Selenium supplementation for critically ill adults (Review)

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[Intervention Review]

Selenium supplementation for critically ill adults

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ABSTRACT

Background

Selenium is a trace mineral essential to health and has an important role in immunity, defence against tissue damage and thyroid function. Improving selenium status could help protect against overwhelming tissue damage and infection in critically ill adults.

Objectives

This review assessed the effects of selenium supplementation, including the selenium-containing compound ebselen, on adults recovering from critical illness.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 3), MEDLINE, EMBASE, CAB NAR, BIOSIS, CINAHL, Current Controlled Trials and reference lists. We contacted investigators and handsearched four journals. The date of the most recent search was August 2007.

Selection criteria

Randomized trials of selenium or ebselen supplementation by any route in adults with critical illness (including patients with burns, head injury, brain haemorrhage, cerebrovascular accident) and after surgery.

Data collection and analysis

Two authors independently extracted data and assessed trial quality. We sought additional information as required from trialists. We undertook pooling of data for outcomes and selected exploratory analyses were undertaken.

Main results

Ten randomized trials involving 1172 participants were included. The quality of trials, as reported, was poor, particularly for allocation concealment. The availability of outcome data was limited and trials involving selenium supplementation were mostly small. Thus the results must be interpreted with caution.

Seven trials of intravenous sodium selenite showed no statistically significant difference in mortality (relative risk (RR) 0.75, 95% confidence interval (CI) 0.53 to 1.06). In general intensive care patients the RR for selenium supplementation was 0.75 (95% CI 0.59 to 0.96). Three trials of ebselen showed no statistically significant difference in mortality (RR 0.83, 95% CI 0.51 to 1.35).

Three trials of intravenous sodium selenite found no statistically significant difference between groups for participants developing infection (RR 1.22, 95% CI 0.67 to 2.23). Three trials of ebselen provided data for participants developing infections (pyrexia, respiratory infections or meningitis), which were not statistically significant (RR 0.60, 95% CI 0.36 to 1.02).

No clear evidence emerged for the benefits of selenium or ebselen supplementation for the outcomes of days on a ventilator, length of intensive care unit stay, length of hospital stay or quality of life.

Authors' conclusions

There is limited evidence to recommend supplementation of critically ill patients with selenium or ebselen. Trials are required which overcome the defects of the reviewed studies, particularly inadequate size and methodology.

PLAIN LANGUAGE SUMMARY

Selenium supplements for adults who are critically ill

Selenium is a mineral that is essential to health. It has an important role in defence against tissue damage and disease and improving selenium status could help protect adults with overwhelming illness. This review assessed the effects of selenium supplementation on adults recovering from critical illness.

Ten trials involving 1172 participants were included. The quality of trials, as reported, was poor. Outcome data were limited and these trials involving selenium supplementation were mostly small. Thus the results must be interpreted with caution.

Seven trials of intravenous sodium selenite showed no effect on mortality. Three trials of the selenium-containing compound ebselen also showed no effect on mortality. No effects on infections or adverse events were found.

No clear evidence emerged for the benefits of selenium or ebselen supplementation for days on a ventilator, length of intensive care unit stay, length of hospital stay or quality of life. There is, therefore, no clear evidence to recommend supplementation of critically ill patients with selenium or ebselen. Trials are required which overcome the defects of the reviewed studies, particularly inadequate size and methodology.

BACKGROUND

Selenium is a trace mineral that is essential to human health. Selenium-containing proteins include glutathione peroxidases and thioredoxin reductases (Angstwurm 2006a), which are antioxidant enzymes essential for the removal of damaging reactive oxygen species (ROS) also known as free radicals. ROS damage proteins, polysaccharides, nucleic acids and polyunsaturated fatty acids, which may lead to cell death (Geoghegan 2006). Selenium deficiency impairs the immune response; and supplementation in replete individuals appears to enhance the immune response (Rayman 2000). The iodothyronine deiodinase enzymes that control the production of the hormone triiodothyronine from thyroxine also require selenium.

Selenium intake from plants (and thus animals) generally reflects the levels present in soils. There is particular concern that intake in most parts of Europe is insufficient (Rayman 2000); intakes are generally higher in North America. Selenium status will be further impaired in those people with poor quality diets, such as alcoholics, and when dietary intake is reduced, for example during a chronic illness and postoperatively.

Ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one) is an organic selenium-containing compound which appears to act as a mimic of glutathione peroxidase; it may thus also have anti-oxidant properties (Parnham 2000).

Evidence suggests that excessive oxidative stress plays an important role in the development of complications of critical illness, such as the systemic inflammatory response which leads to acute respiratory distress syndrome (ARDS) and multiple organ failure (Bulger 2001). Berger 1998a found that providing an antioxidant trace element supplement containing selenium, zinc and copper was associated with fewer infections after major burns compared with placebo. Porter 1999a also found that antioxidant supple-

mentation with selenium, vitamin C, vitamin E and N-acetylcysteine for patients after severe trauma was associated with fewer infectious complications and less organ dysfunction compared to placebo.

A systematic review of randomized controlled trials of antioxidant nutrients in critical illness found a statistically significant reduction in mortality but not infections (Heyland 2005). There was a trend for lower mortality for antioxidants containing selenium (relative risk 0.59, 95% confidence intervals 0.32 to 1.08, P = 0.09).

The organic selenium-containing compound ebselen has also been investigated for its antioxidant properties in critical illness (Parnham 2000). We wished to systematically review randomized controlled trials of either selenium or ebselen supplementation in adults with critical illness.

OBJECTIVES

The primary objective was to examine the effect of nutrition supplemented with selenium or ebselen on mortality and number of infections in critically ill patients.

The secondary objective was to examine the relationship between selenium or ebselen supplementation and duration of mechanical ventilation, length of intensive care unit stay and length of hospital stay.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials of selenium supplementation or ebselen supplementation in critically ill patients, given in addition to their routine care.
Trials were included despite lack of blinding or placebo treatment.
We included unpublished studies and abstracts.

