. The estimated mean survival time was 20.3 days in treated patients (solid line) compared with 17.6 days in the placebo group (dotted line) (p = .098). Se1, treatment group; Se0, placebo group.

Thus, the absolute reduction in mortality was 14.3%; the number of patients needed to treat was seven. The differences in mortality rate between both groups was already significantly lower at day 21 in the treatment group (Se1) compared with placebo (p = .045; OR, 0.55; 95% CI, 0.31–0.99) (Table 1). The estimated mean survival time was 19.7 days in Se1 patients compared with 16.4 days in the Se0 group (p = .0476) (Fig. 2). The proportion of deaths during the first 2 days after inclusion was similar in the two treatment groups. After exclusion of these deaths (16 of 92 in Se1 and 15 of 97 in Se0), the absolute mortality reduction with adjuvant selenium treatment was 17.6% (p = .024; OR, 0.48; 95% CI, 0.25–0.91).

Predefined Subgroup Analyses

Those patients with an APACHE III score >102 (75% quartile of all patients, n = 27 in each group) revealed a significantly lower mortality rate (p = .040; OR, 0.28; 95% CI, 0.08–0.97) in the Se1 group (Table 4). Those patients with more than three organ failures also had a significantly improved survival rate of 22.6% (23 of 40 in Se1 group and 15 of 43 in Se0 group; p = .039; OR, 0.40; 95% CI, 0.16–0.96). Patients with the sepsis criteria, a continuous decrease in platelet counts below 50,000/μL (indicating disseminated intravascular coagulation), and septic shock had a survival rate of 59.5% (22 of 37) in the Se1 group, compared with 33.3% (15 of 45) in the Se0 group (p = .018; OR, 0.34; 95% CI, 0.14–0.84). Patients receiving intensified insulin treatment with tight glucose control (n = 54) had a significantly lower mortality rate (−28.4%) in the Se1 group compared with placebo (−8.2%; p = .034; OR, 0.30; 95% CI, 0.10–0.93). There were no significant differences in the survival rate of patients identified with pneumonia or peritonitis alone, without other systemic signs of septic shock, or surgical or internal medicine patients.

Whole Blood Selenium and Mortality

Mortality rate was inversely correlated with the whole blood selenium concentrations in both groups. In Se1 patients, the mortality rate was 50.0%, if whole blood selenium was constantly within the...
Table 4. 28-day mortality rate in predefined subgroups of per protocol analysis

