Use of selenium in intensive care as adjunctive therapy for sepsis, ischaemia/reperfusion and reanimation

**selenase®**

- improves selenium status
- eliminates selenium deficiency
- reduces mortality
High dose for sepsis – so that selenium works

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Treatment ideally begins within 6 hours after admission to the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>as bolus</td>
</tr>
<tr>
<td></td>
<td>2,000&lt;sup&gt;1-3&lt;/sup&gt; µg Se</td>
</tr>
<tr>
<td></td>
<td>then as continuous infusion</td>
</tr>
<tr>
<td></td>
<td>1,600&lt;sup&gt;1-3&lt;/sup&gt; µg Se</td>
</tr>
<tr>
<td>at least 7 days</td>
<td>maintenance therapy</td>
</tr>
<tr>
<td></td>
<td>1,600&lt;sup&gt;1-3&lt;/sup&gt; µg Se / Day</td>
</tr>
</tbody>
</table>

**Literature**

1 Manzanares W et al. 2012, *Crit Care; 16:R66*
2 Huang TS et al. 2013, *PLoS One 8:e54431*
3 Alhazzani W et al. 2013, *Crit Care Med 41:1555–1564*

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**selenase® for sepsis**

- A high dose selenium bolus significantly reduces the death rate for sepsis patients by 27%. [1]
- A high dose of ≥ 1,000 µg selenium as sodium selenite pentahydrate (selenase®) per day significantly reduces the mortality by 23%. [1]
- A maintenance therapy of ≥ 7 days significantly improves survival. [1]

selenase® for cardiac surgery

<table>
<thead>
<tr>
<th>1 week before</th>
<th>Elective cardiac surgery</th>
<th>500¹ µg Se / day oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Bolus ideally within 30 minutes after administration of anaesthesia; termination of the bolus before initiation of the cardiopulmonary bypass</td>
<td>2,000¹² µg Se</td>
</tr>
<tr>
<td></td>
<td>Intraoperative as bolus (for about 30 min.)</td>
<td>2,000¹² µg Se</td>
</tr>
<tr>
<td></td>
<td>Bolus directly after admission to ICU</td>
<td>2,000¹² µg Se</td>
</tr>
<tr>
<td>From day 2 of the ICU stay</td>
<td>maintenance therapy</td>
<td>1,000¹² µg Se / day</td>
</tr>
</tbody>
</table>

Literature

1 Stoppe C et al 2013, *Nutrition* 29:1, 158–165

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**selenase® for cardiac surgery**

- The selenium status correlates with the extent of cardiac damage [¹]
- An intraoperative decrease of selenium is associated with the postoperative development of multi-organ failure [²]
- The postoperative decrease of selenium concentration is not attributed to the use of a heart-lung machine [³]
- Perioperative administration of selenase® prevents the strong postoperative decrease of selenium concentration [⁴]

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Sodium selenite for stroke

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Treatment ideally begins within 6 hours after admission to the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bolus directly after admission to ICU</td>
</tr>
<tr>
<td></td>
<td>1,000 µg Se</td>
</tr>
<tr>
<td></td>
<td>then as continuous infusion</td>
</tr>
<tr>
<td></td>
<td>500 µg Se</td>
</tr>
<tr>
<td>From day 2 of the ICU stay</td>
<td>maintenance therapy</td>
</tr>
<tr>
<td></td>
<td>500 µg Se / day</td>
</tr>
</tbody>
</table>

By now a randomized, double-blinded, placebo controlled trial with the title „Selenium and ischemic stroke outcome“ (NCT02505295) is under way, which investigates, if 2,000 µg selenium in form of selenase® directly after patient admission plus 1,000 µg selenium per day (selenase®) for five days reduces mortality and neurological damage.

Sodium selenite for stroke

- Stroke patients show significantly reduced selenium values [1]
- High glutathione peroxidase concentration correlates with low neurological deficiency and a positive outcome after a stroke [1]
- Significantly reduced Selenoprotein P concentration in patients after an acute stroke [2]
- Reduced Selenoprotein P status is associated with a significantly higher risk for stroke [2]


### Sodium Selenite for Burns

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Treatment ideally begins within 12 hours after admission to the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>then as continuous infusion</td>
</tr>
<tr>
<td>14 days for burns &lt; 60% of the body surface</td>
<td>500–3 µg Se</td>
</tr>
<tr>
<td>21 days for burns ≥ 60% of the body surface</td>
<td>maintenance therapy</td>
</tr>
<tr>
<td></td>
<td>500–3 µg Se / day</td>
</tr>
</tbody>
</table>

#### Literature


### Sodium Selenite for Burns

**Sodium selenite:**

- reduces the number of infections [2]
- improves wound healing [3, 4]
- shortens the antibiotic treatment [2]
- shortens the hospital stay [1, 2]

---


## selenase® after reanimation

<table>
<thead>
<tr>
<th>Day 1</th>
<th>The beginning of treatment directly after reanimation or ICU admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>as continuous infusion</td>
</tr>
<tr>
<td></td>
<td>1,000µg Se</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 2 – 5</th>
<th>maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,000µg Se / day</td>
</tr>
</tbody>
</table>

### Literature


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### selenase® after reanimation

- Low selenium status in the post-reanimation phase [1]
- Length of reanimation correlates negatively with the selenium level [2]
- Early administration of selenase® improves the neurological outcome of patients after cardiac arrest [3]

---


### Miscibility

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 5% glucose solution</td>
<td>• Cytostatic agent solutions [1]</td>
</tr>
<tr>
<td>• Ringer solution</td>
<td>• Amino acid solutions that contain cysteine [2]</td>
</tr>
<tr>
<td>• Carbohydrate solutions (stability 72 hours (3 days))</td>
<td>• Solutions that contain glutathione (GSH) [3]</td>
</tr>
<tr>
<td>• Colloidal volume expander solutions (stability 72 hours (3 days))</td>
<td>• Vitamin solutions that contain vitamin C [4]</td>
</tr>
<tr>
<td>• Electrolyte solutions with increased potassium concentration (stability 48 hours (2 days))</td>
<td>[1] selenase&lt;sup&gt;®&lt;/sup&gt; should generally be administered 1 hour before cytostatic agent application for timely incorporation in the endogenous protective systems.</td>
</tr>
<tr>
<td>• Crystalloid electrolyte solutions (stability 48 hours (2 days))</td>
<td>[2,3] SH groups react with Na-selenite; Na-selenite can no longer satisfy its task as a radical scavenger</td>
</tr>
<tr>
<td>• Amino acid solutions without cysteine (stability 36 hours (1.5 days))</td>
<td>[4] Selenium (Se&lt;sup&gt;IV&lt;/sup&gt;) in sodium selenite is reduced by vitamin C to the elementary selenium (Se&lt;sup&gt;0&lt;/sup&gt;) and is thereby ineffective.</td>
</tr>
<tr>
<td>• Fat emulsions (stability 24 hours (1 day))</td>
<td>Literature:</td>
</tr>
</tbody>
</table>
### Products for injection therapy

**Prescription only**

<table>
<thead>
<tr>
<th>selenase® 100 µg pro injectione</th>
<th>selenase® T pro injectione</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>100 µg</strong> Selenium / ampoule</td>
<td><strong>500 µg</strong> Selenium / injection vial</td>
</tr>
<tr>
<td>10 (N2) and 50 ampoules</td>
<td>2, 10 (N2), 30 (3 × 10) and 50 (5 × 10) glass vials with 10 ml solution for injection</td>
</tr>
</tbody>
</table>

**selenase® 100 µg / T**

**Active substance:** Sodium selenite pentahydrate, 50 µg selenium per ml.  
**Indications:** Clinically proven selenium deficiency that cannot be compensated by nutritional sources. Selenium deficiencies may occur as a result of states of malnutrition and malabsorption, as well as in malnutrition (e.g. due to complete parenteral nutrition).  
**Composition:** selenase® 100 µg pro injectione: 1 ampoule of 2 ml solution for injection contains: 0.333 mg sodium selenite pentahydrate, corresponding to 100 µg (micrograms) selenium. selenase® T pro injectione: 1 injection vial of 10 ml / 20 ml solution for injection contains: 1.67 mg / 3.33 mg sodium selenite pentahydrate, corresponding to 500 µg / 1000 µg selenium. selenase® 100 µg peroral: 1 drinking ampoule of 2 ml oral solution contains: 0.333 mg sodium selenite pentahydrate, corresponding to 100 µg selenium. selenase® T peroral: 1 ml oral solution contains: 0.167 mg sodium selenite pentahydrate, corresponding to 50 µg selenium. Excipients: Sodium chloride, hydrochloric acid, water for injections.  
**Contra-indications:** Selenium poisoning.  
**Undesirable effects:** None known to date if the medicinal product is administered according to prescription. selenase® 100 µg / T pro injectione: General disorders and administration site conditions: Frequency not known (cannot be estimated from the available data). After intramuscular administration local pain at the site of administration has been reported. Form of administration, size of packages: selenase® 100 µg pro injectione: 10 or 50 ampoules of 2 ml solution for injection. selenase® T pro injectione: 2 or 10 injection vials of 10 ml solution for injection, hospital-size pack 30 (3 x 10) or 50 (5 x 10) injection vials of 10 ml solution for injection, 2 or 10 injection vials of 20 ml solution for injection, hospital-size pack 30 (3 x 10) or 50 (5 x 10) injection vials of 20 ml solution for injection. selenase® 100 µg peroral: 20, 50, 90 or 160 ampoules of 2 ml oral solution. selenase® T peroral: 10 drinking bottles of 10 ml oral solution plus one measuring cup.
## General facts about sepsis

16 Sepsis: Incidence
18 The problem: Diagnosis
18 The problem: Costs

## Details on sepsis

20 Sepsis in Europe
22 Major influence of organ failure on ICU mortality rates
24 ICU mortality rate significantly higher in sepsis patients
26 Postoperative sepsis

## Selenium and sepsis

28 Selenium level declines in correlation to sepsis severity
29 Selenium concentration is inversely correlated with APACHE II and SAPS II scores
31 Minimum selenium concentration: independent predictor of ICU mortality
32 Where does selenium intervene in the process of sepsis?
34 Which effect does ROS production have on survival?
34 Why does the selenium status decline in patients with sepsis?
36 Why is early administration of sodium selenite crucial (within ≤ 6 hours)?
38 Why inject sodium selenite as bolus?

## selenase® for sepsis

40 Meta analysis of 9 sepsis trials
42 Pilot study
50 SIC trial (Selenium in Intensive Care)
54 Various trials
60 Overview of trials

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82 Important role of ROS with I/R

## Challenges posed by complications in cardiac surgery

84 Increased severe complications in cardiac surgery
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<td>108</td>
<td>Selenium is essential for the brain</td>
</tr>
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</tr>
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<td>Sodium selenite acts neuroprotectively even hours after induction of the damage</td>
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<td>120</td>
<td>Selenium deficit massively increases susceptibility to excitotoxicity and increased neuronal cell loss</td>
</tr>
<tr>
<td>122</td>
<td>Principle of action of neuronal protection by sodium selenite</td>
</tr>
<tr>
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<td>Impact of a selenium deficit on the brain affected by stroke</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
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<td>----------------------------------------------------------------------</td>
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<td>152</td>
<td>Additional information</td>
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<td>154</td>
<td></td>
</tr>
</tbody>
</table>
## Summary

<table>
<thead>
<tr>
<th>Sepsis</th>
<th>Details on sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td>Germany registers over 175,000 sepsis patients each year</td>
</tr>
<tr>
<td></td>
<td>Despite medical progress in general, these numbers keep rising</td>
</tr>
<tr>
<td></td>
<td>Diagnosis is encumbered by non-specific symptoms and a lack of generally valid biomarkers</td>
</tr>
<tr>
<td></td>
<td>Exorbitant costs for treating sepsis patients</td>
</tr>
<tr>
<td><strong>Details on sepsis</strong></td>
<td>Correlation between ICU mortality and sepsis incidence in Europe</td>
</tr>
<tr>
<td></td>
<td>Organ failure strongly affects ICU mortality rate</td>
</tr>
<tr>
<td></td>
<td>The number of failed organs increases significantly in severe sepsis</td>
</tr>
<tr>
<td></td>
<td>Increasing number of postoperative sepsis cases</td>
</tr>
<tr>
<td><strong>Selenium and sepsis</strong></td>
<td>Selenium level declines in correlation with sepsis severity</td>
</tr>
<tr>
<td></td>
<td>Selenium concentration is inversely correlated with APACHE II and SAPS II scores</td>
</tr>
<tr>
<td></td>
<td>Minimum selenium concentration is an independent predictor of ICU mortality</td>
</tr>
<tr>
<td></td>
<td>Cut-off value of 36 µg/l selenium in serum for sepsis patients</td>
</tr>
<tr>
<td></td>
<td>Early (≤ 6 hours) administration of selenase® is crucial</td>
</tr>
<tr>
<td></td>
<td>A bolus administration reverses the pro-inflammatory state via an early, transient, pro-oxidative effect of high-dose sodium selenite</td>
</tr>
</tbody>
</table>
selenase® for sepsis

<table>
<thead>
<tr>
<th>Meta analysis</th>
<th>Parenteral sodium selenite treatment significantly reduces total mortality rate by 17% (p = 0.04)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Higher significant reduction of mortality when a bolus is administered (~ 27%; p = 0.01), a maintenance therapy ≥ 7 days (~ 23%; p = 0.01) and a dosing of ≥ 1,000 µg selenium as sodium selenite-pentahydrate (selenase®) per day (~ 23%; p = 0.04)</td>
</tr>
<tr>
<td>Pilot study</td>
<td>Supplementation with selenase® increases the selenium level to values within the normal range</td>
</tr>
<tr>
<td></td>
<td>selenase® supplementation significantly reduces mortality in patients with APACHE III score &gt; 53</td>
</tr>
<tr>
<td>SIC trial</td>
<td>Significant reduction in mortality in the selenase®-supplemented group by 14.3% (p = 0.049)</td>
</tr>
<tr>
<td></td>
<td>Significant reduction in mortality in the subgroups (septic shock, APACHE III ≥ 102, &gt; 3 organ failure) in the selenase®-supplemented group by up to 26%</td>
</tr>
<tr>
<td>Various trials</td>
<td>Possible correlation between selenium supplementation and procalcitonin</td>
</tr>
<tr>
<td></td>
<td>Supplementation with high-dose sodium selenite reduces the incidence of nosocomial pneumonia and improves sepsis severity</td>
</tr>
<tr>
<td></td>
<td>SIGNET trial: Fewer new infections in patients receiving selenase® supplementation for &gt; 5 days</td>
</tr>
<tr>
<td></td>
<td>REDOXS trial: Compared to glutamine, selenium does not have any negative effect on mortality, although the beneficial effect of selenium supplementation is reduced by the lack of selenium deficiency</td>
</tr>
<tr>
<td></td>
<td>Significantly more critically ill patients in the intervention group impacted the analysis of the retrospective trial on selenium supplementation in patients with severe sepsis</td>
</tr>
<tr>
<td>Ischaemia/reperfusion</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td></td>
</tr>
<tr>
<td><strong>General information</strong></td>
<td></td>
</tr>
<tr>
<td>Ischaemia and reperfusion (I/R) cause tissue damage</td>
<td></td>
</tr>
<tr>
<td>Reactive oxygen species play an important role in I/R</td>
<td></td>
</tr>
<tr>
<td><strong>Challenges posed by complications in cardiac surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Severe complications in cardiac surgery despite great advancements present a major problem</td>
<td></td>
</tr>
<tr>
<td>Affect up to 16% of patients</td>
<td></td>
</tr>
<tr>
<td>Three pathophysiological mechanisms are responsible: ischaemia, reperfusion and perioperative inflammation</td>
<td></td>
</tr>
<tr>
<td>Selenium supplementation intervenes at the same site of action as established pharmacological strategies</td>
<td></td>
</tr>
<tr>
<td><strong>Selenium in the cardiovascular system</strong></td>
<td></td>
</tr>
<tr>
<td>Selenoproteins play a large role in the cardiovascular system</td>
<td></td>
</tr>
<tr>
<td>50% increase in the selenium concentration is associated with a 24% risk reduction of coronary heart disease</td>
<td></td>
</tr>
<tr>
<td>Least risk of a cardiovascular disease by 150 – 160 µg/l selenium in serum</td>
<td></td>
</tr>
<tr>
<td>A selenium deficiency negatively influences Keshan disease and infectious myocarditis</td>
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<tr>
<td>Perioperative administration of selenase® prevents the strong postoperative decrease of the selenium concentration below the original value</td>
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<td><strong>Selenase® for cardiac surgery</strong></td>
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<td>Glutathione peroxidase-1 influences the infarct volume</td>
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<tr>
<td>Glutathione peroxidase 4 is essential in brain development and neuropathological diseases</td>
<td></td>
</tr>
<tr>
<td>The lack of the selenium transport proteins Selenoprotein P causes severe neurological dysfunction, which can be attenuated by sodium selenite supplementation</td>
<td></td>
</tr>
</tbody>
</table>
### Sodium selenite for stroke

Sodium selenite acts neuroprotectively even hours after induction of the damage.

Selenium deficit results in a massive increase in susceptibility for excitotoxicity and increased neuronal cell loss.

The neuroprotective effect of sodium selenite is based on:

- the reduction of the oxidative stress in neurons
- the preservation of the mitochondrial respiratory chain
- the inhibition of NFκB and AF1 activation
- the inhibition of ischaemia-induced DNA oxidation
- the normalization of ischaemia-activated autophagy

### Selenium status and selenoprotein activity in the event of a stroke

Stroke patients show significantly reduced selenium values.

High glutathione peroxidase concentration correlates with a low neurological deficit and a favorable outcome for strokes.

Significantly reduced Selenoprotein P concentration in patients with an acute stroke.

A reduced Selenoprotein P level is accompanied by an associated significantly higher risk of stroke.

### Sodium selenite for burns

Sodium selenite:

- reduces the number of infections
- improves wound healing
- shortens antibiotic therapy
- shortens the hospital stay

### Selenase® after reanimation

Low selenium status in the post-reanimation phase.