Types of participants

We included studies on adults with critical illness (including patients with burns, head injury, brain haemorrhage, cerebrovascular accident) and those undergoing elective major surgery.
We did not include studies on neonates and paediatric patients (that is aged less than 18 years).
Studies reporting mixed groups of participants (for example combined data of critically ill and medical patients) were included only if data could be provided separately for patients with critical illness.

Types of interventions

We examined nutritional interventions by the enteral or parenteral route, or both routes, supplemented with additional selenium versus nutritional care by the same route without additional selenium. We examined all types of selenium compounds including ebselen. We did not include immunonutritional interventions where selenium was one of several nutrients given together (for example with arginine and omega-3 fatty acids).

Types of outcome measures

We sought information on the following primary outcomes:
1. mortality (including early and late mortality, in the first month or later);
2. number of infectious complications (as defined in each of the included studies).
We also sought information on:
3. number of days on a ventilator;
4. length of stay in an intensive care unit (ICU);
5. length of hospital stay;
6. quality of life after discharge (as defined in the included studies);
7. adverse events;
8. economic outcomes.

Search methods for identification of studies

Electronic searches

In our original review we searched databases from inception until 2003. In this updated review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 3). We updated our search of MEDLINE (to July Week 2 2007), EMBASE (to Week 30 2007), CAB abstracts (to June 2007), BIOSIS (to 2 August 2007), CINAHL (to July Week 3 2007) and HEALTHSTAR (to September 2002). In MEDLINE and HEALTHSTAR the first two levels of the standard Cochrane search strategy for the identification of randomized controlled trials (Higgins 2005) were used with specific search terms (Appendix 1). Similar strategies were used for EMBASE and CINAHL. Search terms for CAB abstracts are given in Appendix 2, BIOSIS in Appendix 3and CENTRAL in Appendix 4.

Searching other resources

We also updated our search of reference lists of previous trials and review articles; books related to critical care, selenium and nutrition support; intensive care and nutrition journals (Clinical Nutrition to volume 26(3) June 2007, Journal of Parenteral and Enteral Nutrition to 31(1) Jan/February 2007, Critical Care Medicine to volume 35(8) August 2007, Intensive Care Medicine to volume

33(8) August 2007); database of ongoing research (Current Controlled Trials July 2007). We communicated with colleagues, particularly published trialists, in order to identify new trials. No language restriction was applied to eligible reports.

Data collection and analysis

Two authors independently screened and classified all citations as potential primary studies, review articles or other. Also independently, two authors examined all potential primary studies and decided on their inclusion in the review. Authors independently abstracted data on methodology and outcomes from each study, in duplicate, utilizing the components of a previously published system (Heyland 1998) to assess methodological quality (see below). Disagreements were resolved within pairs by consensus.

Methodological quality assessment criteria

1. Allocation concealment:
   i) concealed allocation, e.g. computer generated allocation by phone from a site remote from recruitment;
   ii) allocation not concealed or not sure (i.e. small but possible chance of disclosure of assignment or author states random but without description);
   iii) quasi-randomized (allocated alternately or by a predictable method, e.g. date of birth).
2. Analysis:
   i) intention to treat (participants analysed according to the arm they were originally allocated whether or not they received or completed the intervention);
   ii) other.
3. Blinding as reported by the investigators:
   i) double blinded;
   ii) single blinded;
   iii) not blinded.
4. Patient selection:
   i) consecutive eligible patients enrolled in the trial;
   ii) selected patients enrolled in the trial or unable to tell.
5. Comparability of groups at baseline:
   i) yes;
   ii) no or not sure.
6. Extent of follow up:
   i) 100% of participants;
   ii) < 100% of participants.
7. Treatment protocol:
   i) described so that it could be replicated by others;
   ii) poorly described.
8. Co-interventions (the extent to which non-trial interventions such as antibiotics, nutritional support, ventilation, oxygen and transfusions were applied equally across groups):
   i) well described and all equal;
   ii) described but not equal or not sure;
   iii) not described.
9. Outcomes:
   i) objectively defined so that others could use this definition (e.g. pneumonia using invasive diagnostic technique criteria);
   ii) partially described;
   iii) not described.

Prior hypotheses regarding sources of heterogeneity

The planned subgroup analyses to explore possible sources of heterogeneity were as follows.

1. Studies of surgical patients or patients with acute pancreatitis compared to studies of other critically ill patients.
2. Since there might be a dose-related response to selenium supplementation, we planned to group together studies evaluating higher selenium content formulae (greater than or equal to the cut-off point) and compare them to studies with lower selenium content formulae (using the median dose of selenium from the studies as the cut off).
3. Studies of ebselen compared with studies of other selenium compounds.
4. Study quality based on concealment of allocation, intention-to-treat analysis or level of blinding.

Data synthesis

The primary outcomes were early (within the first month) and late mortality and the incidence of infectious complications. We defined the infectious complication rate as the number of patients who developed infectious complications. The secondary outcomes were length of stay in ICU and hospital stay, in days. We combined data to estimate the common relative risk of death and infectious complications and we also calculated the associated 95% confidence intervals (CI). We used relative risk (RR) to summarize the treatment effect. We used the more conservative random-effects model to estimate overall relative risk and effect size due to the presence of study heterogeneity. Heterogeneity was expressed as the I^2 statistic (Higgins 2003), with a value of 0% indicating no heterogeneity and larger values showing increasing heterogeneity where, for example, 50% suggested moderate heterogeneity.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Of the 24 studies identified via the search strategy, 10 were included, 11 were excluded, two are ongoing and two are awaiting

assessment. The reasons for excluding the 11 studies are given in the table 'Characteristics of excluded studies'. Three included studies and three excluded studies were published in German only. Translations from German to English were performed for these studies. Unpublished studies were sought but not found. Some trials had multiple full text publications (Angstwurm 1999; Berger 2001; Saito 1998; Zimmermann 1997).