<table>
<thead>
<tr>
<th>Age distribution</th>
<th>Se1 Deceased (%)</th>
<th>Se0 Deceased (%)</th>
<th>p-value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>16 3 18.8</td>
<td>12 3 25.0</td>
<td>0.690</td>
<td>0.69 (0.11-4.24)</td>
</tr>
<tr>
<td>50 to &lt;65</td>
<td>26 8 30.8</td>
<td>27 12 44.4</td>
<td>0.305</td>
<td>0.56 (0.18-1.71)</td>
</tr>
<tr>
<td>65 to &lt;80</td>
<td>40 19 47.5</td>
<td>45 29 64.4</td>
<td>0.116</td>
<td>0.50 (0.21-1.19)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>10 9 90.0</td>
<td>13 11 84.6</td>
<td>0.704</td>
<td>1.64 (0.13-21.3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>74 25 33.8</td>
<td>64 35 54.7</td>
<td>0.014</td>
<td>0.42 (0.21-0.84)</td>
</tr>
<tr>
<td>Females</td>
<td>18 14 77.8</td>
<td>33 20 60.6</td>
<td>0.214</td>
<td>2.28 (0.61-8.45)</td>
</tr>
<tr>
<td>APACHE III score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;102</td>
<td>65 24 36.9</td>
<td>70 33 47.1</td>
<td>0.230</td>
<td>0.66 (0.33-1.31)</td>
</tr>
<tr>
<td>≥102</td>
<td>27 15 55.6</td>
<td>27 22 81.5</td>
<td>0.040</td>
<td>0.28 (0.08-0.97)</td>
</tr>
<tr>
<td>No. of organs failing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>52 22 42.3</td>
<td>54 27 50.0</td>
<td>0.427</td>
<td>0.73 (0.34-1.58)</td>
</tr>
<tr>
<td>4-6</td>
<td>40 17 42.5</td>
<td>43 28 65.1</td>
<td>0.039</td>
<td>0.40 (0.16-0.96)</td>
</tr>
<tr>
<td>Type of admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Surgical</td>
<td>37 19 51.4</td>
<td>38 24 63.2</td>
<td>0.301</td>
<td>0.62 (0.24-1.55)</td>
</tr>
<tr>
<td>Internal</td>
<td>49 19 38.8</td>
<td>56 30 53.6</td>
<td>0.130</td>
<td>0.35 (0.25-1.20)</td>
</tr>
<tr>
<td>Gram staining</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>26 9 34.6</td>
<td>19 8 42.1</td>
<td>0.690</td>
<td>0.73 (0.22-2.46)</td>
</tr>
<tr>
<td>Negative</td>
<td>12 6 50.0</td>
<td>12 8 66.7</td>
<td>0.408</td>
<td>0.50 (0.10-2.60)</td>
</tr>
<tr>
<td>Type of infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pneumonia</td>
<td>38 14 36.8</td>
<td>44 25 56.8</td>
<td>0.071</td>
<td>0.44 (0.18-1.08)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>13 5 38.5</td>
<td>11 6 54.5</td>
<td>0.431</td>
<td>0.53 (0.21-2.66)</td>
</tr>
<tr>
<td>Death attributable to sepsis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Septic shock with DICb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 15 40.5</td>
<td>45 30 66.7</td>
<td>0.018</td>
<td>0.34 (0.14-0.84)</td>
</tr>
<tr>
<td>No</td>
<td>55 24 43.6</td>
<td>52 25 48.1</td>
<td>0.645</td>
<td>0.84 (0.39-1.8)</td>
</tr>
<tr>
<td>Tight blood glucose control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 11 44.0</td>
<td>29 21 72.4</td>
<td>0.034</td>
<td>0.30 (0.10-0.93)</td>
</tr>
<tr>
<td>No</td>
<td>67 28 41.8</td>
<td>68 34 50.0</td>
<td>0.339</td>
<td>0.72 (0.36-1.42)</td>
</tr>
</tbody>
</table>

Se1, treatment group; Se2, placebo group; APACHE, Acute Physiology and Chronic Health Evaluation.

*Mean (95% confidence interval); bdecrease of platelet count >50% or platelet count <150,000/mL.

Table 5. Relationship between the maximal whole blood selenium concentrations after day 1 and mortality rate in selenium-treated group (Se1) and control group (Se0) except those patients who died within the first 2 days

<table>
<thead>
<tr>
<th>Selenium Whole Blooda (Normal 0.96-1.78 μmol/L)</th>
<th>Se1 Deceased</th>
<th>Se0 Deceased</th>
<th>p-value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.75</td>
<td>24 12 50.0</td>
<td>41 27 65.8</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>1.75 to &lt;2.1</td>
<td>25 6 24.0</td>
<td>37 9 24.3</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>≥2.1</td>
<td>26 6 23.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aMaximum after day 1.

lower third of all values (<1.75 μmol/L, n = 25) but 24.0% and 23.1% when selenium was within the upper two thirds of selenium concentrations (p = .019). In Se0 patients, the mortality rate was 65.8% if the selenium levels were below the median of 0.88 μmol/L but 24.3% (p < .001) in patients with selenium levels >0.88 μmol/L (Table 5).

Secondary End Points

APACHE III Score. The variable part of the APACHE III score decreased from day 1 to day 28 in the Se1 group (−27.6%, p = .0002), comparable to the Se0 group (−24.1%, p = .0002).