Length of reanimation correlates negatively with the selenium level.

Early administration of selenase® improves the neurological outcome of patients after cardiac arrest.
General facts about sepsis

**General information**

- Germany registers over 175,000 sepsis patients each year
- Despite medical progress in general, these numbers keep rising
- Diagnosis is encumbered by non-specific symptoms and a lack of generally valid biomarkers
- Exorbitant costs for treating sepsis patients

---

**Sepsis: High incidence rate**

Sepsis involves a complex systemic inflammatory reaction affecting the entire body and impairs tissue, organs and thereby all vital functions. If sepsis is not diagnosed and treated in a timely manner, it will invariably lead to septic shock, multiple organ failure and death. One third to one half of all patients do not survive sepsis.

Sepsis is the most common infection-related cause of death. Older figures reported 1.5 million sepsis patients annually worldwide \(^1\). In Germany, the incidence is 154,000 per year (Fig. 1) \(^2\). New publications even reported 175,000 cases \(^1\). However, the experts meanwhile assume that approx. 18 million people per year become afflicted given that the majority of deaths ascribed to HIV/AIDS, malaria, pneumonia and other infectious diseases are most likely attributable to sepsis \(^3\).

Despite general progress in medicine, these numbers are rising dramatically. The number of sepsis cases treated in hospital have doubled over the past 10 years \(^4\) and meanwhile exceed the number of hospital admissions due to heart attacks (Fig. 2) \(^5, 6\). Only 20 – 40% of sepsis patients acquired their sepsis outside of the hospital \(^7\). By contrast, for example, the incidence of postoperative sepsis in the USA tripled from 1997 to 2006.
Incidence and mortality of sepsis depending on age. [10]

More hospital admissions due to sepsis than to myocardial infarction. [5, 6]
Sepsis: problematic diagnostics

The diagnosis is frequently confirmed too late because the clinical symptoms and laboratory values (body temperature, heart rate, respiratory rate and white blood cell count) are relatively non-specific and can occur in a large number of other diseases as well. Particularly in children, these symptoms are less meaningful because the onset of sepsis symptoms is usually very subtle, with the clinical picture suddenly worsening dramatically.

The high rate of misdiagnoses or cases diagnosed after it was too late is attributable to deficits still existing in the definition of the condition, insufficient diagnostic criteria and frequently insufficient compliance with clinical guidelines. An additional problem is, that for a diagnosis using blood parameters (“biomarkers”), there are still no generally approved biomarkers, in contrast to other acute diseases. Some national and international guidelines recommend procalcitonin for guiding antibiotic therapy and verifying diagnosis of sepsis.

Sepsis: High costs

Between 1997 and 2008, inflation-corrected costs of hospital treatment for sepsis patients rose annually by an average of 11.9% to approx. $14.6 billion in 2008 [6]. These numbers do not take into account the costs for long-term effects, because they are so far unknown. Sepsis survivors suffer from a large number of severe physical, cognitive and mental problems, which lead to a mortality risk twice as high as that of a population control group even 5 years after surviving sepsis [8].

Over the past 10 years, the mean costs for hospital treatment per sepsis patient increased in the same magnitude to a current level of approx. €55,000 in Germany as well [9].
**Literature**


## Details on sepsis

### General information

- Correlation between ICU mortality and sepsis incidence in Europe
- Organ failure strongly affects ICU mortality rate
- The number of failed organs increases significantly in severe sepsis
- Increasing number of postoperative sepsis cases

### Sepsis in Europe

More exact figures on the topic of sepsis in Europe can be found in the SOPA trial 2006\(^1\).

Europe-wide, 37% of patients had sepsis during their ICU stay. This number of patients illustrates the high prevalence of sepsis. This combined with the fact, that the sepsis mortality rate in europe is 27% during an ICU stay and increases to 50% in severe sepsis, shows clearly how important the topic of sepsis is, even in industrialized nations with very good medical care.

A large proportion of sepsis patients display a severe sepsis (79%) and 39% even suffer from septic shock. That means that 15% of all patients admitted to an ICU suffered from septic shock.

ICU mortality in sepsis patients ranges between 10% in Switzerland and 35% in Italy; Germany has 16%, the second lowest ICU mortality rate. The hospital mortality in patients with sepsis in Germany and Switzerland was lowest at 20%, with the Netherlands registering the highest at 47%. A clear correlation between overall ICU mortality and the sepsis rate is evident across the different countries (Fig. 1). Overall, ICU mortality in patients with sepsis was significantly higher than in patients without sepsis (27% vs. 14%; p < 0.001). In patients with severe sepsis and/or septic shock, ICU mortality increased on average to 32.2% and 54.1%, respectively (Fig. 2). In Germany, ICU mortality in severe sepsis was 24%.
**Fig. 1** Correlation between ICU mortality of all patients and sepsis incidence in Europe. [1]

- **Switzerland**
- **Germany**

Countries licensed for selenase®

- **Belgium**
- **Spain**
- **Austria**
- **Scandinavia**
- **Greece**
- **France**
- **Eastern Europe**
- **Netherlands**
- **UK + Ireland**
- **Portugal**

- **0%**
- **10%**
- **20%**
- **30%**
- **40%**

**Y = 0.51 x - 0.11**

**R² = 0.80**

**Fig. 2** Comparison of sepsis incidence in ICU patients with ICU mortality in Europe. [1]

- **Incidence**
  - No sepsis: 63%
  - Sepsis: 37%
  - Severe sepsis: 30%
  - Septic shock: 15%
- **ICU mortality**
  - No sepsis: 30%
  - Sepsis: 27%
  - Severe sepsis: 32%
  - Septic shock: 32%
Major influence of organ failure on ICU mortality rates

At ICU admission, 81% of patients displayed organ failure \(^1\). 41% of these patients had sepsis. In 38% of ICU patients without sepsis but with organ failure, no organ failure occurred. Also, ICU mortality in this group was barely 2%. In the remaining 62% of ICU patients without sepsis, ICU mortality increased to 21%. In comparison, all ICU patients with severe sepsis had organ failure, and ICU mortality increased further significantly to 32% \((p < 0.01)\) (Fig. 3).

Independent of an existing sepsis, there was a direct connection between the number of failed organs and ICU mortality (Fig. 4). In patients with no organ failure at ICU admission, the ICU mortality was 6%. In patients with 4 or more failed organs, ICU mortality increased to 65%.

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**Details on sepsis**
Fig. 4 Frequency of organ failure at ICU admission and the corresponding ICU mortality. [1]
ICU mortality rate significantly higher in sepsis patients

Severe sepsis does not impact ICU mortality rate depending on the number of failing organs. But the number of organs that fail in sepsis patients is significantly increased (Fig. 5). Therefore, ICU mortality in ICU patients with severe sepsis is still significantly higher compared to those without sepsis, but with organ failure. If the frequency of multiple organ failure (MOF) could be lowered in patients with sepsis, the high mortality rate in this group of patients would also be markedly reduced.

---

**Literature**


Diagnostic criteria for sepsis

According to: Reinhart K, Brunkhorst FM, Bone HG et al. [Prevention, diagnosis, treatment, and follow-up care of sepsis. First revision of the S2k. Guidelines of the German Sepsis Society (DSG) and the German Interdisciplinary Association for Intensive and Emergency Care Medicine (DIVI)].* Anaesthesist 2010; 59: 347–370.

<table>
<thead>
<tr>
<th>Sepsis</th>
<th>Severe sepsis</th>
<th>Septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of an infection</td>
<td>Evidence of an infection</td>
<td>Evidence of an infection</td>
</tr>
<tr>
<td>SIRS</td>
<td>SIRS</td>
<td>SIRS</td>
</tr>
<tr>
<td></td>
<td>Acute organ dysfunction</td>
<td>Cardiovascular instability</td>
</tr>
</tbody>
</table>

**Evidence of an infection:**

Diagnosis of infection based on microbiological proof or clinical criteria

**Systemic inflammatory response syndrome (SIRS) – at least 2 of the following criteria:**

- **Fever** (≥ 38°C) or **hypothermia** (≤ 36°C), confirmed through rectal, intravascular or intravesical determination
- **Tachycardia** with a heart rate ≥ 90/min
- **Tachypnea** (respiratory rate ≥ 20/min) or **hyperventilation** (PaCO₂ ≤ 4.3 kPa/ ≤ 33 mmHg)
- **Leukocytosis** (≥ 12,000/mm³) or **leukopenia** (≤ 4,000/mm³) or ≥ 10% immature neutrophils in the differential blood count

**Acute organ dysfunction – at least 1 of the following criteria:**

- **Acute encephalopathy:** Reduced vigilance, disorientation, agitation, delirium.
- **Relative or absolute thrombocytopenia:** Drop in platelet count >30% within 24 hours or platelet count ≤ 100,000/mm³. Thrombocytopenia due to acute bleeding or immunological causes must be ruled out.
- **Arterial hypoxemia:** PaO₂ ≤ 10 kPa (≤ 75 mmHg) in room air or a PaO₂/FiO₂ ratio ≤ 33 kPa (≤ 250 mmHg) on oxygen. Overt cardiac or pulmonary disease as the cause of the hypoxemia must be ruled out.
- **Renal dysfunction:** Diuresis of ≤ 0.5 ml/kg/h for at least 2 hours despite adequate volume replacement and/or a rise in serum creatinine to more than twice the reference range.
- **Metabolic acidosis:** Base excess ≤ 5 mmol/l or lactate concentration more than 1.5 times the reference range.

**Cardiovascular instability:**

Systolic arterial blood pressure ≤ 90 mmHg and/or mean arterial blood pressure ≤ 65 mmHg lasting for at least 1 hour or use of vasopressor required to stabilize systolic arterial blood pressure ≥ 90 mmHg or arterial mean pressure ≥ 65 mmHg. Hypotension despite adequate volume resuscitation not explained by other causes.
Postoperative sepsis

Sepsis is a major cause of postoperative mortality. A trial conducted in 2010 investigated the development of postoperative sepsis from 1997 – 2006 using the largest patient database in the USA (more than 2 million patients) [2]. During the analysis period, the incidence of postoperative sepsis increased from 0.7% to 1.3% (p < 0.001) and of severe postoperative sepsis from 0.3% to 0.9% (p < 0.001) (Fig. 6). The higher increased rate of severe postoperative sepsis was found in all surgical intervention categories (Fig. 7). A counter trend was observed for hospital mortality rate. The mortality rate declined from 44.4% in 1997 to 34% in 2006 (p < 0.001) (Fig. 8). Even after accounting for potential confounders, a multivariate regression model showed a decline in mortality (OR 0.94; 95% CI, 0.93–0.95 per year increase in the trial period; p < 0.001). Overall, the decline in mortality cannot compensate the increase in postoperative sepsis. Therefore the number of deaths from postoperative stress increases.
Increased number of severe postoperative sepsis is independent of the type of surgical intervention. [2]

Fig. 7

10% reduced mortality between 1997 – 2006 in severe postoperative sepsis. [2]

Fig. 8
### General information

- Selenium level declines in correlation with sepsis severity
- Selenium concentration is inversely correlated with APACHE II and SAPS II scores
- Minimum selenium concentration is an independent predictor of ICU mortality
- Cut-off value of 36 µg/l selenium in serum for sepsis patients
- Early (≤ 6 hours) administration of selenase® is crucial
- A bolus administration reverses the pro-inflammatory state via an early, transient, pro-oxidative effect of high-dose sodium selenite
Selenium level declines in correlation with sepsis severity

One trial conducted in 2007 compared 45 ICU patients with SIRS (systemic inflammatory response syndrome), mainly after cardiac surgery, with a group of 15 ICU patients without SIRS [1]. The 45 patients were subdivided into the following groups SIRS, severe SIRS and severe sepsis or septic shock: SIRS (n = 15), severe SIRS (n = 15), severe sepsis or septic shock (n = 15). Already at ICU admission, 92% of all patients had a serum selenium value below the German reference range. During their ICU stay, the selenium concentration continued to decline in all groups except for the control group without SIRS. The mean serum selenium levels at ICU admission correlated negatively with sepsis severity (Fig. 1).

Fig. 1 Serum selenium levels in sepsis patients at ICU admission decline depending on sepsis severity. [1]
Selenium concentration is inversely correlated with APACHE II and SAPS II scores

Minimum serum selenium concentration is inversely correlated with maximum number of leucocytes ($R^2 = 0.22; p < 0.01$), maximum serum C reactive protein (CRP) ($R^2 = 0.28; p < 0.01$), maximum serum procalcitonin (PCT) ($R^2 = 0.3; p < 0.01$) and maximum serum interleukin 6 (IL-6) ($R^2 = 0.42; p < 0.01$).

APACHE II and SAPS II scores, both indicators for inflammation and the degree of organ failure during an ICU stay, correlated inversely with the minimum serum selenium value (APACHE II: $R^2 = 0.31; p < 0.01$; SAPS II: $R^2 = 0.29; p < 0.01$) (Fig. 2). Furthermore the minimum serum selenium concentration is inversely correlated with the maximum degree of organ dysfunction respectively failure during an ICU stay ($R^2 = 0.42; p < 0.01$).

---

**Fig. 2** Inverse correlation of serum selenium levels with APACHE II and SAPS II scores. [1]

---

* SIRS = systemic inflammatory response syndrome
Minimum selenium concentration: independent predictor of ICU mortality

Both the initial serum selenium value as well as the minimum serum selenium concentration were significantly lower in non-surviving compared to surviving patients (Fig. 3). A receiver operating characteristic (ROC) analysis for predicting ICU mortality showed that the SAPS II score (AUC = 0.903; 95% CI: 0.819–0.987, p < 0.01) and minimum serum selenium concentration (AUC = 0.867; 95% CI: 0.753–0.981, p < 0.01) were the most significant predictive factors.

A cut-off value for the minimum serum selenium concentration was set. A cut-off value of 36 µg/l selenium in serum has a sensitivity of 89%, specificity of 71% and positive predictive value of 35%. Most importantly, however, it has a negative predictive value of 95%.

Therefore the probability to die increases below 36 µg/l selenium in serum.

Fig. 3  The serum selenium level in surviving patients is significantly higher. [1]

<table>
<thead>
<tr>
<th>Serum selenium concentration at ICU admission (µg/l)</th>
<th>Minimal serum selenium concentration (µg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors (51)</td>
<td>Non-survivors (9)</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

p < 0.05
Selenium and sepsis

Cytokines:
- TNFα
- IL-1
- IL-6

Invasion of bacteria and toxins

NF-κB activation

Activation of coagulation

Disseminated intravascular coagulation (DIC)

iNOS

NO

Hypotension
Cardiovascular hyporeactivity

Tissue hypoperfusion
Hypoxia

Multiple organ dysfunction (MOD)

Multiple organ failure (MOF)

Tissue damage

Se
[13]

Se
[13]

Fever
Tachycardia
Leukocytosis

Neurological abnormalities

Purpura
Petechia

Signaling processes

Tissue damage

Fever
Tachycardia
Leukocytosis

Neurological abnormalities

Purpura
Petechia
Invasion of bacteria and toxins

Signaling processes

NF-κB activation

Se [16]

COX-2
5-LO

Adhesion molecules

Neutrophil infiltration + activation

Prostaglandins
Leukotrienes
Thromboxanes

ROS

Endothelial injury

Capillary leakage

Tissue damage

Death

Se [16]

Se [17]

Se [13]

Where does selenium intervene in the process of sepsis?

Fig. 4

Effect of selenium

Selenium-supplementatum [References]
Which effect does ROS production have on survival?

Huet et al. conducted a trial investigating the extent to which the production of reactive oxygen species (ROS) correlates with the severity of septic shock [2]. For this purpose, naive human umbilical vein endothelial cells (HUVEC) were treated with plasma collected from 21 patients with septic shock and the induced ROS production was quantified. Compared to controls, the plasma-induced ROS production by HUVEC was significantly higher in septic shock and ROS production significantly correlated with the SAPS II score ($p = 0.028$) and the SOFA score ($p = 0.0012$). Moreover, ROS production in non-survivors was significantly higher compared to survivors ($p = 0.0015$) (Fig. 5). These results demonstrate that an early reduction of ROS production, as it can be achieved by application of selenase®, can increase the chance of survival of septic patients.

Why does the selenium status decline in patients with sepsis?

Clinical sepsis is associated with a significant decrease in selenium level [3, 4]. Lipopolysaccharides (LPS) are key players in the development of sepsis. These toxic compounds are produced when attacking bacteria divide, but also when antibiotics actively attack pathogens. An injection of LPS in rats induces an acute-phase response and leads to significantly reduced serum and liver selenium values [4]. Several recent trials have been able to elucidate some of the underlying mechanisms. It was demonstrated that an LPS-induced acute-phase response leads to a reduction in selenoprotein biosynthesis in the liver [5]. The liver is the main location of biosynthesis of selenoprotein P, which is released into the plasma and transports selenium to other tissues. The human selenoprotein P promoter is negatively regulated by pro-inflammatory cytokines in human hepatocytes [6].

In sepsis, a pathogenic cycle may be triggered in which selenoprotein P synthesis in the liver is diminished by sepsis and inflammatory cytokines. This lowers selenium status in other tissues as well, increasing oxidative stress which further amplifies the inflammatory response (Fig. 6). For the immune system, this means that a low selenium status not only diminishes the transport capacity of the lymphocytes and the cells of the innate immune system, but also leads to stress-induced lymphopenia [7].
Fig. 5  Significant difference in ROS production in surviving and non-surviving patients ($p = 0.0015$). [2]

Fig. 6  Cyclic reduction of selenium level in sepsis and intervention of selenium supplementation in this cycle. [8]

- Sepsis or LPS-treatment
- Loss of circulating selenium-containing proteins via leaky vessels
- Increased oxidative stress
- Liver downregulates Selenoprotein P expression
- Secretion of IL-6 and TNFα
- Decreased Selenium transport to tissues
- Decreased Selenium transport to tissues
- Pathogenic cycle of stress-induced immune suppression
- Selenium supplementation
Why is early administration of sodium selenite crucial (within ≤ 6 hours)?