Of the three new included studies, one was found by handsearching, one was found by contact with the author after finding the trial in a conference proceeding and one was found in both MEDLINE and EMBASE. All seven of the previously included studies were identified via the MEDLINE search strategy. We sought further details from trial investigators for all seven studies and obtained them for two (Angstwurm 2007; Angstwurm 1999).

The included trials were all published between 1997 and 2007 except for one trial which was published in 1991 (Kuklinski 1991). Three trials of ebselen were Japanese multicentre trials (Ogawa 1999; Saito 1998; Yamaguchi 1998). One trial was a multicentre trial in German (Angstwurm 2007). The remaining trials were single centre trials in Germany, Switzerland and the UK. All selenium trials were of selenium given as sodium selenite (Angstwurm 2007; Angstwurm 1999; Berger 2001; Kuklinski 1991; Lindner 2004; Mishra 2007; Zimmermann 1997).

The 10 included studies involved a total of 1172 participants. The details of the included studies are provided in the table 'Characteristics of included studies'. Six trials recruited more male than female participants (Angstwurm 1999; Berger 2001; Ogawa 1999; Yamaguchi 1998). One trial recruited only men (Kuklinski 1991), one did not report the sex of the participants (Zimmermann 1997) and two studies had more women than men (Mishra 2007; Saito 1998). Where reported, the mean age of participants was more than 50 years. Two trials excluded participants older than 75 and 71 years, respectively (Berger 2001; Saito 1998).

Trials of selenium recruited participants with the following conditions: sepsis or systemic inflammatory response syndrome (Angstwurm 2007; Angstwurm 1999; Mishra 2007; Zimmermann 1997), severe multiple injury (Berger 2001) and more serious cases of acute pancreatitis (Kuklinski 1991; Lindner 2004). The three trials of ebselen were conducted in participants with acute neurological conditions: acute middle cerebral artery occlusion (Ogawa 1999), aneurysmal subarachnoid haemorrhage (Saito 1998) and acute ischaemic stroke (Yamaguchi 1998). It is unclear whether ebselen and selenium have similar mechanisms of action so all trials were not combined. For the ebselen trials no details were provided concerning the need for ventilation or the level of critical illness care required.

The three neurological trials of ebselen (Ogawa 1999; Saito 1998; Yamaguchi 1998) all used an enteral dose of 300 mg daily for 14 days that was compared to a matching placebo. Seven trials of selenium used intravenous sodium selenite, usually given as a continuous infusion over 24 hours, with doses of selenium ranging from 155 mcg to 2000 mcg (Angstwurm 2007; Angstwurm 1999, Berger 2001; Kuklinski 1991; Lindner 2004; Mishra 2007; Zimmermann 1997). Only Zimmermann 1997 had no comparison infusion. No study examined selenium or ebselen supplementation for more than 28 days.

The study by Berger 2001 included three study groups: selenium only, selenium combined with alpha-tocopherol and zinc, and placebo control. Only the comparison between selenium and placebo was presented here.

There were insufficient data to explore studies with better methodology compared to those with lesser methodology and studies evaluating higher selenium doses compared to those with lower selenium doses.

Risk of bias in included studies

The quality of trial methodology, as reported, was disappointing. The trials often failed to report trial methodology in sufficient detail. One trial had improved methodology after further details were obtained from one author (Angstwurm 1999).

All included studies were randomized controlled trials; no quasi-randomized clinical trials were included. Concealment of allocation was confirmed in only one of the seven trials: Cochrane allocation concealment score A (Berger 2001). The other trials did not clearly report the method of concealment of allocation: Cochrane allocation concealment score of B. Although not always explicitly stated, intention-to-treat analysis was undertaken in five of the 10 trials (Angstwurm 1999; Kuklinski 1991; Ogawa 1999; Saito 1998; Zimmermann 1997). Seven trials were reported to be blinded or double blinded (Angstwurm 2007; Berger 2001, Lindner 2004; Mishra 2007; Ogawa 1999; Saito 1998; Yamaguchi 1998). For the outcomes assessed in this review, it was unclear to whom the blinding referred. Only Angstwurm 2007 and Angstwurm 1999 recruited consecutive eligible patients.

In five trials (Angstwurm 1999; Kuklinski 1991; Lindner 2004; Ogawa 1999; Yamaguchi 1998) groups were clearly comparable at baseline. All but four trials (Angstwurm 2007; Lindner 2004; Yamaguchi 1998; Zimmermann 1997) clearly reported following up all participants for all outcomes until the end of the study. All trials clearly reported the treatments given for the trial but no trial clearly described the co-interventions as being equally provided to all groups. Four trials (Angstwurm 1999; Berger 2001; Ogawa 1999; Yamaguchi 1998) gave objectively described definitions of trial outcomes.

None of the authors provided a conflict of interest statement. Three trials reported receiving pharmaceutical company funding (Ogawa 1999; Saito 1998; Yamaguchi 1998).

Effects of interventions

The outcomes reported in the included studies are listed in the table of 'Characteristics of included studies'. Where available, mortality results have been presented using denominators based on the numbers of participants at randomization. Generally, the results for other outcomes have been presented using denominators based on the numbers of participants available at follow up.

Mortality

All 10 included studies provided mortality data, seven trials using selenium as intravenous sodium selenite (Angstwurm 2007; Angstwurm 1999; Berger 2001; Kuklinski 1991; Lindner 2004; Mishra 2007; Zimmermann 1997) and three trials of ebselen (Ogawa 1999; Saito 1998; Yamaguchi 1998).