Logistic Organ Dysfunction System. The resolution of organ dysfunction, calculated by changes of the logistic organ dysfunction system score during the observation time, was also similar in both groups (−2.6 ± 4.7 in Se1, −2.0 ± 4.0 in Se0).

Duration of Intensive Care Unit Stay. There was little difference between groups. The mean treatment duration was 15.1 ± 10 days in the Se1 group and 12.7 ± 9 days in the Se0 group.

Other End Points. Incidence of ventilation, hours requiring mechanical ventilation, and need for hemodialysis or vasopressor therapy were similar in both groups. The incidence of new infections was not significantly different between groups—the development of hospital-acquired pneumonia was ten (10.9%) in Se1 and ten (10.3%) in Se0 patients—and the incidence of acute respiratory distress syndrome also was not significantly different in Se1 (5.4%) and Se0 (4.1%) patients.

Tertiary End Points. C-reactive protein and procalcitonin decreased in both groups, but without a significant difference between the groups (Table 6).

The Gpx-3 activity significantly increased in the Se1 group compared with
the placebo group (p < .001). The median change from baseline was 48.8 units/L in the Se1 group, whereas it was 6.0 units/L in Se0 patients (Table 6).

**Safety**

**Adverse Effects.** All safety criteria were analyzed including all randomized patients (n = 246) except three patients who withdrew informed consent. Without significant differences, adverse events occurred in 110 of 122 (90.2%) and 119 of 124 (96.0%) Se1 and Se0 patients, respectively. The sum of adverse events was 539 in Se1 and 591 in Se0 patients leading to an incidence of serious adverse events per patient year of 54.1 and 65.8 in Se1 and Se0, respectively. There were no specific adverse effects associated with the high-selenium supplementation.

**Selenium Concentrations.** Selenium levels were low at baseline (Se1, 0.48 μmol/L; Se0, 0.46 μmol/L) and increased significantly (p ≤ .001) only in Se1 patients. In Se1 patients, the maximum serum selenium concentrations were found on day 14 with the highest value in one patient being 5.34 μmol/L; the maximum whole blood concentration was 3.57 μmol/L. The median concentrations were 2.05 μmol/L in serum and 1.83 μmol/L in whole blood. In patients with acute renal failure, selenium levels increased to a maximum median level of 1.80 μmol/L in serum and to 1.89 μmol/L in whole blood.

Urine selenium concentrations increased in Se1 patients from 0.20 to 1.90 μmol/L (p ≤ .001), whereas in Se0 patients selenium excretion remained low (0.13 μmol/L).

Liver function assessed by the levels of albumin, liver enzymes, or global coagulation variables, as well as rates of renal or pulmonary failures, were not different between Se1 and Se0 patients and not related to high selenium levels.

**DISCUSSION**

The results of this randomized and placebo-controlled trial indicate that high-dose sodium-selenite supplementation is a new and important adjuvant therapeutic approach to improve outcome in sepsis and septic shock: The intention-to-treat analyses of all patients confirm the data of our previous pilot studies (20, 21) but the similar odds ratios (0.66, 0.65, and 0.64, respectively) indicate an underpowered study population. In the per-protocol analysis, however, the 28-day mortality rate was with 14.3%, significantly lower, in patients receiving adjuvant selenium treatment. This corresponds to a number needed to treat of seven patients. Assuming that about 140,000 sepsis-associated deaths occur per year in Germany, around 20,000 could be prevented with this adjuvant therapy. The total additional costs per saved life would only be around 1050 Euros. In the subgroup of patients with septic shock, the mortality rate was even 26.2% lower in Se1 patients, and the number needed to treat was four.

There was a direct correlation between selenium concentrations in whole blood and survival rate. High normal selenium concentrations associated with optimal selenoenzyme function obviously are necessary for the organism to cope with the challenges of severe sepsis. As the subgroup with the highest selenium whole blood concentrations had no further reduction in mortality, it could be speculated that lower dosages of selenium might be sufficient. However, there was no harm to these patients, and no selenium-specific side effects were observed.