Levy et al. demonstrated that oxidation of cytochrome c by myocardial cytochrome c oxidase is completely inhibited early in sepsis. Myocardial cytochrome c oxidase is the terminal oxidase in the electron transport chain [9]. This oxidative stress in mitochondria leads to mitochondrial dysfunction and is irreversible after 48 hours after the onset of tissue hypoxia (Fig. 7). Irreversible inhibition disrupts oxidative phosphorylation, which leads to sepsis-associated cardiac depression. For an effective antioxidant strategy, selenium must be administered as soon as possible after onset of sepsis.

In a phase I dose-escalating clinical trial, it was shown that the glutathione concentration was not decreased by increasing selenium dose in severely ill patients (p = 0.03) [10]. Furthermore, an increasing selenium dose decreased the concentrations of thiobarbituric acid reactive substances (TBARS) significantly (p = 0.03) and thus lowered oxidative stress. Motoyama et al. showed that increasing TBARS concentrations in sepsis patients correlated with a higher SOFA score (p < 0.001) [11]. Plasma TBARS concentration was significantly higher in sepsis patients with multi organ failure (MOF) than in patients without MOF (57.1% vs. 15.8%, p <0.001). Analysis of the ratio of mitochondrial DNA as an indirect marker of mitochondria function showed, that the function of mitochondrias improved with increasing selenium dosage (p = 0.001) (Fig. 8) [10].
Only a high selenium dosage improves mitochondrial function, reduces oxidative stress and increases antioxidative capacity in sepsis. [10]

Fig. 7
Irreversible inhibition of the cytochrome c oxidase after 48 hours in severe sepsis. [9, 10, x]

0h
competitive inhibition of cytochrome c oxidase

6h
antioxidant concentration ↓
ROS ↑
oxidation of mitochondrial DNA

24h
non-competitive inhibition of cytochrome c oxidase
irreversible mitochondrial damage

48h
organ failure

Why inject sodium selenite as bolus?

The effect of a bolus injection of 2,000 µg selenium as sodium selenite pentahydrate was compared to a continuous infusion of 4 µg/kg per hour in an experimental animal model for sepsis in sheep [12]. Only the bolus showed a positive effect on sepsis progression, although the overall dosage was comparable. The likely explanation for this is an early transient pro-oxidative effect of sodium selenite, that can be used as therapeutic strategy to reverse the pro-inflammatory state existing in severe sepsis and septic shock. This excessive pro-inflammatory state is characterized by high levels of circulating cytokines and ROS, phagocytic hyperactivity of leucocytes due to delayed apoptosis, and a prolonged NFkB activation.

A bolus injection in the early phase of septic shock inhibits NF-κB binding to DNA via stabilization of disulfide bonds. This regulates gene expression and synthesis of pro-inflammatory cytokines [13]. Additionally a bolus administration induces apoptosis and cytotoxicity in activated, pro-inflammatory cells along with a direct virucidal or bactericidal effect [14, 15].

High dose for sepsis – so that selenium works

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Treatment ideally begins within 6 hours after admission to the ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>as bolus</td>
<td>2,000&lt;sup&gt;1-3&lt;/sup&gt; µg Se</td>
</tr>
<tr>
<td>then as continuous infusion</td>
<td>1,600&lt;sup&gt;1-3&lt;/sup&gt; µg Se</td>
</tr>
<tr>
<td>at least 7 days</td>
<td>maintenance therapy</td>
</tr>
<tr>
<td></td>
<td>1,600&lt;sup&gt;1-3&lt;/sup&gt; µg Se / Day</td>
</tr>
</tbody>
</table>

1 Manzanares W et al. 2012, Crit Care; 16:R66
2 Huang TS et al. 2013, PLoS One 8:e54431
3 Alhazzani W et al. 2013, Crit Care Med 41:1555–1564
# selenase® for sepsis

<table>
<thead>
<tr>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Supplementation with sodium selenite increases the selenium level to values within the normal range</td>
</tr>
<tr>
<td>• Significant reduction in mortality in the selenium-supplemented group</td>
</tr>
<tr>
<td>• Possible correlation between selenium supplementation and procalcitonin [4]</td>
</tr>
<tr>
<td>• Supplementation with high-dose sodium selenite reduces the incidence of nosocomial pneumonia and improves sepsis severity</td>
</tr>
</tbody>
</table>
### Meta analysis

Parenteral sodium selenite treatment significantly reduces total mortality rate by 17% (p = 0.04)

Higher significant reduction of mortality when a bolus is administered (− 27%; p = 0.01), a maintenance therapy ≥ 7 days (− 23%; p = 0.01) and a dosing of ≥ 1,000 µg selenium as sodium selenite-pentahydrate (selenase®) per day (− 23%; p = 0.04)

### Pilot study

Supplementation with selenase® increases the selenium level to values within the normal range

Selenase® supplementation significantly reduces mortality in patients with APACHE III score > 53

### SIC trial

Significant reduction in mortality in the selenase®-supplemented group by 14.3% (p = 0.049)

Significant reduction in mortality in the subgroups (septic shock, APACHE III ≥ 102, > 3 organ failure) in the selenase®-supplemented group by up to 26%

### Various trials

Possible correlation between selenase® supplementation and procalcitonin

Supplementation with high-dose sodium selenite reduces the incidence of nosocomial pneumonia and improves sepsis severity

SIGNET trial: Fewer new infections in patients receiving selenase® supplementation for > 5 days

REDOXS trial: Compared to glutamine, selenium does not have any negative effect on mortality, although the beneficial effect of selenium supplementation is reduced by the lack of selenium deficiency

Significantly more critically ill patients in the intervention group impacted the analysis of the retrospective trial on selenium supplementation in patients with severe sepsis
Meta analysis of 9 sepsis trials
With correct application, sodium selenite significantly reduces mortality.

<table>
<thead>
<tr>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A large-bolus injection significantly reduced mortality in sepsis patients by 27%</td>
</tr>
<tr>
<td>• Maintenance therapy lasting ≥ 7 days significantly improved the probability of survival</td>
</tr>
<tr>
<td>• A high dose of ≥ 1,000 µg selenium in the form of sodium selenite pentahydrate (selenase®) per day significantly reduced mortality by 23%</td>
</tr>
</tbody>
</table>

Parenteral sodium selenite treatment significantly reduces total mortality by 17% (p = 0.04).

Twelve trials were included in the meta analysis, whereby the meta analysis was carried out in nine of these (Table 1) [3]. In total, 965 patients took part in the nine studies; 482 participants received a sodium selenite supplementation and 483 a placebo. A total of 148 patients (30.7%) died in the intervention group, while 180 participants (37.3%) died in the placebo group. The mortality varied greatly between the studies, from 24% to 52%. Also the administration scheme differed considerably, both with respect to the duration and dose as well as the strategy. The use of sodium selenite was uniform as the only approved selenium form for the drug product, whereby more than half of the trials were carried out with selenase®. All trials had a low risk of “detection bias”, since mortality was defined as the result. In addition, most trials had a low risk of “attrition bias” e.g. protocol noncompliance.

In total, the meta analysis shows that a parenteral sodium selenite supplementation significantly reduces total mortality (RR 0.83, 95% CI 0.70–0.99; p = 0.04).
<table>
<thead>
<tr>
<th>Tab. 1</th>
<th>Included trials</th>
</tr>
</thead>
</table>

selenase®: Studies were carried out with selenase®
Positive significant impact of selenium as sodium selenite on total mortality in the event of sepsis. [changed according to 1]

At ICU-admission (< 6 h):
Bolus: 2,000 µg Se as sodium selenite
▶ Mortality rate ↓
(RR 0.73; p = 0.01) [3]

Early death
overwhelming immune response

Minimum 5 days Se as sodium selenite
▶ New infections ↓
(RR 0.53; p = 0.03) [2]

1,600 µg Se as sodium selenite per day

Bolus 2,000 µg Se as sodium selenite

At ICU-admission (< 6 h):
Bolus: 2,000 µg Se as sodium selenite
▶ Mortality rate ↓
(RR 0.73; p = 0.01) [3]

Early death
overwhelming immune response

Minimum 5 days Se as sodium selenite
▶ New infections ↓
(RR 0.53; p = 0.03) [2]

1,600 µg Se as sodium selenite per day

Bolus 2,000 µg Se as sodium selenite

6h Day 1 Day 2 Day 3 Day 4

Immunosuppression

Immune response

Meta analysis
(9 studies, n = 965) [3] A sodium selenite supplementation significantly reduces mortality for sepsis patients (RR (relative risk) 0.83 CI (confidence interval) 0.77–0.99; p = 0.04)
Fig. 1 Positive significant impact of selenium as sodium selenite on total mortality in the event of sepsis.

<table>
<thead>
<tr>
<th>Day</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nosocomial infections</td>
<td>Day 1, 6h Bolus: 2,000 µg Se as sodium selenite</td>
</tr>
<tr>
<td>2-4</td>
<td>Day 2-4</td>
<td>Without sodium selenite supplementation</td>
</tr>
<tr>
<td>5</td>
<td>Late Death</td>
<td>Early death: Mortality rate ↓ (RR 0.73; p = 0.01) [3]</td>
</tr>
<tr>
<td>6</td>
<td>Late Death</td>
<td>Without sodium selenite supplementation</td>
</tr>
<tr>
<td>7</td>
<td>Late Death</td>
<td>Mortality rate ↓ (RR 0.77; p = 0.01) [3]</td>
</tr>
<tr>
<td>10-14</td>
<td>Survival</td>
<td>With sodium selenite supplementation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimum 7 days Se as sodium selenite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality rate ↓ (RR 0.83; CI 0.77–0.99; p = 0.04) [3]</td>
</tr>
</tbody>
</table>

Se = selenium

Survival

Without sodium selenite supplementation

With sodium selenite supplementation

**Late Death**

Impaired immunity

Nosocomial infections

Viral reactivation

Meta analysis (9 studies, n = 965) [3]
Meta analysis of 9 sepsis trials

A high-dose bolus significantly reduces mortality in sepsis patients by 27%.

A bolus in the early phase of sepsis has several effects:

1. Down-regulation of the synthesis of pro-inflammatory cytokines
2. Apoptosis and cytotoxicity in activated pro-inflammatory cells
3. Direct virucidal and bactericidal effects

These effects prevent an unchecked immune response (cytokine storm) and thus an early death from sepsis (Fig. 1).

In a comparison of the sodium selenite supplementation with a bolus to a sodium selenite therapy without a bolus, a lower mortality could be shown in the intervention group with bolus (−7%; \( p = 0.14 \)). A parenteral sodium selenite supplementation with bolus, however, reduced the total mortality with a higher significance (RR 0.73, 95% CI 0.58–0.94; \( p = 0.01 \)).

A maintenance therapy of ≥ 7 days significantly improves the probability of survival.

The impact of the duration of treatment on mortality was determined by means of uni-variant “random effects meta-regression” analysis. A statistically significant association between the relative risk of mortality and duration of treatment (Fig. 2) was thereby demonstrated. A sodium selenite supplementation of ≥ 7 days reduced total mortality by 23% (RR 0.77, 95% CI 0.63–0.94; \( p = 0.01 \)).
Fig. 2: Dependency of the relative risk (RR) on the duration of treatment [3]

Every circle represents one trial, whereby the size of the study correlates with the size of the circle. A negative effect (circle below the regression plot) stands for the reduction of the mortality rate.
Meta analysis of 9 sepsis trials
A high dosing of ≥ 1,000 µg selenium as sodium selenite-pentahydrate per day significantly reduces mortality by 23%.

In their meta analysis, Huang et al. distinguished between sodium selenite supplementation with a high selenium dose (≥ 1,000 µg/day) and a low dose (< 1,000 µg/day). A dosing of ≥ 1,000 µg selenium per day significantly reduced the total mortality (RR 0.77, 95% CI 0.61–0.99; p = 0.04). In a comparison of several sepsis trials, Manzanares et al. could show that only a high sodium selenite supplementation (2,000 µg bolus (day 1) and 1,600 µg/day selenium (day 2 – 10)) suffices to elevate serum selenium concentration into the low reference range or to increase the activity of glutathione peroxidase 3 to a physiological level (Fig. 3) [4]. A low sodium selenite therapy (1,200 µg bolus (day 1) and 800 µg/day (day 2 – 10)) is neither in the position to sufficiently increase the serum selenium concentration nor to sufficiently influence the activity of glutathione peroxidase 3 (Fig. 4).

![Development of the serum selenium concentration for high and low-dosed sodium selenite supplementation](image-url)
Figure 4: Increase of glutathione peroxidase 3 activity to a physiological level takes place only with a high-dose sodium selenite supplementation \cite{4}.

![Graph showing the increase of GPx-3 activity over time with low-dosed and high-dosed sodium selenite.]
Pilot study

Supplementation with selenase® increases the selenium level to values within the normal range

A controlled, randomized, prospective, open-label pilot trial analyzed the effects of selenase® supplementation in SIRS patients [1]. The selenase®-supplemented group (n = 21) received descending doses of selenase® of 535 µg selenium per day for 3 days, 285 µg selenium per day for 3 days, 155 µg selenium per day for 3 days, and 35 µg selenium per day thereafter. The control group (n = 21) received 35 µg/day selenium during the entire treatment period.

The serum selenium concentrations were below the defined reference value for selenium in Germany (80 µg/l selenium in serum) at admission to the ICU. Glutathione peroxidase activity was also significantly too low. While the serum selenium levels in the control group did not change over the observation period, the serum selenium concentration increased in the normal range from day 3 in the selenase®-supplemented group (Fig. 5).

The data show that SIRS patients need a selenium dose > 500 µg to reach normal range and that 155 µg selenium per day is not sufficient to maintain a low normal level already achieved.
Significant increase in serum selenium concentration in the selenase®-supplemented group in the reference range. [6]
Pilot study
Supplementation with selenase® improves clinical outcomes in SIRS patients

In both groups, the baseline APACHE III score was the same and decreased during their ICU stay. However, the APACHE III score in the selenase®-supplemented group improved significantly more pronounced (day 7: p = 0.019; day 14: p = 0.041). Moreover, only 12% of the patients in the selenase®-supplemented group but 42% in the control group had a higher APACHE III score on day 14 compared to ICU admission (p < 0.05).

Mortality at discharge from the hospital was 33.4% in the selenase®-supplemented group and 52.4% in the control group (p = 0.135) (Fig. 6). A comparison of patients with an APACHE III score > 53 highlights the beneficial effect of selenase® on mortality rate. Although the patient population in this subgroup analysis was reduced to 20 (selenase®-supplemented group (n = 11) and control group (n = 9)), there was a significant decrease in mortality in the selenase®-supplemented group (4 of 11 patients (36%)) versus the control group (8 of 9 patients (89%)) (p = 0.0053) (Fig. 7).
Intention-to-treat analysis of survival time in the selenase®-supplemented group (n = 21) and control group (n = 21). [5]

![Fig. 6](image1)

Intention-to-treat analysis of survival time in patients with an APACHE III score > 53 (selenase®-supplemented group (n = 11) and control group (n = 9)). [5]

![Fig. 7](image2)
SIC trial (Selenium in Intensive Care)
Phase III trial with selenase®

A prospective, randomized, double-blind, multicenter phase III trial conducted at 11 intensive care units in Germany, analyzed whether the results obtained in the pilot study were reproducible in a phase III trial [2]. Overall, 249 patients with SIRS, sepsis, septic shock and an APACHE III score > 70 were randomized. The selenase® doses administered were increased to a 30-minute bolus infusion of 1,000 µg selenium, followed by 1,000 µg/day selenium as a continuous infusion for 14 days. In the placebo group, a dose of up to 100 µg/day selenium was allowed with the parenteral nutrition.

Eleven of the 249 randomized patients were excluded for various reasons. Thus, the intention-to-treat analysis included 238 patients (Fig. 8). Another 49 of these 238 patients had to be excluded further for the per-protocol analysis either because inclusion criteria were not met (n = 14) or due to severe violations of the trial protocol (n = 35). Therefore, the per-protocol analysis only covered 189 patients, 92 in the selenase®-treated group and 97 in the placebo group.
Study profile of the SIC trial. [6]

Randomized patients
N=249

- 5 consent withdrawn
- 1 suicide
- 2 lost for follow up
- 1 non-compliant
- 2 termination of treatment

Intention-to-treat analysis
N=238

- 14 ex/inclusion criteria failure
- 30 trial drug administration failure
- 5 additional selenium substitutions
  > 100 µg/day

selenase®-supplemented
group
N=116

Per-Protocol analysis
N=189

Placebo group
N=122

selenase®-supplemented
group
N=92

Placebo group
N=97
The SIC trial also showed that selenium values at ICU admission were very low (Table 2). The selenium concentration increased significantly in the selenase®-supplemented group only ($p < 0.001$). Despite high-dose daily selenase® supplementation, the median selenium values only increased to 161.9 µg/l selenium in the serum and 144.5 µg/l selenium in whole blood on the last day (day 14) of selenase® supplementation. After completing the intervention, the selenium level decreased markedly within a week (Fig. 9). In the trial, no specific adverse reactions were attributed to supplementation with high-dose selenase®. Overall, there was no significant difference in the adverse reactions in the intervention group (90.2%) and the placebo group (96%).

The positive effect of selenase® supplementation showed in both the selenium concentration in blood and the glutathione peroxidase activity. Both parameters increased from suboptimal baseline values during intervention and decreased again significantly after ending the selenase® supplementation (Fig. 9). The curve characteristics reveals, that an optimal selenium supply during and after sepsis is not sufficient, when a selenium dosage, as is currently used in parenteral nutrition respectively normal nutrition, is applied. Simultaneously the increase in glutathione peroxidase activity during intervention with 1,000 µg selenium as selenase® shows that a daily selenium intake of 100 µg in sepsis patients does not result in a plateau of selenoprotein activity, but increases till ending of intervention. After selenase® supplementation the glutathione peroxidase activity decreased again, though the patients still received up to 100 µg selenium with parenteral nutrition.