Overall mortality (table 'comparison and data' 01.01) from trials of selenium showed a relative risk of 0.75 (95% CI 0.53 to 1.06, I^2 = 22%). Mortality after 28 days showed a relative risk of 0.71 (95% 0.43 to 1.17, I^2 = 37%) and at 90 days a relative risk of 0.87 (95% CI 0.35 to 2.14, I^2 = 36%).

Mortality (table 'comparison and data' 01.02) in trials of selenium in general intensive care patients (Angstwurm 1999; Angstwurm 2007; Berger 2001; Mishra 2007; Zimmermann 1997) was compared with trials in patients with acute pancreatitis (Kuklinski 1991; Lindner 2004). The relative risk in general intensive care patients was 0.75 (95% CI 0.59 to 0.96, I^2 = 0%). In patients with acute pancreatitis the relative risk was 0.40 (95% CI 0.01 to 12.30, I^2 = 81%).

Pooling of the data (table 'comparison and data' 01.02) from the three trials of ebselen showed no statistically significant difference in mortality (RR 0.83, 95% CI 0.51 to 1.35) and no evidence of statistical heterogeneity (I^2 = 0%). Mortality at 30 days was given by Ogawa 1999 (RR 1.78, 95% CI 0.53 to 5.95) and at three months by Saito 1998 and Yamaguchi 1998 (RR 0.72, 95% CI 0.42 to 1.22).

Infectious complications

Four trials of intravenous sodium selenite provided data. Berger 2001 provided data for participants developing infections based on the number of participants requiring antibiotics. Angstwurm 2007 reported that the incidence of new infections, for example the development of hospital acquired pneumonia, as well as the incidence of acute respiratory distress syndrome was not significantly different between the groups. Lindner 2004 provided data on the participants developing sepsis or peritonitis. Pooling (table 'comparison and data' 02.01) these three trials gave a relative risk of 1.22 (95% CI 0.67 to 2.23, I^2 = 0%). Mishra 2007 reported no significant difference between groups.

All three trials of ebselen (Ogawa 1999; Saito 1998; Yamaguchi 1998) provided data for participants developing infections (pyrexia, respiratory infections or meningitis) (table 'comparison and data' 02.01), with no statistically significant difference (RR 0.60, 95% CI 0.36 to 1.02).

Days on a ventilator

Two trials of intravenous sodium selenite provided data for the number of days on a ventilator. In the trial by Angstwurm 1999 days of ventilation were not statistically different between the supplemented and unsupplemented groups (median of 9 days with a range of 3 to 23 days compared with 10 days and range of 1 to 43 days, respectively). In the trial by Berger 2001 the supplemented group was ventilated for a median of 5 days (range 2 to 12 days) and the control group a median of 2 days (range 1 to 19 days), which was also reported as not statistically significant. Angstwurm 2007 reported that the incidence and hours of mechanical ventilation were not statistically significantly different between groups.

Length of stay in intensive care unit

Three trials of intravenous sodium selenite provided data on the length of stay in intensive care (Angstwurm 2007; Berger 2001; Mishra 2007). Angstwurm 2007 reported no significant difference for intensive care length of stay between the two groups. In Berger 2001 the supplemented group stayed for a median of 7 days (range 2 to 14 days) while the control group stayed a median of 4.5 days (range 2 to 25 days). This was reported as not significantly different. Mishra 2007 reported a length of stay of 21.3 (SD 16.2) days in the supplemented group and 20.8 (SD 21.8) days in the control group (reported P = 0.94)

Length of hospital stay

Two trials, both of intravenous sodium selenite, provided data for the length of hospital stay (Angstwurm 1999; Berger 2001). Angstwurm 1999 reported no significant difference between groups for survivors: median stay of 28 days (range 8 to 90 days) for the selenium group and a median of 36 days (range 16 to 70 days) for the control group. Berger 2001 also reported no significant difference between groups: median stay 35 days (range 13 to 249 days) for the selenium group and a median of 57.5 days (range 16 to 120 days) for the control group.

Quality of life after discharge

Trials of ebselen (Ogawa 1999; Saito 1998; Yamaguchi 1998) reported no statistically significant difference in Glasgow Outcome Scales (Jennett 1975) at final follow up. However the Modified Barthel Index Score (Shah 1989), an assessment of functional status, was reported as significantly improved by ebselen at a final follow-up time of three months in the trial by Yamaguchi 1998. No trials of selenium provided quality of life data.

Adverse events

Trial investigators reported a wide variety of individual adverse events, including: organ failure, shock, requirement for inotropic

support, requirement for fluids or transfusion, gastrointestinal bleeding, cerebral infarction and haemorrhage, nausea and vomiting, acute myocardial infarction, pulmonary embolism, enterocolitis, pancreatitis and skin rash. Angstwurm 1999 reported that renal failure requiring continuous veno-venous haemodialysis was required for three of the 21 participants receiving intravenous sodium selenite and nine of the 21 participants in the control group. Angstwurm 2007 reported that the need for haemodialysis or vasopressor therapy was identical in the two groups and that adverse events occurred in 110/122 of the intravenous sodium selenite group and 119/124 of the placebo group. Mishra 2007 reported that five of the 18 selenium supplemented participants required renal replacement compared with seven of the 22 controls. The relative risk of adverse event from these three trials was 0.75 (95% CI 0.40 to 1.43, I^2 = 57%).

In the three trials of ebselen, the overall incidence of adverse events in the ebselen and placebo groups were reported as 7.3% and 3.3%, respectively (Yamaguchi 1998); 10% and 14%, respectively (Saito 1998); and as not significant different (Ogawa 1999). Combining the results for Saito 1998 and Yamaguchi 1998 (no meta-analysis data were available for Ogawa 1999) yielded a relative risk of 1.16 (95% CI 0.40 to 3.36, I^2 = 68%).

Economic outcomes

No trials provided details of costs or economic outcomes.