In previous pilot studies, similar effects of selenium supplementation were found with a reduced mortality rate in the most critically ill patients (20, 21). However, due to low quality of data and no comparable supplementation regimens, a Cochrane analysis concluded, “There is insufficient evidence to recommend supplementation of critically ill patients with selenium or ebselen” (27). The results of this larger, multiple-centre trial now confirm the efficacy of high-dose sodium-selenite supplementation in patients with severe sepsis and septic shock. In patients with severe burn trauma, an adjuvant selenium substitution reduced mainly pulmonary infections (28). This could not be confirmed in our study, as the infectious complications were similar in both groups.

The mechanisms responsible for improved survival in sepsis and septic shock by selenium supplementation are still unknown. As a typical sign of an acute phase reaction (29), selenium levels are below normal already at admission to the intensive care unit (19, 20, 30). The severity of selenium depletion is correlated with survival as already shown (15). Selenium blood levels might be an unreliable marker of intracellular selenium and selenoenzyme content. It is supposed that high blood selenium supplies the organs with sufficient selenium to synthesize selenoenzymes (31, 32). As the difference in mortality rate between both groups was similar within the first days, selenoenzymes rather than sodium-selenite per se are responsible for these effects (12, 33).

Septic shock is associated with multiple organ failures and disseminated intravascular coagulation. Especially in those patients, the adjuvant selenium supplementation was most effective. One hypothesis is that under selenium supplementation, selenoprotein P is rapidly generated (13), preventing endothelial cell activation by selenium-depletion is correlated with survival as already shown (15). Selenium blood levels might be an unreliable marker of intracellular selenium and selenoenzyme content. It is supposed that high blood selenium supplies the organs with sufficient selenium to synthesize selenoenzymes (31, 32). As the difference in mortality rate between both groups was similar within the first days, selenoenzymes rather than sodium-selenite per se are responsible for these effects (12, 33).

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normalizes all known selenoenzymes like intracellular GPx and thioredoxin reductase activities. These enzymes reduce hydrogen peroxide, lipid, and phospholipid hydroperoxides; dampen the propagation of free radicals and reactive oxygen species; reduce hydroperoxide intermediates in the cyclo-oxygenase and lipooxygenase pathways; diminish the production of inflammatory prostaglandins and leukotrienes; and modulate the respiratory burst (37).

Endogenous glutathione plays an important role in reducing vascular hypotrophy to exogenous norepinephrine due to its deactivation by superoxide (38) and endothelial dysfunction in response to peroxynitrite and endotoxic shock. Depletion of glutathione also enhances the cytotoxic effects of hydrogen peroxide and free oxygen radicals in endothelial cells and smooth muscle cells in shock (39) and, specifically, the peroxynitrite-induced injury (40, 41). A low activity of GPx (42) in plasma, platelets, and leukocytes in different acute and chronic illnesses (11, 12, 13) might contribute to increased oxidative stress in several compartments and contribute to multiple or- gan failure but might be prevented by selenium supplementation. High GPx activity regenerates the oxidized glutathione. Whether additional glutathione sup- plementation would augment the effect of selenium supplementation alone has to be established.

CONCLUSION

This multiple-center trial shows that an adjuvant, high-dose selenium supplement- tion reduced the mortality rate in patients with severe sepsis and especially in septic shock. This therapy is inexpensive, the number needed to treat is less than seven, it is easy and safe to handle, and it is not associated with overt adverse side effects. A larger trial is now needed to confirm the results of this trial.

The exact mechanisms of the benefi- cial effects of this adjuvant selenium sup- plementation are not known. There is, however, strong evidence that selenium might enhance the activities of important selenoenzymes involved in the mainte- nance of redox-homeostasis and immune and endothelial cell function.

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