### Tab. 2 Comparison of selenium concentration in the selenase®-supplemented versus the placebo group $p < 0.001$. [2]

<table>
<thead>
<tr>
<th></th>
<th>selenase®-supplemented group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum selenium concentration at ICU admission in all randomized patients ($n = 249$)</td>
<td>37.9 ± 18.2 µg/l</td>
<td>36.3 ± 12.6 µg/l</td>
</tr>
<tr>
<td>Selenium concentration in whole blood at ICU admission in all randomized patients ($n = 249$)</td>
<td>58.4 ± 17.4 µg/l</td>
<td>58.4 ± 12.6 µg/l</td>
</tr>
<tr>
<td>Serum selenium concentration at ICU admission in patients included in the per-protocol analysis ($n = 189$)</td>
<td>37.9 µg/l</td>
<td>35.5 µg/l</td>
</tr>
<tr>
<td>Serum selenium concentration after 14 days</td>
<td>161.9 µg/l</td>
<td>47.4 µg/l</td>
</tr>
<tr>
<td>Selenium concentration in whole blood after 14 days</td>
<td>144.5 µg/l</td>
<td>64.0 µg/l</td>
</tr>
</tbody>
</table>
Development of selenium concentration and glutathione peroxidase activity during and after selenase® supplementation. [6]

---

SIC trial
Significant reduction in mortality in the selenase®-supplemented group

In the intention-to-treat analysis (n = 238), 46 of 116 patients in the selenase®-supplemented group died and 61 of 122 in the placebo group. Thus, selenase® supplementation reduced mortality non-significantly by 10.3% (p = 0.109; OR, 0.66; 95% CI, 0.39–1.10) (Fig. 10). Mean overall survival increased from 17.6 days in the placebo group to 20.3 days in the intervention group (p = 0.098) (Fig. 11).

As previously mentioned in the SIC trial description, 49 patients were excluded from the per-protocol analysis. Either the inclusion criteria were not met (n = 14) or severe violations of the trial protocol occurred (n = 35). Therefore, the per-protocol analysis only covered 189 patients, 92 in the selenase®-treated group and 97 in the placebo group.

In the per-protocol analysis, 28-days mortality decreased significantly from 56.7% to 42.4% in the selenase®-supplemented group (p = 0.049; OR, 0.56; CI, 0.32–1.00) (Fig. 12). Mean overall survival increased from 16.4 days in the placebo group to 19.7 days in the intervention group (p = 0.048) (Fig. 13).
**Fig. 11** Survival time in the intention-to-treat analysis. [6]

Survival %

<table>
<thead>
<tr>
<th>Days</th>
<th>Placebo ≤ 100 µg Se/day</th>
<th>selenase® ≥ 1,000 µg Se/day</th>
<th>n = 116</th>
<th>n = 122</th>
<th>p = 0.098</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>75</td>
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<tr>
<td>14</td>
<td>50</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>21</td>
<td>25</td>
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<tr>
<td>28</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 13** Survival time in the per-protocol analysis. [6]

Survival %

<table>
<thead>
<tr>
<th>Days</th>
<th>Placebo ≤ 100 µg Se/day</th>
<th>selenase® ≥ 1,000 µg Se/day</th>
<th>n = 92</th>
<th>n = 97</th>
<th>p = 0.048</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
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<td>7</td>
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<tr>
<td>28</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**SIC trial**

**Significant reduction in mortality in the subgroups of the selenase®-supplemented group**

The trial plan had already included a subgroup analysis. Patients with an APACHE III score > 102 (n = 27 in each group) benefited even more from a selenase® supplementation (Fig. 14). 28-days mortality decreased in this subgroup by 25.9% from 81.5% to 55.6% (p = 0.04; OR, 0.28; 95% CI, 0.09–0.97). In patients with septic shock, 28-days mortality decreased by 26.2% from 66.7% in the placebo group (30 of 45) to 40.5% in the selenase®-supplemented group (15 of 37 patients) (p = 0.018; OR, 0.34; 95% CI, 0.14–0.84). In patients with more than triple organ failure, 28-days mortality decreased by 22.6% in the comparison between the intervention group (42.5%; 17 of 40 patients) and the placebo group (65.1%; 28 of 43 patients) (p = 0.039; OR, 0.40; 95% CI 0.16–0.96).

The subgroup analysis highlights the fact, that the beneficial effect by selenase® supplementation increases with sepsis severity.

**SÉRÉNITÉ trial**

**Comparison of SIC and SÉRÉNITÉ trials**

Like SIC, the SÉRÉNITÉ trial was a prospective, randomized, double-blind, multicenter trial conducted in France. However, this trial only included a total of 60 patients, i.e. a quarter of the number in the SIC trial [7]. The study included only patients with severe septic shock. While the SIC trial enrolled patients within 6 hours after ICU admission and administered a bolus infusion directly after trial enrollment, 90% of the patients in the SÉRÉNITÉ trial were enrolled within 48 hours of ICU admission. Furthermore, a bolus was not given. Instead, 4,000 µg selenium were administered as a continuous infusion. The significance of a bolus

---

### Fig. 14

**Considerably reduced 28-days mortality in the selenase®-supplemented group across the predefined subgroups in the SIC trial.** [6]

<table>
<thead>
<tr>
<th>Reduction in mortality</th>
<th>NNT (Number needed to treat)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIC trial total</strong></td>
<td>- 14.3% (p = 0.049)</td>
</tr>
<tr>
<td><strong>Defined subgroups:</strong></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>- 26.2% (p = 0.018)</td>
</tr>
<tr>
<td>APACHE III &gt; 102</td>
<td>- 25.9% (p = 0.040)</td>
</tr>
<tr>
<td>&gt; 3 organ failure</td>
<td>- 22.6% (p = 0.039)</td>
</tr>
</tbody>
</table>
consists of improving the selenium status of the sepsis patient as early and as rapidly as possible. This enables the body to fight oxidative stress, and to have an anti-inflammatory effect. The considerably later and slower administration of sodium selenite was not able to compensate the resulting damage even though twice the amount of sodium selenite was used. In the SÉRÉNITÉ trial, the selenium value was not measured at ICU admission nor over the course of the study. Therefore, it is not possible to verify the patients’ selenium concentration at ICU admission. Since many studies have shown that the selenium value at ICU admission is inversely correlated with mortality, the question arises as to whether the patient cohort in the SÉRÉNITÉ trial was more severely ill than in the SIC trial. Another difference was the shorter daily selenium supplementation given for 9 versus 14 days. Here, as well, there is no way to verify which effect the shorter selenium supplementation had on the selenium value; whether the selenium concentration decreased below reference range after the intervention ended, respectively to which degree. In view of these differences, it is no surprise that a reduction in mortality was lacking in the selenium-supplemented group (Fig. 15).

In the SÉRÉNITÉ trial, no adverse reactions were attributed to selenium. This is particularly noteworthy because 4,000 µg selenium were given on day 1, without any adverse effects on the patients.

Fig. 15 Mortality in the SÉRÉNITÉ trial in the sodium selenite-supplemented and placebo group. [7]

![Mortality in the SÉRÉNITÉ trial in the sodium selenite-supplemented and placebo group.](image-url)
Valenta et al., 2011

Evidence of a correlation between selenase® supplementation and procalcitonin (PCT)

The trial by Valenta et al. in 2011, produced another interesting result [8]. This prospective, randomized, open-label, single-centre clinical trial enrolled 150 patients with SIRS/sepsis and a SOFA score of >5. 75 patients were supplemented with 1,000 µg selenium (selenase®) on day 1 and 500 µg on days 2 – 14, administered as a 30-minute infusion in the morning. Patients in both, the intervention group and the control group received a standard dose of < 75 µg/day selenium with their parenteral nutrition.

This trial also revealed 3 effects of selenase® supplementation:

- In the intervention group, the selenium value and the glutathione peroxidase activity increased from a very low baseline value in the reference range as compared to the control group (Fig. 16).
- Patients in both groups surviving 28 days showed a trend for a higher serum selenium level compared to non-survivors (59.2 ± 45.7 vs. 56.1 ± 44.2 µg/l; p = 0.068).
- Despite the high-dose selenase® supplementation, no specific adverse reactions or toxic effects occurred. Only 17 of the 799 serum selenium samples taken from 9 patients in the intervention group showed selenium values above the reference range (163.4 ± 14.2 µg/l, reference range 80 – 120 µg/l). All 9 patients survived.

This trial also showed a negative correlation between serum selenium level and several inflammatory markers and sepsis severity at ICU admission (Table 3).
**Fig. 16** Development of serum selenium concentration during selenase\textsuperscript{®} supplementation compared to the control group. \[8\]

<table>
<thead>
<tr>
<th>Days</th>
<th>Serum selenium concentration [μg/l]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>14</td>
<td>120</td>
</tr>
</tbody>
</table>

Reference range

- p < 0.001

**Tab. 3** Negative correlation between the serum selenium level at ICU admission, inflammatory markers and sepsis severity. \[8\]

<table>
<thead>
<tr>
<th></th>
<th>r-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procalcitonin (PCT)</td>
<td>-0.172</td>
<td>0.035</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>-0.187</td>
<td>0.022</td>
</tr>
<tr>
<td>SOFA score</td>
<td>-0.277</td>
<td>0.001</td>
</tr>
</tbody>
</table>
The trial showed no significant difference in 28-days mortality between intervention vs. control group (25.3% vs. 32%; \( p = 0.367 \)). A subgroup analysis produced a trend to a lower mortality in the selenase\textsuperscript{®}-supplemented group for patients with APACHE II score > 28 (32.6% vs. 51.6%; \( p = 0.100 \)).

However, Valenta et al. made an interesting discovery in this trial. The comparison of PCT and CRP values between the intervention and the placebo group showed a decrease of both values independently of selenase\textsuperscript{®} supplementation over the course of the 14 days observation period. But the reduction in the intervention group was more pronounced. For PCT, the difference between the selenase\textsuperscript{®}-supplemented group and the control group on day 7 was even significant (Fig. 17). These data suggest a biological interaction between selenium and PCT.
Significantly greater decrease in PCT in the selenase®-supplemented group. There was no significant difference, despite the difference in PCT values between the two groups on day 0 ($p = 0.108$). [8]
Supplementation with high-dose sodium selenite reduces the incidence of nosocomial pneumonia and improves sepsis severity

This placebo-controlled, randomized prospective, single-blind phase II trial enrolled 35 patients with SIRS and APACHE II scores of ≥ 15 \(^9\). The intervention group received a bolus of 2,000 µg selenium and 1,600 µg/day for another 10 days. Both groups received an average of 77 respectively 73 µg/day selenium enterally.

In the sodium selenite-supplemented group, the incidence of early ventilator-associated pneumonia was significantly reduced by 31\% (p = 0.04) (Fig. 18). The incidence of nosocomial pneumonia was also reduced in the intervention group by 19\% (p = 0.03). The authors attributed this beneficial effect to the administered large bolus, because all three effects of a bolus administration can influence the development of early ventilator-associated pneumonia.

Early ventilator-associated pneumonia in the ICU is a major cause of morbidity, mortality and costs. A reduction in the incidence of early ventilator-associated pneumonia via sodium selenite might make an important contribution.

Furthermore, the SOFA score was reduced in the sodium selenite-supplemented group versus the placebo group on day 10 (p = 0.0001). While the SOFA score in the intervention group continued to significantly decline from day 3 to day 10, the SOFA score in the placebo group remained virtually the same (Fig. 19).
Sodium selenite reduced the probability for a patient to acquire nosocomial pneumonia. \[9\]

![Graph showing probability of remaining free of hospital-acquired pneumonia within the first 28 days for sodium selenite and placebo.](image)

Sodium selenite significantly improved sepsis severity based on the SOFA value \((p = 0.0001)\). \[9\]

![Graph showing SOFA score means for placebo and sodium selenite.](image)
SIGNET trial
Fewer new infections in patients receiving selenase® supplementation for > 5 days

The SIGNET trial was a randomized, double-blinded, factorial, controlled multicenter trial with 502 participants [6]. Because of the factorial design, the patients were randomized to the following study arms: Placebo group (n = 125) parenteral nutrition containing standard formulation; selenase® group (n = 127) standard formulation with addition of 500 µg selenium; glutamine group (n = 126) formulation including 20.2 g glutamine; selenase® + glutamine group (n = 125) formulation with addition of 500 µg selenium and 20.2 g glutamine.

Only 56% of the patients had sepsis. The selenase®-supplemented group showed a decreased rate of new infections by 5% (p = 0.24) in contrast to glutamine supplementation. selenase® supplementation significantly reduced new infections in patients who received intervention for ≥5 days by 13% (p = 0.03) (Fig. 20).
At least 5 days selenase® supplementation significantly reduced new infections. [10]
**REDOXS trial**

Compared to glutamine, selenium did not have any negative effect on mortality, although the beneficial effect of selenium supplementation was reduced by the lack of selenium deficiency

The REDOXS trial was a randomized, controlled, double-blind, 2x2 factorial, multicenter trial with 1,223 severely ill patients with multiple organ failure [11]. Within 24 hours after ICU admission, the patients received either glutamine, antioxidants (including 500 µg selenium as selenase®), both or placebo for a maximum of 28 days (Table 4).

Only in 31% of patients the primary diagnosis was sepsis at ICU admission. Compared to other sepsis trials, the selenium value at ICU admission was not outside the normal range in any of the 66 analyzed trial patients. It is not known whether these patients were sepsis patients. However, the median serum selenium level at 86 µg/l in the antioxidant group and 80 µg/l in the non-antioxidant group was far above the means in sepsis patients at 30 – 40 µg/l selenium in the serum. The aforementioned sepsis trials were exclusively conducted in Europe where the average selenium level in the population is clearly below the reference range of 80 µg/l selenium in the serum.

The REDOXS trial was conducted both in Canada, the USA and Europe. Both in Canada and the USA, the selenium status is markedly above the reference range of 80 µg/l.

In the antioxidant group, the selenium value in the serum increased significantly (p < 0.001), whereas the selenium status in the non-antioxidant group only showed a slight increase (Table 5). Despite the significant increase in selenium concentration, the authors reported that the median selenium level in both groups remained within the normal range at all measurement time points.

Supplementation with antioxidants had no effect on 28-days mortality (30.8% vs. 28.8%; p = 0.48). In addition to the above-mentioned restrictions in the REDOXS trial, the positive effect of selenium might have been negated by the late initiation of supplementation with antioxidants, the too low selenium dose and the interaction of vitamin C with selenium due to its concurrent administration.
### Tab. 4
**Trial arms in the REDOXS trial.** [11]

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Number</th>
<th>Supplementation</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Glutamine (Gln)</td>
<td>303</td>
<td>0.5 g Gln/kg body weight</td>
<td>Parenteral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 g Gln</td>
<td>Enteral</td>
</tr>
<tr>
<td>2. Antioxidants (AOX)</td>
<td>308</td>
<td>500 µg selenium as selenase®</td>
<td>Parenteral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 µg selenium, 20 mg zinc, 500 mg vitamin E, 10 mg beta-carotene, 1,500 mg vitamin C</td>
<td>Enteral</td>
</tr>
<tr>
<td>3. Gln + AOX</td>
<td>310</td>
<td>1 + 2</td>
<td></td>
</tr>
<tr>
<td>4. Placebo</td>
<td>302</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

### Tab. 5
**Increase in serum selenium value in the antioxidant group.** [11]

<table>
<thead>
<tr>
<th></th>
<th>Antioxidants</th>
<th>No antioxidants</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>median [Q1, Q3] (µg/l)</td>
<td>n</td>
</tr>
<tr>
<td>ICU day 1</td>
<td>31</td>
<td>86 (71 – 98)</td>
<td>30</td>
</tr>
<tr>
<td>ICU day 4</td>
<td>28</td>
<td>142 (137 – 164)</td>
<td>26</td>
</tr>
<tr>
<td>ICU day 7</td>
<td>25</td>
<td>156 (134 – 174)</td>
<td>19</td>
</tr>
</tbody>
</table>
Sakr et al., 2014
Doctors give selenase® primarily severely ill patients

In a large retrospective study conducted in 2014, Sakr et al. analyzed the effect of a selenium supplementation in 1,047 patients with severe sepsis treated over a period of more than 6 years in a surgical ICU \[12\]. Due to the retrospective nature of the study, the selenium-supplemented group had only 413 (39%) patients. The control group received 100 µg/day selenium and selenium-supplemented group received a bolus of 1,000 µg selenium (selenase®) and 1,000 µg/day selenium (selenase®) for a maximum of 14 days. The median duration of adjuvant selenium therapy was 8 days (IQR = 4 – 12). The two groups presented with significantly different patient characteristics. Particularly, the higher SAPS II score (50.8 vs. 47.7, \( p = 0.001 \)) and the higher proportion of patients with cancer (32.4% vs. 24.6%; \( p = 0.005 \)) may have affected the study analysis. This is also evident in the parameters measured to test inflammation and organ function (C-reactive protein, PCT, blood lactate) (Table 6).

Do surgical sepsis patients need a different (higher) dosage than medical sepsis patients?