DISCUSSION

This review found weak evidence that selenium supplementation, as intravenous sodium selenite, improves mortality in critically ill adults. The evidence was more suggestive of a benefit on mortality in the first month for general intensive care unit patients rather than patients with severe pancreatitis. The evidence is weak as a result of the poor methodological quality of the trials, for example only one trial clearly reported concealment of allocation. Few trials reported on outcomes other than mortality or clearly defined the reported outcomes. Periods of follow up were short and did not allow for the prolonged recovery from critical illness. There were insufficient data to examine the effect of methodological superiority or dose of selenium on the outcomes.

There was no clear evidence of benefit from the use of ebselen in patients with stroke or subarachnoid haemorrhage. The results of one large trial are still awaited (Yamaguchi 2003).

There was also no evidence to suggest that these interventions were harmful.

Four trials (Angstwurm 2007; Angstwurm 1999; Berger 2001; Mishra 2007) found significantly increased activity of the antioxidant selenoenzyme glutathione peroxidase, demonstrating the potential for intravenous sodium selenite to improve antioxidant capacity in participants. The measurement of selenium levels in the blood may be an unreliable marker of selenium status because levels fall with an acute phase response provoked by injury or infection (Sattar 1997).

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to recommend the supplementation of critically ill patients with selenium or ebselen except as interventions being investigated in the setting of a randomized clinical trial.

Implications for research

Large, well-designed, adequately powered trials of selenium and ebselen supplementation are required. The design and reporting of any future trial should conform to the CONSORT statement (Moher 2001) or any future development of it. Future research should examine functional status, patient perceived quality of life and include an economic evaluation. Independent observers should assess outcomes and the period of follow up should be for at least one year.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Angstwurm 1999

Methods	Method of randomization: states stratified randomization only Assessor blinding: states open label Intention to treat: carried out Lost to follow up: none
Participants	Location: intensive care unit, Klinikum Innenstadt, University of Munich, Germany Period of study: recruitment March 1995 to August 1996 42 patients Inclusion criteria: APACHE score greater or equal to 15, and clinical and laboratory signs of new systemic inflammatory response syndrome (SIRS) according to sepsis criteria (American College of Chest Physicians/Society of Critical Care Medicine), first 24 hours after admission Exclusion criteria: age < 18 years, pregnancy, after cardiopulmonary resuscitation, severe gastrointestinal bleeding, trauma, surgery, chronic renal failure, refusal to participate Sex: 29 males, 13 females Age: mean age 56 years (range 18 to 83 years)
Interventions	Timing of intervention: from day of admission to intensive care for additional supplementation for nine days a: continuous intravenous sodium selenite (535 mcg selenium for 3 days, 285 mcg selenium for 3 days, 155 mcg selenium for 3 days, 35 mcg selenium for remainder of total treatment time; and standard parenteral nutrition including glutamine 20 g/L b: continuous placebo of saline and intravenous 35 mcg selenium as sodium selenite, and standard parenteral nutrition including glutamine 20 g/L Allocated: 21/21 Assessed: 21/21
Outcomes	Length of follow up: until discharge Main outcomes: Mortality Other outcomes: Number of days on a ventilator Length of hospital stay
Notes	Request for further details of interventions sent 24th October 2003, reply received 17th November 2003

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Angstwurm 2007

Methods	Method of randomisation: states randomised but no further details Assessor blinding: carried out Intention to treat: not carried out Lost to follow up: reported
Participants	Location: 11 independent German intensive care units Period of study: enrolment December 1999 to October 2004 249 patients Inclusion criteria: men and women > 18 years with APACHE III score (22) > 70 and at least two of the following criteria: rectal body temperature > 38 °C or hypothermia < 36 °C, heart rate > 90 per minute, respiratory frequency > 20 per minute and PaCO2 < 32 mmHg (< 4.3 kPa), leucocytes > 12 000/µl or < 4 000/µl or > 10 % immature leucocytes, decrease of platelet count > 50 % within the first 24 h or platelets < 150 000/µl at admission; admission into the study after diagnosis within 24 h; beginning of treatment within 1h after inclusion. Exclusion criteria: pregnancy; missing informed consent of patient or relative/intimate friend; withdrawal of informed consent after inclusion into study; participation in any clinical trial within last 30 days; prior participation in this clinical trial; cerebral injury due to hypoxia after cardiopulmonary resuscitation; primary concomitant disease with expected high mortality within 2 months; not for resuscitation; malignant primary disease as cause of systemic inflammatory response syndrome or sepsis, e.g. agranulocytosis as result of chemotherapy or idiopathic bone marrow aplasia; haemorrhagic - necrotising pancreatitis without infectious complications. Sex: 162 males, 76 females Age: 64.6 years (SD 14.0)
Interventions	Timing of intervention: admission into study after diagnosis within 24 hours, study treatment beginning within 1 hour after inclusion a: 48 ml vial as bolus intravenous injection over 30 minutes of sodium selenite providing 1000 mcg selenium, followed by continuous infusion of 2 ml/hour over 24 hours for 14 days, total dose 15,000 mcg selenium. Allowed selenium from other preparations of up to 100 mcg/day. b: Matching placebo of 0.9% sodium chloride give as same regimen. Allowed selenium from other preparations of up to 100 mcg/day. Allocated: ???/??? Assessed: 116/122
Outcomes	Length of follow up: 28 days Main outcomes: 28 day mortality Participants with new infections Other outcomes: Number of hours on a ventilator Length of ICU stay Participants with adverse events
Notes	Emailed 8th August 2006 asking for further details on participants with all infections, length of ventilation, total numbers randomised to each group, and further details of the randomisation process

Risk of bias

Item	Authors' judgement	Description

Angstwurm 2007 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Berger 2001

Methods	Method of randomization: concealed Assessor blinding: states double-blind but no further details Intention to treat: carried out Lost to follow up: none
Participants	Location: surgical intensive care unit (ICU) of the Central Hospitalier Universitaire Vaudois, Lausanne, Switzerland Period of study: before 2000 21 patients Inclusion criteria: severe multiple injury (injury Severity Score, ISS, > 15) involving at least two body systems, pathophysiological changes requiring ICU support, age 18 to 75 years, admission within 24 hours of injury Exclusion criteria: pre-existing renal or hepatic failure, foreseeable imminent death, no informed consent, documented hypothyroidism prior to accident Sex: 15 males, 6 females Age: age range 18 to 74 years
Interventions	Timing of intervention: from day of admission for five days a: slow intravenous infusion over 24 hours of 500 mcg selenium as sodium selenite/day b: infusion vehicle over 24 hours c: slow intravenous infusion over 24 hours of 500 mcg selenium/day and 13 mg zinc/day, 150 mg alpha-tocopherol in 5 ml 10% lipid emulsion (Lipovenös, Fresenius, Stans, Switzerland) as slow injection once daily upon initiation of intravenous infusion (data for this group not used in this review) Allocated: 9/12/11 Assessed: 9/12/11
Outcomes	Length of follow up: appears followed up until died or left hospital, maximum length of stay 249 days Main outcomes: Mortality Numbers of patients with infection (defined as requiring antibiotics) Other outcomes: Number of days on a ventilator Length of intensive care unit stay Length of hospital stay
Notes	Intention to treat data taken from paper in Nutrition Research

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Kuklinski 1991

Methods	Method of randomization: states randomized but no further details Assessor blinding: not reported Intention to treat: carried out Lost to follow up: none
Participants	Location: hospital, Rostock, Germany Period of study: before 1991 17 patients Inclusion criteria: contrast CT scan showed pancreatic necrosis, less than 72 hours since onset of pancreatitis Exclusion criteria: mild pancreatitis Sex: all male Age: range 28 - 65 years
Interventions	Timing of intervention: unclear ?8 days a: intravenous 500 mcg sodium selenite daily duration unclear (Selenase pro injectione, GN PHARM, Arzneimittel GmbH, Stuttgart) b: no treatment Allocated: 8/9 Assessed: 8/9
Outcomes	Length of follow up: Main outcome: Mortality
Notes	Request for further details on dose of selenium given sent 20th October 2003. Letter returned as author no longer at address in publication

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lindner 2004

Methods	Method of randomisation: states randomised but no further details Assessor blinding: not reported Intention to treat: not reported Lost to follow up: details provided
Participants	Location: medical centre, Chemnitz, Germany Period of study: enrolment January 1997 to November 1998 70 patients Inclusion criteria: severe acute pancreatitis managed on medical wards, severe abdominal pain, 3 fold increase of amylase and lipase, onset within 72 hours Exclusion criteria: none given Sex: 39 males, 28 females (completers) Age: median 50-52 years

Lindner 2004 (*Continued*)

Interventions	Timing of intervention: start unclear, given until discharged a: day 1 2000 mcg selenium as sodium selenite, days 2-5 1000 mcg/d, day 6 until discharged 300 mcg/d b: 0.9% sodium chloride placebo, Allocated: 35/35 Assessed: 32/35
Outcomes	Length of follow up: until discharge Main outcomes: Mortality Number of patients with infectious complications (sepsis)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Mishra 2007

Methods	Method of randomisation: states randomised but no further details Assessor blinding: states double-blind Intention to treat: not reported Lost to follow up: no details provided
Participants	Location: intensive care unit, Liverpool, UK Period of study: before 2005 40 patients Inclusion criteria: APACHE II score > 15, clinical suspicion of infection and > 1 organ dysfunction Exclusion criteria: chronic renal failure, alcoholic liver disease, immunodeficiency Sex: 19 males, 21 females Age: mean age 66 years
Interventions	Timing of intervention: within 24 hours of admission to intensive care and within 72 hours since diagnosis of sepsis, given until discharged a: intravenous selenium 470 mcg/d for 3 days, then 320 mcg/d for 3 days, then 160 mcg/d for 3 days, and 30 mcg/d thereafter b: 30 mcg/d Allocated: 18/22 Assessed: 18/22 for mortality
Outcomes	Length of follow up: 28 days Main outcomes: Mortality at 28 days Infections Other outcomes:

Mishra 2007 (*Continued*)

	Length of intensive care unit stay Renal replacement therapy
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ogawa 1999

Methods	Method of randomization: states randomized list but no further details Assessor blinding: states double-blind but no further details Intention to treat: ITT for mortality only Lost to follow up: none
Participants	Location: 28 Japanese neurosurgical and neurological units Period of study: recruitment June 1994 to November 1996 105 patients Inclusion criteria: acute stroke with complete occlusion of the M1 (M2) portion of the middle cerebral artery (MCA) on cerebral angiography and no low-density area (LDA) in the MCA territory on computed tomography (CT), could start drug treatment within 12 hours of stroke Exclusion criteria: distinct fresh LDA in the MCA territory on CT scans; stenosis or occlusion of trunk arteries, other than MCA; haemorrhagic stroke including subarachnoid haemorrhage; pregnancy; severe hepatorenal or metabolic disease Sex: 67 males, 32 females Age: mean age 66 years
Interventions	Timing of intervention: started within 12 hours of middle cerebral artery occlusion, given for 14 days a: oral ebselen 150 mg twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness b: oral placebo granules twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness Allocated: 48/57 Assessed: 48/57 for mortality
Outcomes	Length of follow up: Main outcomes: Mortality Numbers of patients with infection Other outcomes: Quality of life - Glasgow Outcome Scale,
Notes	Request for further details of denominators and infections sent October 22nd 2003, no reply received