It is known that, among other things, a surgical intervention triggers oxidative stress which significantly heightens the body’s selenium consumption during and after surgery. It can therefore be assumed that, to achieve the same beneficial effect, surgical sepsis patients require higher selenium doses than medical sepsis patients. As trials on selenium supplementation in cardiac surgery have shown, without selenium supplementation surgery causes the selenium concentration to decrease by around one quarter of the baseline value. In this study, the fact that no selenium levels were measured or stated makes it impossible to draw conclusions as to whether selenium concentration at ICU admission in surgical sepsis patients was lower than in medical sepsis patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control group</th>
<th>Selenium group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II</td>
<td>47.7 ± 17</td>
<td>50.8 ± 17.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>24.6%</td>
<td>32.4%</td>
<td>0.005</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>78 (13 – 193)</td>
<td>146 (46 – 235)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>2.3 (0.7 – 7.2)</td>
<td>3.7 (0.9 – 12.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Blood lactate</td>
<td>2.5 (1.6 – 5.3)</td>
<td>2.9 (1.7 – 5.6)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Tab. 6 Significantly different patient characteristics in the selenium and control group. \[12\]
|---|---|
Significantly more critically ill patients in the intervention group impacted the analysis of the retrospective trial on selenium supplementation in patients with severe sepsis

In this retrospective study, overall ICU mortality was 31.3% and hospital mortality 41.8%. Whereas the ICU mortality did not significantly differ in the two groups (29.5% vs. 33.9%; p = 0.135), the selenium supplemented group displayed a higher hospital mortality (39.15% vs. 46%; p = 0.027). Both the ICU and hospital stays were significantly longer in the intervention group (p = 0.01 and p = 0.001, respectively). However, a multivariate analysis showed, that adjuvant selenium therapy was not independently associated with worse hospital mortality (OR = 1.19, 95% CI = 0.86–1.65; p = 0.288). The multivariate analysis included age, gender, SAPS II score, surgery type, co-morbidities, focus on sepsis, SOFA sub-scores and blood lactate levels.

The authors themselves point out, that the higher hospital mortality and the longer ICU and hospital stays are attributable to the significantly higher number of severely ill patients in the selenium-supplemented group. Furthermore, the authors also point out that unlike early trials, in which the proportion of surgical patients fluctuated between 13% and 40%, their study contained 100% surgical cases (Fig. 21).
Percentage of medical and surgical sepsis patients in different sepsis trials. [5–8, 10]
## Overview of trials

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Number of patients</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angstwurm et al. (1999) controlled, randomized, prospective, open-label</td>
<td>N (selenase®) = 21 N (control) = 21</td>
<td>Intervention group (selenase®): 535 µg/day selenium for 3 days, 285 µg/day selenium for 3 days, 155 µg/day selenium for 3 days and 35 µg/day selenium thereafter Placebo group: 35 µg/day selenium</td>
</tr>
<tr>
<td>pilot trial (single center)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angstwurm et al. (2007) Prospective, randomized, double-blind, multicenter</td>
<td>N (selenase®) = 92 N (placebo) = 97</td>
<td>Intervention group (selenase®): Bolus: 1,000 µg 1,000 µg/day selenium as selenase® for 14 days Placebo group: &lt; 100 µg/day selenium</td>
</tr>
<tr>
<td>phase III trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forceville et al. (2007) prospective, randomized, double-blind, multicenter</td>
<td>N (sodium selenite) = 31 N (placebo) = 29</td>
<td>Intervention group: Bolus: 4,000 µg selenium 1,000 µg/day selenium for 9 days</td>
</tr>
<tr>
<td>trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valenta et al. (2011) Prospective, randomized, open-label trial (single</td>
<td>N (selenase®) = 75 N (control) = 75</td>
<td>Intervention group: 1,000 µg selenium as selenase® on day 1 500 µg/day selenium as selenase® for 14 days Control group: &lt; 75 µg/day selenium</td>
</tr>
<tr>
<td>center)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manzanares et al. (2011) placebo-controlled, randomized, prospective,</td>
<td>N (sodium selenite) = 15 N (placebo) = 16</td>
<td>Intervention group: Bolus: 2,000 µg selenium 1,600 µg/day selenium for 10 days Placebo group: 73 ± 16 µg/day selenium</td>
</tr>
<tr>
<td>single-blinded, phase II trial (single center)</td>
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<td></td>
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</tbody>
</table>
### Trial design

**Number of patients**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>N (selenase®)</th>
<th>N (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group (selenase®):</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Placebo group:</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

**Intervention**

- Intervention group (selenase®):
  - 535 µg/day selenium for 3 days,
  - 285 µg/day selenium for 3 days,
  - 155 µg/day selenium for 3 days
  - 35 µg/day selenium thereafter
- Placebo group:
  - 35 µg/day selenium

**Result**

- Selenium level at ICU admission markedly below normal
  - Intervention group (selenase®):
    - Selenium level ↑ (p = 0.003)
    - APACHE III score ↓ (p = 0.041)
    - Mortality ↓ (-19%; p = 0.135)
  - Patients with APACHE III > 53:
    - Mortality (at hospital discharge) ↓ (-53%; p = 0.0053)
    - No adverse reactions from selenase®
    - No toxic symptoms
- Selenium level at ICU admission markedly below normal
  - Intervention group (selenase®):
    - 28-days mortality ↓ (-14%; p = 0.048)
  - Pat. with septic shock:
    - 28-days mortality ↓ (-26%; p = 0.018)
  - Pat. with APACHE III > 102:
    - 28-days mortality ↓ (-26%; p = 0.040)
  - Pat. with > triple organ failure:
    - 28-days mortality ↓ (-23%; p = 0.039)
  - No adverse reactions from selenase®
  - No toxic symptoms
  - Intervention group:
    - Duration of mechanical ventilation = no significant difference
    - Mortality = no significant difference
    - No adverse reactions from sodium selenite
    - No toxic symptoms
- Selenium level at ICU admission markedly below normal
  - Intervention group (selenase®):
    - 28-days mortality ↓ (-7%; p = 0.367)
  - Pat. with APACHE II < 28:
    - 28-days mortality ↓ (-19%; p = 0.100)
  - Significant reduction in PCT vs. control group (p < 0.05)
  - No adverse reactions from selenase®
  - No toxic symptoms
- Intervention group:
  - SOFA ↓ (p = 0.0001)
  - Early ventilator-associated pneumonia ↓ (-31%; p = 0.04)
  - Nosocomial pneumonia ↓ (-19%, p = 0.03)
  - No adverse reactions from sodium selenite
  - No toxic symptoms

### Limitations

- • trial size
- • no placebo group
- • low selenase® doses
- • trial size
- • Patients enrolled too late (not until after 48h)
- • baseline selenium value unknown
- • selenium value not measured
- • no bolus
- • trial size
- • baseline selenium value unknown
- • selenium value not measured
<table>
<thead>
<tr>
<th>Trial design</th>
<th>Number of patients</th>
<th>Intervention</th>
</tr>
</thead>
</table>
| **Andrews et al. (2011)** | N (selenase®) = 127  
N (glutamine) = 126  
N (selenase® + glutamine) = 124  
N (placebo) = 125 | **Placebo group:**  
Standard parenteral nutrition  
**Glutamine group:**  
+ 20.2 g glutamine  
**selenase® group:**  
+ 500 µg selenium  
**selenase® + glutamine group:**  
+ 500 µg selenium + 20.2 g glutamine |
| **Heyland et al. (2013)** | N (antioxidants) = 308  
N (glutamine) = 303  
N (antioxidants + glutamine) = 310  
N (placebo) = 302 | **Antioxidant group:**  
500 µg/day selenium as selenase® parenteral  
+ 300 µg selenium, 20 mg zinc, 500 mg vitamin E, 10 mg beta-carotene, 1500 mg vitamin C enteral  
**Glutamine group:**  
0.5 g/kg body weight parenteral + 30 g enteral |
| **Sakr et al. (2014)** | N (selenase®) = 413  
N (control) = 634 | **Intervention group:**  
Bolus: 1,000 µg selenium  
1,000 µg/day selenium for 14 days  
**Control group:**  
100 µg/day selenium |
### Trial design

**Andrews et al. (2011)**
- Randomized, controlled, double-blind, factorial, multicenter trial
- **Intervention**
  - N (selenase®) = 127
  - N (glutamine) = 126
  - N (selenase® + glutamine) = 124
  - N (placebo) = 125

| Placebo group: | Standard parenteral nutrition |
| Glutamine group: | + 20.2 g glutamine |
| Selenase® group: | + 500 µg selenium |
| Selenase® + glutamine group: | + 500 µg selenium + 20.2 g glutamine |

- **Result**
  - New infections ↓ (-5%, p = 0.24)
  - New infections in patients with ≥ 5 days selenase® supplementation ↓ (-13%, p = 0.03)
  - Mortality after 6 months = no significant difference

- **Limitations**
  - Only 56% of participants were sepsis patients
  - Baseline selenium value unknown
  - Selenium value not measured

### Selenium level at ICU admission within reference range

**Antioxidant group:**
- Selenium level ↑ (p < 0.001)
- 28-days mortality = no significant difference

- **Limitations**
  - Only 31% of participants were sepsis patients
  - Late initiation of selenium supplementation
  - Low selenium dose
  - Interaction through concomitant vitamin C

### selenase® group:
- ICU mortality = no significant difference
- Hospital mortality ↑ (+7%; p = 0.027)
- ICU stay ↑ (p = 0.01)
- Hospital stay ↑ (p = 0.001)
- Selenium supplementation not independently associated with worse outcome (OR = 1.19, p = 0.288)
- Selenium supplementation after a multivariate analysis not associated with hospital mortality

- **Limitations**
  - Retrospective trial
  - Selenium group contains significantly more severely ill patients
  - No precise criteria for initiation of selenium supplementation
  - All patients were surgical patients with sepsis
General facts about Ischaemia/reperfusion

<table>
<thead>
<tr>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ischaemia and reperfusion (I/R) cause tissue damage</td>
</tr>
<tr>
<td>• Reactive oxygen species play an important role in I/R</td>
</tr>
</tbody>
</table>

Tissue damage with ischaemia/reperfusion

Ischaemia and reperfusion (I/R) are characterized by an initial restriction of the blood flow to an organ followed by the re-establishment of the blood circulation and associated reoxygenation. This re-establishment of the blood flow and the oxygen supply is often accompanied by a worsening of the tissue damage (“oxygen paradox”), a comprehensive inflammatory response, and can lead to organ failure (Tab. 1).
### Examples of ischaemia and reperfusion injuries. \[1\]

<table>
<thead>
<tr>
<th>Affected organ</th>
<th>Example for clinical manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischaemia and reperfusion in an individual organ</strong></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>Kidney</td>
<td>Acute kidney damage</td>
</tr>
<tr>
<td>Intestine</td>
<td>Multiorgan failure</td>
</tr>
<tr>
<td>Brain</td>
<td>Stroke</td>
</tr>
<tr>
<td><strong>Ischaemia and reperfusion with several organs</strong></td>
<td></td>
</tr>
<tr>
<td>Trauma and resuscitation</td>
<td>Multiorgan failure; acute kidney damage; intestinal damage</td>
</tr>
<tr>
<td>Circulatory arrest</td>
<td>Hypoxial brain damage; multiorgan failure; acute kidney damage</td>
</tr>
<tr>
<td>Sickle-cell anemia</td>
<td>Acute breast syndrome</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>High blood pressure; diabetes</td>
</tr>
<tr>
<td><strong>Ischaemia and reperfusion during major surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>Acute heart failure</td>
</tr>
<tr>
<td>Thorax surgery</td>
<td>Acute lung damage</td>
</tr>
<tr>
<td>Peripheral vascular surgery</td>
<td>Compartment syndrome of the extremities</td>
</tr>
<tr>
<td>Major vascular surgery</td>
<td>Acute kidney damage</td>
</tr>
<tr>
<td>Organ transplantation</td>
<td>Acute transplantation failure; early rejection of transplanted organs</td>
</tr>
</tbody>
</table>
Important role of ROS with I/R

Many factors are involved in the pathogenic mechanisms which contribute to I/R-induced damage and infarct. The significance of the individual factors has not yet been fully clarified. However, there are increasingly indications that Reactive Oxygen Species (ROS) play a critical role in the damage to cellular components and the initiation of the apoptosis (Fig. 1).
Impact of ischaemia/reperfusion at a cellular level. [2]

**Ischaemia**
- Hypoxia
- ATP
- CA²⁺ + Na⁺
- Anaerobic glycolysis

**Reperfusion**
- ROS
- Lipid peroxidation + DNA damage + protein modification
- Lipid peroxidation + DNA damage + protein modification
- NO/superoxide interactions + leucocyte and platelet activation/infiltration
- Inflammation

**Reperfusion (repair)**
- ROS ↓
- Proliferation differentiation migration
- Capillary No-Reflow effect
- Cell change
- Remodeling angiogenesis
- Necrosis, apoptosis

**Literature**


Challenge posed by complications in cardiac surgery

General information

- Severe complications with patients undergoing cardiac surgery despite great advancements is a major problem
- Affects up to 16% of the patients
- Three pathophysiological mechanisms are responsible: ischaemia, reperfusion and perioperative inflammation
- Selenium supplementation intervenes at the same site of action as established pharmacological strategies

Increased severe complications in cardiac surgery

Roughly one million patients per year require cardiac surgery. This number will probably further increase in the next 10 years because of an aging society [1]. Despite great advancements in the strategies for protecting the heart, cardiac surgery is still associated with serious complications. These include death, myocardial infarction, cardiac arrest and failure, renal failure, stroke, gastrointestinal complications and respiratory arrest for up to 16% of the patients [2]. Most of these systemic complications are associated with three pathophysiological mechanisms: ischaemia, reperfusion and perioperative inflammation [3].

In the case of cardiac surgery using a heart-lung machine, the patient is exposed to numerous ischemic stimuli [3]:

1. Induction of a cardioplegic cardiac arrest
2. Micro-embolic events
3. Reperfusion of the myocardium through surgical revascularization
4. Termination of the cardioplegic cardiac arrest

All this leads to an inflammatory response associated with fever, leucocytosis, tachycardia, hypotension, fluid accumulation in tissue, and organ failure [4]. Diverse procedures are applied in practice to reduce these causal mechanisms or effects, such as the reduction of oxidative stress and organ failure, to improve chances of the patient’s survival. There are both pharmacological as well as non-pharmacological strategies that intervene at various points in the pathophysiological mechanisms. Selenium supplementation can advantageously intervene at every one of these points (Fig. 1) [3].

The comparison of pharmacological strategies and selenium supplementation in the event of complications shows the immense significance of selenium for cardiac surgery (Fig. 2) [4].
Complications posed by cardiac surgery, treatment approaches and the positive influence of selenium supplementation. \[3\]
Fig. 2  Site of action of pharmacological strategies and selenium supplementation to reduce complications of cardiac surgery. [3]

- Inhibition or inactivation
- Promotion or activation

### Cell membrane

- Formation of NO
- Formation of protein kinase
  - Methylene blue statins
  - Selenium [6]
  - Selenium [7]
  - Phosphodiesterase inhibitor

### Cytokines bacteria viruses
- Selenium [5]

### Cytokines
- Selenium [8]

### IKK complex
- Selenium [9]

### Phosphorylation of IκBα

### Antimediator therapy
- Glucocorticoids
- Aprotinin statins
- Sildenafil
- Insulin
- Selenium [6]
- Selenium [7]
- Selenium [12]
- Selenium [13]

### Multiple organ failure
- Tissue damage
- Surface activation leads to increased leucocyte activation + release of inflammatory mediators

### Activation of NF-κB
- Cell nucleus
Selenium [10]

Sildenafil

insulin statins

Degradation of ROS


N-acetyl-cysteine

Phosphodiesterase

Cell membrane

protein kinase

Fig.

Formation of NO

inhibitor

complications of cardiac surgery.

Site of action of pharmacological strategies

Promotion or activation

Inhibition or inactivation

Selenium [5]

Methylene blue

Selenium [8]

statins

Selenium [6]

Selenium [7]

Selenium [12]

therapy

Antimediator

Selenium [9]

therapy

aprotinin

statins

Insulin

release of inflammatory

adhesion molecules

other inflammatory

leads to increased

Surface activation

Tissue damage

Multiple organ

cell nucleus

Activation

of NF-κB

mediators

Cytokines

viruses

of IκBα

Ahn;133(5):1083-93

Kretz-Remy


Selenium in the cardiovascular system

General information

- Selenoproteins play a major role in the cardiovascular system
- 50% increase in the selenium concentration is associated with a 24% reduction of risk of coronary heart disease
- Least risk of cardiovascular disease at 150 – 160 µg/l selenium in the serum
- A selenium deficiency negatively influences Keshan disease and infectious myocarditis
- Positive effect of selenium supplementation on existing cardiovascular diseases
- Selenium reduces the cardiotoxicity of doxorubicin

Fig. 1 Functions of selenoproteins in the cardiovascular system. [1]

<table>
<thead>
<tr>
<th>Selenoprotein S</th>
<th>Glutathione peroxidase 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involved in the development of subclinical cardiovascular disorders for patients with type 2 diabetes</td>
<td>Knock-out → infarct size ↑</td>
</tr>
<tr>
<td>Overexpression reduces intracellular ROS and protects cardiomyocytes</td>
<td>Overexpression protects the heart</td>
</tr>
<tr>
<td>Regulates CD36 expression in macrophages</td>
<td></td>
</tr>
<tr>
<td>Contributes to the formation of foam cells and atherogenesis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selenoprotein K</th>
<th>Selenoprotein R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overexpression reduces intracellular ROS and protects cardiomyocytes</td>
<td>Involved in dynamic actin reorganization during cardiac stress</td>
</tr>
<tr>
<td>Regulates CD36 expression in macrophages</td>
<td>Protects cardiomyocytes stressed by ROS</td>
</tr>
<tr>
<td></td>
<td>Regulates CD36 expression in macrophages</td>
</tr>
</tbody>
</table>
Selenoproteins influence the cardiovascular system

Oxidative stress is connected to several cardiovascular diseases. The selenoprotein glutathione peroxidase limits oxidative stress by the degradation of hydroperoxides (Fig. 1). The cell is thus protected from lipoprotein and/or DNA damage. Thioredoxin reductases induce changes in the redox status and thereby regulate functions in the cardiovascular system. A subfamily of selenoproteins, SelW, SelV, SelT and SelH among others, form mixed disulfides with substrate proteins and bind DNA in a redox-sensitive manner. Selenoprotein T (SelT) is involved in calcium mobilization and glucose metabolism. However, the selenoproteins SelM and Sep15 are oxidoreductases in the lumen of the endoplasmic reticulum. Selenoprotein K, an endoplasmic reticulum protein, is involved in the antioxidant defense system of cardiomyocytes, while Selenoprotein R is overexpressed in the myocardium during a hypertrophy.