Risk of bias

Ogawa 1999 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Saito 1998

Methods	Method of randomization: states randomized lists but no further details Assessor blinding: states double-blind and blinded outcome assessment Intention to treat: carried out Lost to follow up: none
Participants	Location: 84 Japanese neurosurgical units Period of study: enrolled November 1992 to April 1994 286 patients Inclusion criteria: subarachnoid haemorrhage (SAH) from aneurysmal rupture within previous 96 hours, and SAH Hunt and Kosnik grade II to IV or World Federation of Neurosurgical Surgeons grade I to IV at admission Exclusion criteria: pregnancy; age < 20 years or > 71 years; major cardiopulmonary, hepatorenal or metabolic disease; large intracerebral or intraventricular clots Sex: 112 males, 174 females Age: mean age 56 years
Interventions	Timing of intervention: started within 96 hours of subarachnoid haemorrhage, given for 14 days a: oral ebselen 150 mg twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness b: oral placebo granules twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness Allocated: 145/141 Assessed: 145/141
Outcomes	Length of follow up: 3 months Main outcomes: Mortality Numbers of patients with meningitis, respiratory infection Other outcomes: Quality of life - Glasgow Outcome Scale
Notes	Request for further details of unpublished trial mentioned in main trial report, and numbers of patients with infections sent 21st October 2003, no reply received

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Yamaguchi 1998

Methods	Method of randomization: states randomized lists but no further details Assessor blinding: states double-blind but no further details Intention to treat: not carried out Lost to follow up: not complete, two patients excluded
Participants	Location: 68 Japanese neurological and neurosurgical units Period of study: recruitment June 1994 to December 1996 302 patients Inclusion criteria: acute ischaemic stroke, including thrombosis and embolism, by symptoms and CT scan; could receive drug treatment within 48 hours of onset Exclusion criteria: transient ischaemic attacks; pregnancy; surgery interfering with the assessment of neurological function; previous stroke with residual neurological impairment; major cardiopulmonary, hepatic, renal or metabolic disease; haemorrhagic stroke Sex: 189 males, 111 females Age: mean age 65 years, range 22 to 85 years
Interventions	Timing of intervention: started within 48 hours of stroke, given for 14 days a: oral ebselen 150 mg twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness b: oral placebo granules twice daily given enterally as fine granules dispersed in water, gastric tube if disturbed consciousness Allocated: 152/150 Assessed: 151/149
Outcomes	Length of follow up: 3 months Main outcomes: Mortality Numbers of patients with respiratory infection Other outcomes: Quality of life - Glasgow Outcome Scale, modified Barthel Index
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Zimmermann 1997

Methods	Method of randomization: states randomized but no further details Assessor blinding: not reported Intention to treat: not reported Lost to follow up: not reported
Participants	Location: university hospital, Dresden, Germany Period of study: before 1997 40 patients

Zimmermann 1997 (*Continued*)

	Inclusion criteria: systemic inflammatory response syndrome and organ failure Exclusion criteria: none given Sex: not given Age: not given
Interventions	Timing of intervention: start unclear, given for 28 days a: 1000 mcg bolus of sodium selenite, thereafter 1000 mcg/24 hours as continuous intravenous infusion, for 28 days b: no treatment Allocated: 20/20 Assessed: ?20/?20
Outcomes	Length of follow up: 28 days Main outcome: Mortality
Notes	Request for details of denominators and infections sent 21st October 2003, no reply received

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Berger 1998	Randomized trial in adults with burns; selenium part of trace element supplement evaluated, which also contained copper and zinc
Berger 2004a	Randomized trial in adults with burns; selenium part of trace element supplement evaluated, which also contained copper and zinc
Berger 2004b	Randomized trial in adults with cardiac surgery; selenium part of antioxidant supplement evaluated
Berger 2005a	Combined results of Berger 2004 and Berger 1998
Berger 2005b	Randomized trial in adults with cardiac surgery, myocardial infarction, trauma or subarachnoid haemorrhage; selenium part of antioxidant supplement evaluated
Börner 1997	Not randomized trial, not adults
Porter 1999	Randomized trial of antioxidant therapy (including selenium) versus placebo in trauma patients

(*Continued*)

Thiele 1997	Not randomized trial, not critical care
Uden 1990	Randomized, crossover trial of antioxidant therapy (including selenium) versus placebo in the prevention of recurrence of pancreatitis
Watters 2002	Randomized trial of micronutrients (including selenium) versus placebo in patients undergoing elective aneurysmectomy
Wollschläger 1997	Not randomized trial, selenium supplementation in acute pancreatitis

Characteristics of ongoing studies *[ordered by study ID]*

Andrews 2004

Trial name or title	SIGNET trial (Scottish multicentre trial of glutamine and selenium supplemented parenteral nutrition for critically ill patients)
Methods	
Participants	500 patients, on intensive care units, requiring at least half nutritional requirements by parenteral route, aged 16 years and over
Interventions	Factorial design with glutamine containing versus non-glutamine containing parenteral nutrition for 7 days, with or without 500 mcg/d selenium as sodium selenite for 7 days
Outcomes	Participants with new infections, length of stay in intensive care, mortality, infections, days of antibiotic use, duration of parenteral nutrition, alive ventilator-free days, acute hospital length of stay, quality of life, economic evaluation
Starting date	June 2004, recruitment due to finish August 2008
Contact information	Dr Peter Andrews; Anaesthetics, Intensive Care and Pain Medicine; University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh, EH24 2XU, UK
Notes	

Yamaguchi 2003

Trial name or title	Forty centre, double-blind, placebo-controlled trial
Methods	
Participants	394 patients with acute non-lacunar stroke (cardio-embolic or atherothrombotic infarction < 24 hours)
Interventions	Ebselen 150 mg twice daily or placebo started within 24 hours of onset for 14 days

Yamaguchi 2003 (*Continued*)