Glutathione peroxidase 3
- Prevents LDL oxidation, vascular inflammation and atherogenesis
- Up-regulated during hypertrophy

Glutathione peroxidase 4
- Mitochondrial overexpression protects from I/R injuries
- Protects cellular lipids from oxidative stress

Deiodinase 2
- Involved in the regulation of the thyroid hormones
- Principal isoform in the heart
- Overexpression improves contractile functionality
- Overexpression normalizes genes involved in pathological remodeling

Thioredoxin reductase 1
- Regulates remodeling by signal pathways
- Trx-1 reduces hypertrophy and oxidative stress
- TrxR1 overexpression during hypertrophy
Cardio-protective effect of selenium

Animal experiments with rats that received either a selenium-poor or a selenium-rich diet furthermore showed that selenium reduces the cardiac content of TNFα \(^3\). A lower TNFα level indicates reduced inflammation. In addition, the selenium-rich diet reduced the dephosphorylation of Connexin-43. Connexin-43 is an important ventricular gap-junction protein that is a decisive factor both for the myocardial infarct magnitude as well as for cardiac remodeling. The dephosphorylation of Connexin-43 inhibits the intracellular communication of gap junctions. This shows that the cardio-protective effect of selenium is at least partially attributed to the prevention of dephosphorylation of Connexin-43. An additional effect of the selenium-enhanced diet was the increased activity of antioxidant selenoproteins, whereby oxidative stress was reduced (Fig. 2). Taken together, this result shows that the quantity of selenium consumed influences remodeling after a cardiac infarct.
Selenium deficit increases the risk of cardiovascular diseases

Both animal experiments as well as studies with humans have shown an inverse association between the selenium status and cardiovascular diseases. An observation trial from 2009 moreover proposes a U-shaped association with a minimum at 150 – 160 µg/l selenium in the serum (Fig. 3) [4].

A meta-analysis of 25 observational trials showed that a 50% increase in the selenium concentration is associated with a 24% reduction in the risk of coronary heart disease [5].

Fig. 3 U-shaped association between the selenium status and cardiovascular diseases. [4]
Connection of selenium with Keshan disease and infectious myocarditis

Keshan disease is probably the best-investigated human disease in connection with a selenium deficit. The disease involves a dilated cardiomyopathy that primarily occurs in children in Keshan province in China, and is characterized by multifocal myocardiac necrosis and calcification, which is usually reversible after selenium supplementation [6].

While selenium deficiency is the primary pathogenic factor for the incidence of Keshan disease, most probably an infectious agent plays also a role. The Coxsackie virus B4 was isolated in patients with this disease. Animal experiments with selenium-deficit mice showed that a selenium supplementation reduced the cardiotoxicity of the Coxsackie virus B4. Furthermore, mice that by nature are resistant against viral-induced myocarditis are vulnerable to this disease with a selenium-deficit diet. Finally Jun et al. demonstrated that mice with a deficit selenium intake showed an increase in Coxsackie virus-induced myocarditis [7].

Selenium plays a major role not only for Keshan disease but also for Chagas disease. Chagas disease is a tropical cardiomyopathy caused by an infection with the parasite Trypanosoma cruzi. Clinical studies have shown that a lower selenium status worsens the heart dysfunction of these patients [8]. Moreover, animal experiments have demonstrated that a selenium supplementation reduces heart damage and improves survival rates.

In the meantime, a randomized double-blind controlled trial is currently being conducted to examine the influence of selenium supplementation on the progression of Chagas cardiomyopathy [9].
Selenium concentration: prognostic marker for acute coronary syndrome

The so-called AtheroGene trial determined the selenium concentration of 1,731 patients suffering from either a Stable Angina pectoris (SAP) or an Acute Coronary Syndrome (ACS) [10]. Within a median follow-up of 6.1 years, 190 patients died due to cardiovascular-related causes. Of the ACS patients, the selenium level for the deceased was significantly lower than for the survivors (61.0 μg/l vs. 71.5 μ/l selenium in serum; \( p < 0.0001 \)). A Cox regression model showed that the probability of death from cardiovascular disease after adjustment for age and sex declines by 58% for a selenium concentration of more than 80 μg/l selenium in the serum compared to a selenium concentration of below 62 μg/l selenium (HR 0.42 [95% CI 0.24–0.72]; \( p = 0.002 \)) (Fig. 4). For patients with SAP, there was no association between the selenium level and the cardiovascular outcome.
Positive effect of a selenium supplementation for existing cardiovascular diseases

This effect is clearest for patients who are fed parenterally. Several case studies described pathological changes in parenterally fed patients who have symptoms similar to Keshan disease. A selenium supplementation reverses this cardiomyopathic process. A trial from 2012 evaluated the causes of cardiomyopathy in 18 obese patients who had both cardiomyopathy as well as an anamnesis with malabsorption. None of the cardiac biopsies showed evidence of a viral infection. However, the cardiac selenium level and the glutathione peroxidase activity were significantly reduced compared to idiopathic cardiomyopathy patients and controls. The 18 patients were randomized and assigned to a group with selenium supplementation (n = 10) and a placebo group (n = 8).

After a six-month treatment, the myocardial selenium content and the glutathione peroxidase activity in the selenium-supplemented group had normalized. This was accompanied by an improvement in myocardic degeneration, autophagy as well as the cardiac function.

A similar trial, though not associated with malabsorption, of 30 patients showed a significant reduction of the left ventricular volume (p = 0.03) after 9 months and thereby an improvement of the left ventricular function compared to the placebo group (Fig. 5) (13). Furthermore the quality of life of the patients in the selenium-supplemented group improved by 9.5 points (p = 0.02) and worsened slightly in the placebo group (Fig. 6).

Literature

<table>
<thead>
<tr>
<th>Page</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Witte KK, Nikitin NP, Parker AC, von Haehling S, Volk HD, Anker SD, Clark AL, Cleland JG. Eur Heart J. 2005 Nov;26(21):2238-44. The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure.</td>
</tr>
</tbody>
</table>
Reduction of the left ventricular volume compared to the placebo group. LVEDV = Left Ventricular End-Diastolic Volume. \[^{[13]}\]

![Graph showing reduction of left ventricular volume](image)

Baseline vs. End of trial with p = 0.03

Selenium Supplementation vs. Placebo

Improvement of the quality of life of the selenium-supplemented group with cardiomyopathy. \[^{[13]}\]

![Graph showing quality of life improvement](image)

Baseline vs. End of trial with p = 0.02

Selenium Supplementation vs. Placebo
Selenium supplementation decreases cardiovascular mortality of elderly people

In a five-year comprehensive prospective randomized double-blind placebo-controlled trial with Swedes between 70–80 years of age, the effect of a combined supplementation of selenium and coenzyme Q10 or a placebo was examined for cardiovascular mortality \[14\]. In total, 443 elderly Swedes participated who were examined every six months using echocardiography and the cardiac biomarkers N-terminal proBNP (NT-proBNP). During the follow-up period of 5.2 years, a significant reduction of the cardiovascular mortality in the intervention group compared to the placebo-group (5.9% vs. 12.6%; \( p = 0.015 \)) was demonstrated. The NT-proBNP level in the selenium/Q10-supplemented group was significantly lower (214 ng/l vs. 302 ng/l after 48 months; \( p = 0.014 \)). Moreover the echocardiography showed significantly better cardiac functions in the intervention group (\( p = 0.03 \)). An invariant proportional hazard regression analysis found a 55% reduction of cardiovascular mortality in the selenium/Q10-supplemented group (HR 0.45 [95% CI 0.24–0.89]; \( p = 0.02 \)) (Fig. 7).

Selenium reduces cardiotoxicity of doxorubicin

Doxorubicin is used to treat a large group of cancer diseases. The most serious side effect of doxorubicin is life-threatening damage to the heart. Numerous studies have demonstrated that oxidative stress plays a decisive role in the cardiotoxicity of doxorubicin. Several animal experiments showed that both a selenium deficit as well as reduced glutathione peroxidase activity leads to an increase of the cardiotoxicity of Doxorubicin \[15, 16\]. In additional animal experiments, the effect of a co-administration of selenium and doxorubicin compared to a sole administration of doxorubicin was examined. The results showed a attenuation of the left-ventricular dysfunction with a co-administration as well as prevention of oxidative stress by an increase of antioxidants and reduction of oxidants \[15, 17\].
Fig. 7  Reduced cardiovascular mortality for the selenium/Q10-supplemented group compared to the placebo group. [14]

Literature


Selenium status correlates with the extent of cardiac damage

In a trial from 2005, the examination of 70 patients with myocardial infarct showed that the selenium concentration declines significantly with increasing damage of the cardiac tissue \( (p = 0.004) \). In order to determine the damage of the cardiac tissue, the following biological markers were determined: cardiac Troponin T (cTNT), cardiac Troponin I (cTNI) and creatine kinase-MB-mass (CK-MBm) (Fig. 1). As a prognostic marker of myocardial infarction, troponins were used in connection with the C-reactive protein (CRP), a marker for inflammation. Increased CRP levels correlate with a higher risk of a cardiological incident for patients with coronary disease. This trial also showed a significant positive correlation of CRP with increasing cardiac damage. Simultaneously, the glutathione peroxidase correlated negatively with these prognostic markers (Fig. 2).
Negative correlation of the selenium status with the extent of cardiac damage. [1]

Positive correlation of CRP and negative correlation of glutathione peroxidase activity with the extent of cardiac damage. [1]
Sodium selenite protects from I/R damage

Venardos et al. analyzed the effect of sodium selenite supplementation on I/R-induced damages in rats [2]. The animals were supplemented with either 0, 50, 240, or 1,000 µg sodium selenite/kg diet for 5 weeks. Then they were submitted to global ischaemia and reperfusion. The group treated with 240 µg sodium selenite/kg diet served as a control group. The ischaemic contraction at the end of the ischaemic phase was determined to identify the extent of ischemic damage. The contraction was significantly greater in the selenite-free group ($p < 0.05$ vs. control) and reduced with increasing sodium selenite concentration (Fig. 3). This demonstrates that the heart shows a greater tolerance to ischaemia with higher selenium levels.

In order to determine the damage by reperfusion, the extent of the recreated cardiac function was compared. A supplementation with 1,000 µg sodium selenite/kg diet improved the recovery of the cardiac function to 57% of the pre-ischaemic level ($p < 0.05$). In comparison, the recovery of cardiac function for the sodium selenite-free group or the group with 50 µg sodium selenite/kg diet were significantly reduced to 38% and 44% respectively ($p < 0.05$). These data indicate a cardio-protective effect of sodium selenite.

---

**Fig. 3**
Reduction of the damage induced by ischaemia with increasing sodium selenite quantity. [2]
### Literature


---

**Fig. 4** Better recovery of cardiac function after I/R with increasing sodium selenite concentration. *RPP (Rate Pressure Product) = product from heart rate and blood pressure.* [2]
Intraoperative decrease of selenium correlates with the postoperative development of multiorgan failure

Cardiac surgery using a cardiopulmonary bypass induces I/R mediated oxidative stress. A prospective observational trial with 60 patients undergoing cardiac surgery investigated whether the intraoperative decrease of circulatory trace elements is involved in this reaction [3]. Already before the operation, 50 patients (83%) showed a significant selenium deficit, while the copper and zinc concentrations were in the reference range. In all patients, the selenium concentration (89.05 ± 12.65 to 70.84 ± 10.46 µg/l selenium in whole blood; p < 0.001) as well as the copper and zinc concentrations after conclusion of the surgery had significantly decreased (Fig. 5). During their stay in the ICU, 12 patients developed multiorgan failure. A multi-logistic regression analysis showed that the selenium concentration at the end of the surgery is an independent predictor with the postoperative appearance of multiorgan failure (HR 0.85 [95% CI 0.76–0.94]; p = 0.026).

Fig. 5 Significant postoperative reduction of selenium concentration. [3]

![Graph showing selenium concentration in whole blood](image_url)
The postoperative decrease of selenium concentration is not attributed to the use of a heart-lung machine

These results were supported by an additional trial from 2014. In this prospective randomized interventional trial with 40 patients, it was examined whether the selenium level in connection with an “Off-Pump Coronary Artery Bypass” procedure (OPCAB), where no heart-lung machine is necessary, declines less strongly compared to an “On-Pump” procedure, since the oxidative stress for this procedure should be small [4]. More pronounced than in the trial by Stoppe et al., all patients displayed a selenium deficit already before the surgery. After conclusion of the surgery, both groups showed a significant decline of selenium concentration (p < 0.001), whereby the decrease in the on-pump group was more significant (31.2 ± 13.6% vs. 20.2 ± 16.3%; p = 0.04) (Fig. 6). Of the measured values (myocardiac-specific creatine kinase, asymmetrical dimethylarginine, glutathione peroxidase), only the postoperative selenium concentration showed a correlation with the development of a postoperative organ dysfunction both for all patients (p = 0.037) as well as for the OPCAB group (p = 0.023).

Fig. 6  Significantly greater postoperative decline of the selenium concentration in the on-pump group. [4]
**Perioperative administration of selenase® prevents postoperative decrease of selenium concentration**

In a prospective observation trial, the effect of perioperative administration of selenase® was examined in 100 patients. Similar to the two other studies described, 75% of the patients already had a selenium deficit before surgery. The perioperative administration of 2,000 µg selenium as selenase® achieved a normalization of the selenium level at ICU admission (Fig. 7). Moreover, this bolus injection prevented a post-operative decrease of the selenium concentration below the perioperative selenium value. The daily administration of 1,000 µg selenium as selenase® during the stay in the ICU stabilized the selenium level in the high reference range. Both the selenium concentration at ICU admission as well as four hours later were significantly lower in patients, who developed an organ dysfunction in the observation period, compared to patients without complications (Table 1). A ROC curve analysis showed that the selenium concentrations at ICU admission and four hours after admission predicted an organ dysfunction, while the perioperative selenium value and the selenium concentration on the first postoperative day had no predictive value.

<table>
<thead>
<tr>
<th>selenase® for cardiac surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week before</td>
</tr>
<tr>
<td>Day 1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td>From day 2 of the ICU stay</td>
</tr>
<tr>
<td>Literature</td>
</tr>
</tbody>
</table>
Significantly lower selenium concentrations for patients with organ dysfunction. Selenium concentration in µg/l in whole blood. [5]

<table>
<thead>
<tr>
<th></th>
<th>Patients with organ dysfunction</th>
<th>Patients without complications</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selenium concentration at ICU admission</td>
<td>118.47 ± 16.38</td>
<td>127.16 ± 17.69</td>
<td>0.030</td>
</tr>
<tr>
<td>Selenium concentration 4 hours after ICU admission</td>
<td>103.47 ± 13.45</td>
<td>110.84 ± 14.41</td>
<td>0.025</td>
</tr>
</tbody>
</table>

A bolus injection of selenase® before surgery prevents the decrease in postoperative selenium concentration below the perioperative selenium level. [5]
For a matched-pair analysis of 42 patients each, who showed no perioperative differences, the selenase®-supplemented group revealed a significantly higher selenium value at ICU admission (Fig. 8). While the selenium level in the control group declined further during the stay in intensive care, the selenium concentration increased from the first postoperative day, whereby the difference from the second postoperative day was highly significant \( (p < 0.001) \) (Fig. 9). On the first postoperative day, the selenase®-supplemented group showed a significantly lower SAPS II and SOFA value \( (p = 0.005 \text{ or } p = 0.007) \). The selenase®-supplemented group moreover revealed fewer respiratory organ dysfunctions \( (p = 0.040) \). The control group more frequently developed severe thrombocytopenia \( (p = 0.035) \) (Table 2).

No side effects occurred during the trial which could be brought in connection with the selenase® application. The dosage regime proved to be safe. In order to better confirm these results, a large-scale international multicentric randomized double-blind controlled trial (SUSTAIN-CSX) for the use of high-dose selenase® for patients undergoing cardiac surgery was initiated in 2015 [6].

![Fig. 8](https://example.com/fig8.png)

**Fig. 8**

Significantly increased selenium concentration during the ICU stay in the selenase®-supplemented group \( (n = 42) \) compared to a historical control group \( (n = 42) \). [5]

<table>
<thead>
<tr>
<th>Selenium concentration in serum [µg/l]</th>
<th>Reference range</th>
<th>selenase®</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>preoperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>postoperative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td></td>
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<tr>
<td>140</td>
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<td></td>
</tr>
</tbody>
</table>

\( p < 0.05 \)
Significant differences between the selenase®-supplemented group and the control group on the first postoperative day. [5]

<table>
<thead>
<tr>
<th></th>
<th>selenase®-supplemented group</th>
<th>Control group</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II</td>
<td>23 ± 7</td>
<td>29 ± 8</td>
<td>0.005</td>
</tr>
<tr>
<td>SOFA</td>
<td>4 ± 2</td>
<td>7 ± 2</td>
<td>0.007</td>
</tr>
<tr>
<td>Respiratory organ dysfunction</td>
<td>0</td>
<td>4</td>
<td>0.040</td>
</tr>
<tr>
<td>Severe thrombocytopenia</td>
<td>3</td>
<td>10</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Significantly higher postoperative selenium concentrations in the selenase®-supplemented group (n = 42) compared to a historical control group (n = 42). [5]
Selenium in the brain

Selenium is essential for the brain

The total amount of selenium in the brain is comparatively low. In the brain, a concentration of 110 ± 21 ng selenium/g wet weight was determined in German adults. In contrast, there is 771 ± 169 ng selenium/g in the kidney and 291 ± 78 ng selenium/g in the liver. The brain thus contains only 2.3% of the entire selenium in a human body [1]. With a long-term low-selenium diet, the available selenium is preferably transported to the brain at the expense of other organs, such as the liver [2]. Approximately 20% of the entire selenium amount in the brain is incorporated in glutathione peroxidase [2]. With a sufficient selenium supply, the glutathione peroxidase activity in the liver is 13 times greater than in the brain. After a selenium-deficit diet of about 6 months, the activity of the glutathione peroxidase was reduced by 92%, while in the brain it only declined negligibly [3]. Selenium plays a decisive role for various diseases of the central nervous system (CNS), among others stroke, brain tumors, brain development and affective disorders. First indications delivered reports about neurological diseases in patients with low selenium status or restricted selenoprotein biosynthesis. Over a long time period, parenterally nourished patients with inadequate selenium content developed progressive encephalopathy [4]. Two rare mutations of the human SEPSECS gene that codes the selenocysteine synthase lead to progressive cerebellar and cerebral atrophy [5].
## Literature

<table>
<thead>
<tr>
<th>#</th>
<th>Reference</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Buckman TD, Sutphin MS, Eckhardt CD. <strong>Biochim Biophys Acta. 1993 May 13;1163(2):176-84.</strong> A comparison of the effects of dietary selenium on selenoprotein expression in rat brain and liver.</td>
<td></td>
</tr>
</tbody>
</table>
Glutathione peroxidase 1 influences the infarct volume

As already long known, glutathione peroxidase 1 (GPx1) in knock-out mice show a 3-fold increase of infarct volume compared with wild-type mice (p < 0.01) (Fig. 1) [6]. This is also reflected in the increased number of necrotic and apoptotic cells (Fig. 2). An earlier activation of caspase 3 in GPx1 knock-out mice moreover indicates increased susceptibility compared to apoptosis in GPx1 knock-out mice.

Furthermore, an investigation with transgenic mice, which overexpressed glutathione peroxidase, revealed a significant reduction in the infarct volume in consequence of I/R damage compared with non-transgenic mice [7]. An overexpression of glutathione peroxidase significantly reduced both necrotic as well as apoptotic cell death in endangered brain regions (p < 0.05). In these animals, the activation of astrocytoma and microglia in the ischemic brain was reduced. In contrast to wild type-mice, glutathione peroxidase overexpressed mice showed a significantly better preserved tissue structure and a reduced infiltration of acute inflammatory cells (p < 0.05).
Significantly increased number of necrotic and apoptotic cells in GPx1 knock-out mice. [6]
Glutathione peroxidase 4: essential for brain development and neuropathological diseases

Glutathione peroxidase 4 (GPx4) is essential for survival. Homozygous GPx4 knock-out mice in the second trimester of pregnancy die in utero because of increased apoptosis and cell death, which result in the malformation of the embryo [8]. GPx4 is expressed in neurons, above all in the hippocampus [9]. Just recently it was demonstrated that the neuronal GPx4 expression plays an essential neuroprotective role in Morbus Parkinson [10]. GPx4 moreover modulates the interneuronal function as well as the expression of parvalbumin [11]. Furthermore, GPx4 prevents seizures and neurodegeneration [11].

GPx4 is a multifunctional antioxidative protein with anti-apoptotic characteristics [9]. This is particularly relevant because neurons, in contrast to glial cells, essentially depend on their GPx activity to detoxify free oxygen radicals (ROS) and lipid peroxides [12]. Increased ROS levels occur in neuropathological disorders such as trauma, seizure and ischaemia. Furthermore, it has been shown that the cytosolic variants of GPx4 are up-regulated after brain injuries [9]. However not in neurons, but rather in reactive astrocytes, a glial cell type that under normal conditions expresses no GPX4. After brain injuries, astrocytes change their cytoskeleton and migrate in the direction of the lesion, where they are involved in the repair of oligodendrocytes and myelination, as well as in the re-establishment of the blood-brain barrier in order to prevent neuroinflammation [9].

The expression of GPx4 in the astrocytes is therefore a response to stress that serves for neuro-protection to prevent additional damage. A sodium selenite supplementation in the physiological range with zebra fish significantly increased the GPx4 expression in the brain compared to selenium-deficit zebra fish ($p = 0.048$) (Fig. 3) [13]. Apart from GPx4, the expression of GPx3 also increased, which also plays an active antioxidative role in the CNS [14]. Overall, these results suggest that a sodium selenite supplementation increases the antioxidative capacity of the brain [13].
Sodium selenite supplementation in the physiological range significantly increases the GPx4 expression in the brain.\textsuperscript{[13]}
Selenoprotein P knock-out causes severe neurological dysfunction

Almost all known selenoproteins occur in the brain, whereby the transport protein for selenium, the selenoprotein P (SEPP1), makes selenium available in the form of selenocysteine for the expression of selenoprotein. Under selenium deficit conditions selenium from SEPP1 is detected in the brain after two hours. The “knock-out” of SEPP1 leads to decreased selenium concentration and selenoprotein activities in the brain. SEPP1 knock-out mice developed brain function disorders and showed limited motor coordination with an adequate selenium diet with sodium selenite. However, the neurological disorders with an adequate selenium diet with selenomethionine were so massive that half of the SEPP1 knock-out mice had to be euthanized. A sodium selenite supplementation above the daily normal selenium requirement could prevent brain function disorders (Fig. 4).

Moreover, significantly greater neurological dysfunction occurred with male animals in SEPP1 knock-out mice (p < 0.001) (Fig. 5). A supplementation with sodium selenite attenuated the motoric deficits of male animals to a greater degree (p < 0.001) (Fig. 6).
Reduced motor coordination in SEPP1 knock-out mice is more pronounced in male animals. [16]

**Control group**

- Turn time [seconds]
- Pole Test [seconds]

**Sodium selenite supplementation**

- Turn time [seconds]
- Pole Test [seconds]

Significance levels: $p < 0.001$ for males and $p < 0.01$ for females.
Sodium selenite acts neuroprotectively even hours after induction of the damage

Savaskan et al. investigated the role of selenium for stroke in vitro and in animal experiments. Glutamate was employed for the simulation of a stroke \(^1\). It is the predominant stimulating neurotransmitter in the brain. Under pathological conditions such as stroke, epilepsy and traumatic brain damage, glutamate can be toxic for neurons. Experiments have showed that simultaneous administration of sodium selenite in a concentration dependent manner prevented glutamate induced cell death \((p < 0.01)\) (Fig. 1), whereby the greatest effect \((98\% \text{ protection})\) was determined for a concentration of 100 nM sodium selenite, a concentration that lies in the human physiological range. Glutamate-induced cell death could not only be prevented with the simultaneous administration of sodium selenite, but also with a sodium selenite administration two hours after the glutamate-induced damage \((p < 0.001)\) (Fig. 2). These results were confirmed in an additional study by Mehta et al. \(^2\). Both a significant neuroprotective effect of sodium selenite with glutamate toxicity as well as with hypoxia \((p < 0.001 \text{ or } P < 0.05)\) was demonstrated (Fig. 3).
Fig. 1
Concentration-dependent neuronal protection of sodium selenite. [1]

Fig. 2
A sodium selenite administration in the physiological range after two hours prevents neuron death. [1]

Fig. 3
Neuroprotective effect of sodium selenite against glutamate toxicity and hypoxia. [2]
The comparison of neurological damage with ischaemia with and without sodium selenite supplements revealed significantly less neurological deficits with an intervention of sodium selenite ($p < 0.05$ or $p < 0.01$) (Fig. 4) [3]. Also the death of brain cells with ischaemia was significantly reduced by 38% with sodium selenite supplementation ($p < 0.05$) (Fig. 5) [3].

A seven-day sodium selenite supplementation before ischaemia in vivo resulted in a significant reduction of brain damage ($p < 0.01$) (Fig. 6) [2]. The infarct volume was thereby reduced from 36.4 ± 24.5% to 11.6 ± 5.0% compared to the control group 24 hours after re-establishment of the circulation. This in vivo result clearly shows the neuroprotective effect of sodium selenite for strokes.

**Fig. 4** Significant improvement of the neurological outcome in sodium selenite supplemented ischaemia group. [3]
Significantly lower induction of apoptosis in the sodium selenite supplemented ischaemia group. [³]

Fig. 5

Sodium selenite supplementation significantly reduces ischaemia induced brain damage. [²]

Fig. 6
Selenium deficit massively increases susceptibility to excitotoxicity and increased neuronal cell loss

In order to confirm this in vitro result, rats were administered a selenium adequate or deficient diet \[1\]. The result confirmed the hierarchy of selenium distribution under selenium-deficit conditions. A selenium-poor diet in rats resulted in a dramatic reduction of the selenium concentration in the liver (\(p < 0.001\)), while in the brain, the selenium level was significantly reduced by 10% (\(p < 0.01\)) (Fig. 7) \[1\].

In a Kainat model for excitotoxicity it was however shown that this 10% reduction of the selenium level in the brain sufficed to produce significantly higher seizure rates (\(p < 0.01\)) (Fig. 8) \[1\]. Moreover, selenium-deficit rats showed significantly more apoptotic neurons and the neuronal cell loss in the hippocampus was significantly higher than in rats fed a selenium adequate diet (\(p < 0.01\)) (Fig. 9).

---

**Fig. 7** Different impact of a selenium deficit on the selenium concentration in the liver and in the brain compared with an adequate selenium intake. \[1\]

![Graph showing selenium concentration in liver and brain under adequate and deficit diets](image-url)
Fig. 8. Selenium deficit leads to significant higher seizure rates in the brain. [1]

Fig. 9. A selenium-poor diet leads to significantly greater neural cell loss in the hippocampus compared to a diet with adequate selenium. [1]
Principle of action of neuronal protection by sodium selenite

Sodium selenite reduces oxidative stress in neurons

A surplus of glutamate induces high levels of reactive oxygen species (ROS) in neurons and thereby strongly increases oxidative stress. Sodium selenite administration prevents the production of ROS \((p < 0.01)\) (Fig. 10), while having no influence on the glutathione level \([1]\). Also in the study by Mehta et al, sodium selenite significantly reduced the production of ROS induced by glutamate toxicity and hypoxia \((p < 0.001)\) or \(p < 0.05\) (Fig. 11) \([2]\). One of the basic mechanisms of sodium selenite-mediated neuronal protection lies in the significant attenuation of oxidative stress.

---

**Fig. 10** Sodium selenite reduces the number of ROS in stroke. \([1]\)
Sodium selenite significantly attenuates ROS formation induced by glutamate (A) and hypoxia (B). [2]
Sodium selenite preserves the mitochondrial respiratory chain after hypoxia

Hypoxia significantly reduces the activity of the complex I – IV of the respiratory chain (p < 0.01) \(^\text{(1)}\) (Fig. 12) \(^\text{(2)}\). A pretreatment with sodium selenite increases the activity of the individual complexes on the basal level and also significantly reduces the inhibitory effect of hypoxia on the respiratory chain (Table 1).

Therefore, a sodium selenite supplementation mitigates the negative effect of hypoxia on the mitochondrial respiratory chain, whereby the activity of the complex either remained at a normal level or significantly improved compared to no sodium selenite administration.

Sodium selenite inhibits NFκB- and AF-1 activation

Glutamate treatment resulted in increased nuclear NFκB and AP-1 level. This increase was inhibited by sodium selenite \(^\text{(1)}\). The gel-shift assay significantly showed that the glutamate-induced activation and bonding of NFκB and AP-1 on their “nuclear response elements” was reduced by sodium selenite. The missing activation of NFκB and AP-1 prevents neuronal cell death and reduces the activation of glial cells. The glial activation raises stress signals and neuronal damage to a higher power, which leads to secondary cell death (“second hit”).

<table>
<thead>
<tr>
<th>Complex</th>
<th>Hypoxia</th>
<th>Hypoxia + sodium selenite</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex I</td>
<td>-37%</td>
<td>-5%</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Complex II + III</td>
<td>-65%</td>
<td>-45%</td>
<td></td>
</tr>
<tr>
<td>Complex IV</td>
<td>-24%</td>
<td>-3%</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>
Sodium selenite preserves the activity of the respiratory chain of mitochondria after hypoxia. [2]
Effect of sodium selenite is dependent on the biosynthesis of selenoproteins

In contrast to sodium selenite, sodium selenate has no direct antioxidative characteristics, but rather is incorporated in selenoproteins. After sodium selenite was replaced by sodium selenate, most of the neuroprotective protection (70%) remained preserved \([1]\). This suggests that the neuroprotective effect of sodium selenite depends on the biosynthesis of selenoprotein. The addition of cycloheximide, which inhibits protein biosynthesis, cancels the neuroprotective effect of sodium selenite thereby supports the hypothesis (Fig. 13).

Sodium selenite reduced ischaemia induced DNA oxidation

In addition, Mehta et al. investigated whether cerebral ischaemia induces oxidative DNA damage \([2]\). The evidence of 8-OHdG revealed a significant increase in the oxidative damage 24 hours after re-establishment of circulation. In comparison to this, a pre-treatment with sodium selenite significantly reduced the oxidative DNA damage \((p < 0.05)\) (Fig. 14). Thus, the antioxidative impact of sodium selenite consists in avoiding the oxidation of DNA and thereby its being damaged.

Literature

Fig. 13 The addition of the protein synthesis inhibitor cycloheximide cancels the neuroprotective effect of sodium selenite. [1]

Fig. 14 Sodium selenite reduces DNA oxidation induced by ischaemia. [2]
Sodium selenite normalizes ischaemia-activated autophagy

In order to remove damaged organelles and cell debris after a cerebral ischaemia, autophagy is activated. LC3-II is a marker of autophagy. The measurement of LC3-II in vivo after an induced ischaemia revealed a significant increase after five hours \((p < 0.001)\) and a decline to the original level after 24 hours (Fig. 15) \([2]\). In rats, that received sodium selenite for seven days, the increase of LC3-II after five hours was significantly lower \((p < 0.01)\). After 24 hours the LC3-II level reduction was highly significant compared to the control group \((p < 0.001)\). A sodium selenite pre-treatment prevents brain damage by ischaemia. Therefore the activation of autophagy is reduced.

---

**Fig. 15** Sodium selenite inhibits the activation of autophagy after cerebral ischaemia. \([2]\)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control</th>
<th>Sodium selenite</th>
<th>Control</th>
<th>Sodium selenite</th>
<th>Control</th>
<th>Sodium selenite</th>
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</thead>
<tbody>
<tr>
<td>Glutamate</td>
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<tr>
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<td><img src="chart11.png" alt="Graph" /></td>
<td><img src="chart12.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

\(p < 0.05\) \(p < 0.001\)
Impact of a selenium deficit on the brain affected by stroke

Fig. 16 Effect of a selenium deficit (right side) on the brain affected by stroke, ischaemia and brain trauma. [1]

**Glutamate-induced seizure**

with sodium selenite pre-treatment

- Glutamate release
- Calcium influx
- Oxidative stress
- NF-κB
- Glia activation
- Neuron cell death
- Tissue damage
- Seizures

Control group

- Glutamate release
- Calcium influx
- Oxidative stress
- NF-κB
- Glia activation
- Neuron cell death
- Tissue damage
- Seizures
## Selenium status and selenoprotein activity in the event of a stroke

<table>
<thead>
<tr>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke patients show significantly decreased selenium values</td>
</tr>
<tr>
<td>Correlation between glutathion peroxidase concentration, neurological deficit, and outcome</td>
</tr>
<tr>
<td>Significantly reduced Selenoprotein P for patients with an acute stroke</td>
</tr>
<tr>
<td>A reduced Selenoprotein P status is significantly associated with a higher risk of a stroke</td>
</tr>
</tbody>
</table>

## Stroke patients show significantly decreased selenium values

A trial by Zimmermann et al. has compared the antioxidant status of patients with acute stroke (n = 11) with patients who suffered a stroke in the previous 12 months (n = 17) [1]. In patients with a stroke anamnesis, the average serum selenium concentration of 73.4 ± 11.1 µg/l was below the reference value of 80 µg/l selenium in serum. Values below 80 µg/l selenium in serum are considered as selenium deficit. In comparison, the serum selenium level in patients with an acute stroke showed significantly lower selenium values (61.6 ± 9.5 µg/l; p < 0.01) at admission (Fig. 1).
Significantly reduced serum selenium concentration in patients with an acute stroke. \cite{1}

![Graph showing reduced serum selenium concentration](image)

\begin{itemize}
\item Patients with stroke within last 12 months
\item Patients with acute stroke Admission to ICU
\item Patients with acute stroke Day 1
\item Patients with acute stroke Day 2
\item Patients with acute stroke Day 7
\end{itemize}

$p < 0.01$

Reference range

Serum selenium concentration [µg/l]

0 10 20 30 40 50 60 70 80 90
Correlation between glutathion peroxidase concentration, neurological deficit, and outcome

Measurement of the selenium-dependent, antioxidant glutathione peroxidase displayed a significant increase of the glutathione peroxidase level in acute stroke patients on day one \( (p < 0.05) \) (Fig. 2). In half of the patients, who suffered a stroke in the previous 12 months, the glutathione levels were below the normal range. However, the glutathione concentration in patients with an acute stroke was significantly increased \( (p < 0.01) \) (Fig. 3). Moreover, there was a negative correlation between the glutathione peroxidase concentration and the NIHSS (National Institute of Health Stroke Scale) at admission \( (r = -0.84; p < 0.001) \) and after seven days \( (r = -0.63; p < 0.05) \). High glutathione peroxidase concentrations correlated with a low neurological deficit (lower NIHSS value at admission) and with a favorable outcome (lower NIHSS value on day seven). These results confirmed findings acquired in animal experiments, i.e. that glutathione peroxidase has a protective effect against brain damage and that a reduced glutathione peroxidase level is associated with increased stroke risk \[^2,3^\].
Fig. 2 Significant increase of glutathione peroxidase concentration in patients with acute stroke. [1]

![Graph showing increased glutathione peroxidase concentration](image)

- Patients with acute stroke within last 12 months
- Patients with acute stroke, admission to ICU
- Patients with acute stroke Day 1
- Patients with acute stroke Day 3
- Patients with acute stroke Day 7

p < 0.05

Fig. 3 Significantly increased glutathione concentration in patients with acute stroke. [1]

![Graph showing increased glutathione concentration in blood](image)

- Patients with stroke within last 12 months
- Patients with acute stroke, admission to ICU
- Patients with acute stroke Day 1
- Patients with acute stroke Day 3
- Patients with acute stroke Day 7

p < 0.01
Significantly reduced Selenoprotein P concentration in patients with an acute stroke

In a population-based embedded case-control trial with 1,632 participants, Koya- 
ma et al. compared the serum selenium and Selenoprotein P concentrations of 30 stroke patients with 30 controls. The serum selenium concentration was lower (105.2 vs. 116.5 µg/l; \( p = 0.054 \)) in stroke patients. The result for the serum selenium values is comparable to the Zimmermann trial. A comparison of the two studies, however, also shows that localization plays a major role in a selenium trial. In studies from Europe, the selenium levels are significantly lower in comparison with Japan, for instance, such as the trial by Koyama. Apart from the serum selenium concentration, the Selenoprotein P concentration with stroke patients was significantly lower (54.5 vs. 63.9 µg/l; \( p = 0.006 \)) (Table 1). A multivariate regression analysis showed, that a reduced Selenoprotein P level is associated with higher stroke risk (OR 0.28; 95% CI 0.1–0.85). Since the Selenoprotein P concentration depends on the selenium status, it can be concluded that the significantly lower serum selenium concentrations in Europe result in lower Selenoprotein P levels. Therefore the question must be posed whether a selenium deficient diet presents an additional risk factor apart from hypertension, smoking and hypercholesterolemia for stroke.

Literature


<table>
<thead>
<tr>
<th>Table 1</th>
<th>Significantly lower serum selenium and Selenoprotein P concentrations in stroke patients. [2]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Stroke</strong></td>
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<tr>
<td>selenium in serum [µg/l]</td>
<td>105.2 ± 19.6</td>
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<tr>
<td>Selenoprotein P [µg/l]</td>
<td>54.5 ± 8.69</td>
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Sodium selenite for stroke

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Treatment ideally begins within 6 hours after admission to the ICU</th>
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<tr>
<td></td>
<td>Bolus directly after admission to ICU</td>
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<td></td>
<td>then as continuous infusion</td>
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<td></td>
<td>1,000¹ µg Se</td>
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<tr>
<td>From day 2 of the ICU stay</td>
<td>maintenance therapy</td>
</tr>
<tr>
<td></td>
<td>500¹ µg Se</td>
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</table>

Literature

**Sodium selenite for burns**

<table>
<thead>
<tr>
<th>General information</th>
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<tbody>
<tr>
<td>Sodium selenite:</td>
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<tr>
<td>• reduces the number of infections</td>
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<tr>
<td>• improves wound healing</td>
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<tr>
<td>• shortens antibiotic therapy</td>
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<tr>
<td>• shortens the hospital stay</td>
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</tbody>
</table>

**Significantly reduced selenium levels in burn victims**

In the first five days after the initial damage, extensive burns cause oxidative stress as shown by the simultaneous reduction of antioxidant vitamins and trace elements, and show a major increase of thiobarbituric acid-reactive substances (TBARS) (Fig. 1) \[1\].

**No decline of selenium values with sodium selenite supplementation**

The influence of selenium supplementation on the selenium concentration in burn victims was examined in several studies. In every trial, with a selenium administration of 229 – 379 µg daily, a normalization of the selenium value could be determined, while the selenium level of the placebo group stayed in the highly deficit range (Fig. 2) \[4\].
Fig. 1 Oxidative stress in burn victims reduces the concentration of antioxidants and increases the concentration on TBARS. [1]

Fig. 2 Significantly increased selenium level in the selenium-supplemented group compared to the placebo group. [4]
A major problem for burn victims is infection. In two randomized double-blind placebo-controlled trials, Berger et al. investigated the influence of sodium selenite supplementation (379 µg selenium per day) on the infection rate of burn victims [3]. The infection rate was reduced from 3.5 episodes per patient in the placebo group (n = 20) to 2.0 episodes per patient in the sodium selenite group (n = 21) (p < 0.001). This reduction was primarily attributed to the reduction of nosocomial pneumonias from 80% in the placebo group to 33% in the sodium selenite group (p < 0.001), as well as to the reduction of respiratory-associated pneumonia from 13 to 6 episodes (p = 0.023) (Fig. 3). In consequence, the number of days for which antibiotic treatment was necessary, was significantly reduced from 20 to 13 days (p = 0.021).
Fig. 3 Lower incidence of nosocomial pneumonia in the sodium selenite-supplemented group of burn victims. [3]

![Graph showing the probability of preventing nosocomial pneumonia over time. The graph compares the placebo group (red line) and the sodium selenite group (blue line). The probability of preventing nosocomial pneumonia decreases with time for both groups. The graph includes a table with data points for each group at different time points. The y-axis represents the probability of preventing nosocomial pneumonia, ranging from 0.0 to 1.0. The x-axis represents days post injury, ranging from 3 to 28. The graph indicates that the sodium selenite group has a significantly lower probability of developing nosocomial pneumonia compared to the placebo group. The p-value for the difference is 0.023.]
Improved wound healing with sodium selenite supplementation

In the trial Berger et al. investigated the influence of sodium selenite supplementation (379 µg selenium per day) on wound healing \(^{[4, 5]}\). Eleven patients were assigned to the sodium selenite group and ten patients to the placebo group for this randomized double-blind placebo-controlled trial. An examination of the burnt tissue after 3, 10 and 20 days revealed that the selenium concentration in burnt tissue of the selenium-supplemented group was significantly increased. Simultaneously the concentration of glutathione, glutathione reductase and glutathione peroxidase was significantly increased in the burnt tissue of the intervention group (Fig. 4). The comparison of healthy and burnt tissue of the burn victims with healthy control tissue revealed a significant reduction of the selenium level in healthy as well as in burnt tissue. After 20 days, the selenium concentration rose significantly in burnt tissue of the selenium-supplemented group on (Fig. 5). This result is mirrored in the required skin grafts, which were significantly less in the sodium selenite -supplemented group \((p = 0.02)\) (Fig. 6).
Comparison of the selenium level in healthy and burnt tissue of the sodium selenite-supplemented and non-supplemented group as well as in a control group. [4, 5]

Sodium selenite-supplementation significantly reduced the number of required skin grafts for burn victims (p = 0.02); BSA = Body Surface Area. [4]
Sodium selenite supplementation shortens hospital stay

A sodium selenite supplementation of 229 – 379 µg selenium per day reduced the hospital stay significantly after normalization for the extent of burn (Tab. 1) [2, 3].

For a burnt body surface of 40% the hospital stay was reduced from 40 days to 25 days on an average.

**Sodium selenite for burns**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Treatment ideally begins within 12 hours after admission to the ICU</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>then as continuous infusion</td>
</tr>
<tr>
<td></td>
<td>500^{1-3} µg Se</td>
</tr>
<tr>
<td>14 days for burns &lt; 60% of the body surface</td>
<td>maintenance therapy</td>
</tr>
<tr>
<td>21 days for burns ≥ 60% of the body surface</td>
<td>500^{1-3} µg Se / day</td>
</tr>
</tbody>
</table>

**Literature**

Tab. 1 Comparison of sodium selenite supplemented patient group with a placebo group (n = 41). [3]

<table>
<thead>
<tr>
<th></th>
<th>Sodium selenite</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay (days)</td>
<td>30 (14 – 46)</td>
<td>39 (18 – 58)</td>
<td>n.s.</td>
</tr>
<tr>
<td>ICU stay dependent on the burnt body surface (days/%)</td>
<td>0.6 ± 0.2</td>
<td>0.9 ± 0.3</td>
<td>0.034</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>28 (9 – 151)</td>
<td>39 (16 – 145)</td>
<td>0.18</td>
</tr>
<tr>
<td>ICU stay dependent on the burnt body surface (days/%)</td>
<td>0.63 (0.23 – 1.64)</td>
<td>0.99 (0.43 – 2.48)</td>
<td>0.002</td>
</tr>
<tr>
<td>Selenoprotein P [µg/l]</td>
<td>54.5 ± 8.69</td>
<td>63.0 ± 9.18</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Literature


General information

- Low selenium values in the post-reanimation phase
- Length of the reanimation correlates negatively with the selenium level
- Early administration of selenase® improves the neurological outcome of patients after cardiac arrest

Low selenium status in the post-reanimation phase

The prognosis of pre-hospital cardiac arrest is still poor. Cardiopulmonary reanimation is only successful for about a third of all patients. Also in the post-reanimation phase, a fatal course or residual neurological damage is not precluded. Probable causes are on the one hand hypoxic organ damage due to the interrupted oxygen supply, and on the other hand reperfusion-caused damage. The sudden backflow of blood to de-oxygenated tissue causes an increase of free oxygen radicals and can furthermore trigger severe systemic immune responses.

The characteristic symptoms, which can be summarized under the term “post-reanimation syndrome”, bear a striking similarity to the clinical picture of sepsis [1, 2]. Whether the post-reanimation syndrome is associated with a reduced selenium level, which is frequently observed with sepsis, was the object of a current trial by Fink et al. [3].

The serum selenium values of 77 patients who were treated in the ICU after successful cardiopulmonary reanimation, were analyzed [3]. The serum selenium level was determined six hours after reanimation (day one), after 24 hours (day two) and after 48 hours (day three). The serum selenium concentrations were compared with the serum values of 50 healthy study subjects without an anamnesis of heart disease, and with those of a control group (n = 50) with a stable cardiac disease. On average, the measured serum values for the resuscitated patients were significantly lower both in comparison to the healthy study subjects (86.0 ± 2.9 µg/l vs. 109.1 ± 1.3 µg/l; p < 0.0001), as well as compared to the cardiac control group (vs. 94.2 ± 2.2 µg/l; p = 0.04). The low serum selenium values of the reanimated group also persisted on day two (84.8 ± 2.9 µg/l) and day three (82.1 ± 3.1 µg/l) after the reanimation.
Comparison of the serum selenium concentration in patients with cardio-pulmonary reanimation (CPR), healthy study subjects, and a control group with stable cardiac disease. \cite{3}

- **Healthy vs. CPR Day 1**: \( p < 0.0001 \)

- **Control group vs. CPR Day 1**: \( p = 0.04 \)
Significantly lower selenium status in non-survivors after reanimation

In the trial by Fink et al, the serum selenium values of patients who survived reanimation were compared. The group was subdivided into survivors and non-survivors, whereby non-survivors were defined as reanimated patients who had not survived in the course of their stay in ICU. Successfully reanimated patients, who survived the period of ICU, showed significantly higher serum selenium values at admission to the ICU (98.1 ± 4.5 µg/l vs. 75.6 ± 3.4 µg/l; p = 0.0007) and on day three after reanimation (89.9 ± 4.9 µg/l vs. 74.1 ± 3.4 µg/l; p = 0.048) (Fig. 2). A ROC curve analysis revealed that the measurement of the serum selenium concentrations within the first hours after ICU admission predicted ICU mortality (AUC = 0.665; p < 0.05). Furthermore, the trial demonstrated that the minimum serum selenium concentration correlates inversely with the maximum damage to organs or with organ failure ($R^2 = 0.27; p < 0.05$).
The length of reanimation correlates negatively with the selenium level

The comparison of the serum selenium values six hours after successful resuscitation with the duration of reanimation indicates a negative correlation between these two parameters (Fig. 3). The longer the reanimation takes, the more rapidly the serum selenium level drops.

Fig. 3 Negative correlation between the serum selenium concentration and the duration of reanimation. [4]
Negative correlation between neurological damage and selenium concentration

The comparison of serum selenium levels of patients in good neurological condition after reanimation with patients with a hypoxic encephalopathy after reanimation showed a significant reduction of the serum selenium concentration after 24 and 48 hours in the latter group (p = 0.01) (Fig. 4)

The results of Busch et al. indicate the important role of selenium for protection from reperfusion damage. After successful reanimation, patients could benefit from early selenium therapy [6].

Literature

Comparison of the selenium level in patients with and without neurological damage. \[4\]

### selenase\textsuperscript{®} after reanimation

<table>
<thead>
<tr>
<th>Day 1</th>
<th>The beginning of treatment directly after reanimation or ICU admission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>as continuous infusion</td>
</tr>
<tr>
<td>Day 2 – 5</td>
<td>maintenance therapy</td>
</tr>
</tbody>
</table>

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selenase® protects the brain after cardiopulmonary reanimation

Brain damage is one of the most frequent causes of death and sequelae after successful cardiopulmonary reanimation [6]. Available treatment options for the attenuation of brain damage was so far primarily restricted to hypothermia treatment of the patient [7]. A currently discussed alternative is the administration of high-dose sodium selenite.

Selenium, which among other things is a component of the protein glutathione peroxidase, protects cells from oxidative stress. It is already successfully used in the prevention of neurological damage after an ischemic stroke [8, 9].

An austrian trial determined the effect of sodium selenite on the neurological course after cardiac arrest [10].

226 patients were included in this retrospective analysis. 124 patients were administered selenase® intravenously for five days directly after resuscitation. The daily dosage was 1,000 µg selenium for 106 patients, 400 µg selenium for two patients, and 200 µg selenium for 16 patients. The patients were evaluated according to the Glasgow-Pittsburgh Cerebral Performance Categories (CPC 1-5).

50% of the patients treated with sodium selenite regained consciousness again and had no or only moderately impaired brain function (CPC 1-2). 17% had severe brain damage (CPC-3; need for long-term care), 22% remained comatose, and 11% died.

In the group of patients who had received no selenase®, only 39% of the patients achieved a CPC of 1-2, 9% were classified as CPC 3, 32% remained comatose, and 20% died (Table 1).

Thus, patients treated with selenase® compared to the control group had a 2.4-fold higher probability of regaining consciousness (p = 0.014; 95%-confidence interval = 1.19 – 4.76) (Table 2).

On the basis of these results, the authors propose the hypothesis that the early administration of selenase® improves the patient’s neurological outcome after cardiac arrest.
Tab. 1  Impact of a therapy with selenase® on the course of disease after cardiac arrest. [10]

<table>
<thead>
<tr>
<th></th>
<th>selenase® (n = 124)</th>
<th>Control (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients who regain consciousness with CPC 1-2</td>
<td>62 (50%)</td>
<td>40 (39%)</td>
</tr>
<tr>
<td>Number of patients who regain consciousness with CPC 3</td>
<td>21 (17%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Number of patients who remained comatose</td>
<td>27 (22%)</td>
<td>33 (32%)</td>
</tr>
<tr>
<td>Number of patients who died</td>
<td>14 (11%)</td>
<td>20 (20%)</td>
</tr>
</tbody>
</table>

Tab. 2  Comparison of the predictors for regaining consciousness after reanimation. [10]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unit</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First monitored rhythm</td>
<td>shockable vs nonshockable</td>
<td>3.73 (1.87 – 7.52)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time until ROSC</td>
<td>1 min (increase)</td>
<td>0.94 (0.91 – 0.96)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Selenium administration</td>
<td>yes vs no</td>
<td>2.38 (1.19 – 4.76)</td>
<td>0.014</td>
</tr>
<tr>
<td>SAPS II</td>
<td>1 point increase</td>
<td>0.96 (0.93 – 0.99)</td>
<td>0.034</td>
</tr>
<tr>
<td>Cardiac arrest location</td>
<td>in the hospital vs outside</td>
<td>1.76 (0.79 – 3.92)</td>
<td>0.169</td>
</tr>
<tr>
<td>Therapeutic hypothermia</td>
<td>yes vs no</td>
<td>1.73 (0.49 – 6.10)</td>
<td>0.393</td>
</tr>
<tr>
<td>Bystander-initiated CPR</td>
<td>yes vs no</td>
<td>1.31 (0.66 – 2.62)</td>
<td>0.443</td>
</tr>
</tbody>
</table>

Statistically significant p < 0.05. ROSC = return of spontaneous circulation. OR = odds ratio. CI = confidence interval.
# Selenium in guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Adults</th>
<th>Infants with low birth weight</th>
<th>Children (premature and term infants)</th>
<th>Burn patients</th>
<th>Sepsis patients</th>
<th>ICU patients in general</th>
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<td>Reinhart K, Brunkhorst FM, AWMF online 2010</td>
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<td>McClave et al., Jpen 33 (2009) 3., 277–316</td>
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<td>National Institute for Clinical Excellence Feb 2006, UK</td>
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biosyn Arzneimittel GmbH

biosyn is the global market leader in high-dose selenium pharmaceuticals

This hidden champion supplies its high-revenue blockbuster selenase® to 22 countries, primarily for oncology and intensive care medicine.

Founded in 1984, biosyn Arzneimittel GmbH was one of the first German biotechnology companies. Now it has around 70 employees in Germany and subsidiaries in Liechtenstein, Austria and the USA.

Its portfolio encompasses some 30 products ranging from biotechnologically engineered medicines through chemotherapeutics to complementary drugs and food supplements for its main fields of intensive care medicine and oncology. The company’s major concern is treating patients as a whole. biosyn, a research-focused pharmaceutical company, puts up to 25 percent of revenues back into its pipeline.

Its mission is to explore, evolve and market highly efficacious drugs with low side effects based on the most up-to-date evidence molecular biology has to offer.

High-quality products from the world’s first GMP-compliant production of sodium selenite

In 2009, biosyn Arzneimittel GmbH was, and presumably still is, the first and only company in the world able to manufacture the active ingredient sodium selenite pentahydrate in internationally prescribed GMP quality – thanks to biosyn’s proprietary and patented production method. Its purification and crystallization technologies allow microbe-free production of high-quality trace element compounds under cleanroom conditions.

This enables the production of injectable liquid pharmaceuticals to meet the particularly stringent demands on quality. biosyn currently manufactures anhydrous sodium selenite and sodium selenite pentahydrate for oral and parenteral formulations.

The biosyn motto “we are research” not only symbolizes our dedication to medical and pharmaceutical progress but also for our drive to develop innovative manufacturing processes.

The company markets its selenium drugs under the brand name selenase® worldwide.

GMP-compliant production of sodium selenite at biosyn:
Vacuum drying system for targeted crystallization of metallic salts with defined portions of hydrated ingredients
Use of selenium in intensive care as adjunctive therapy for sepsis, ischaemia/reperfusion and reanimation