Outcomes	Glasgow Outcome Scale three months post stroke, National Institute of Health Stroke Scale and Barthel Index scores at one and three months
Starting date	March 2000, recruitment finished September 2002
Contact information	Takanori Yamaguchi, for the Ebselen Study Group, National Cardiovascular Center, Osaka, Japan
Notes	Letter requesting further details sent 20th October 2003. Reply received 3rd November 2003, giving further details of inclusion criteria and trial intervention from Dr T Motohashi, Daiichi Pharmaceutical Co Ltd. Email sent to Dr Motohashi requesting results of trial 12th June 2006, reply received 19th June 2006 stating that publication is still planned

DATA AND ANALYSES

Comparison 1. Selenium versus no selenium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality by duration (sodium selenite)	7	476	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.53, 1.06]
1.1 Selenium 28 day	5	364	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.43, 1.17]
1.2 Selenium 90 day	2	112	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.35, 2.14]
2 Selenium mortality ICU and pancreatitis (sodium selenite)	7	476	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.53, 1.06]
2.1 General intensive care patients	5	389	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.96]
2.2 Acute pancreatitis	2	87	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.01, 12.30]
3 Mortality by duration (ebselen)	3	693	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.51, 1.35]
3.1 Ebselen 30 day	1	105	Risk Ratio (M-H, Random, 95% CI)	1.78 [0.53, 5.95]
3.2 Ebselen 3 month	2	588	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.42, 1.22]

Comparison 2. Selenium versus no selenium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of infected participants	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Selenium	3	337	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.67, 2.23]
1.2 Ebselen	3	685	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.36, 1.02]

Comparison 3. Selenium versus no selenium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with adverse event	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Selenium	3	328	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.40, 1.43]
1.2 Ebselen	2	588	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.40, 3.36]

Analysis 1.1. Comparison 1 Selenium versus no selenium, Outcome 1 Mortality by duration (sodium selenite).

Review: Selenium supplementation for critically ill adults

Comparison: 1 Selenium versus no selenium

Outcome: 1 Mortality by duration (sodium selenite)

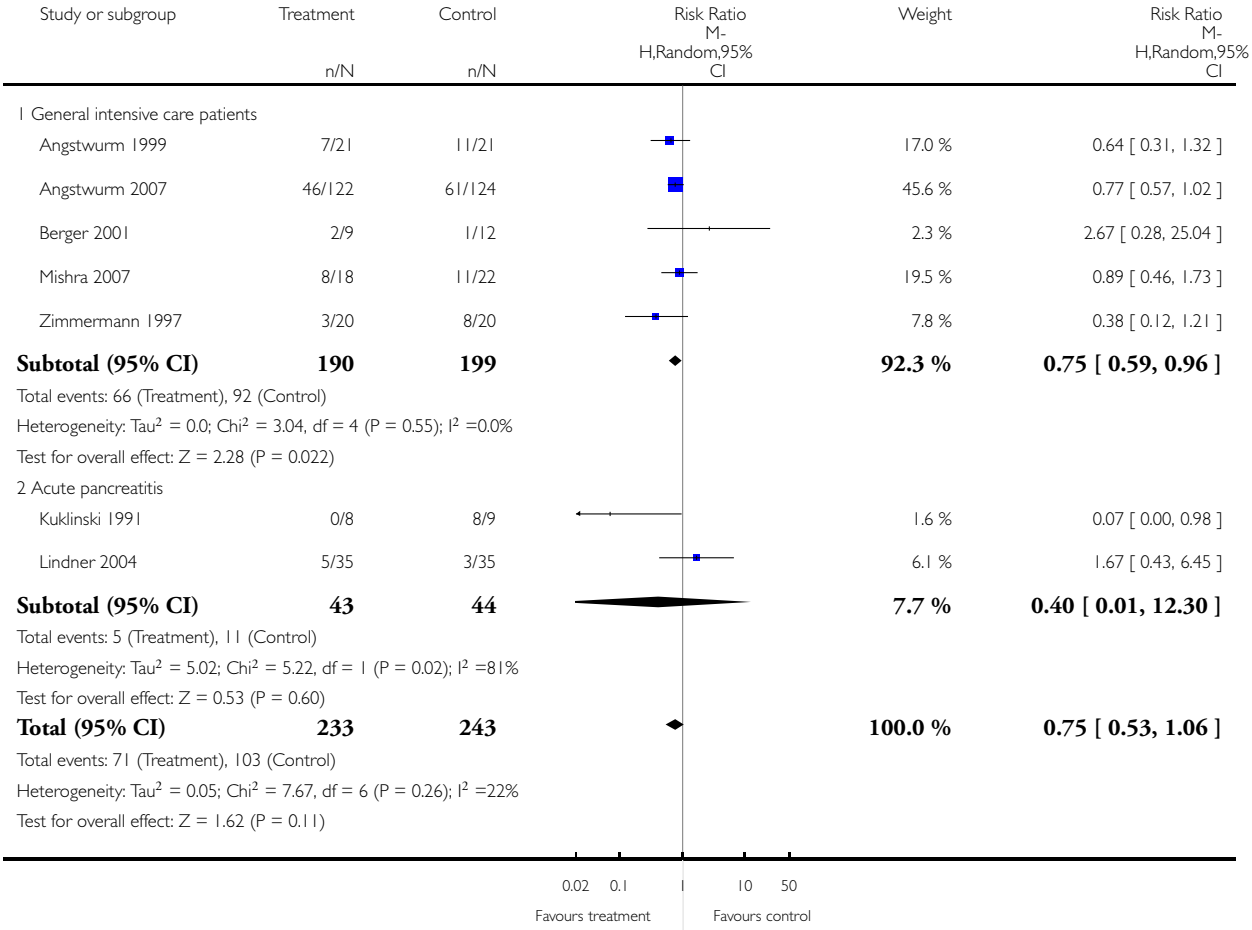
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Selenium 28 day					
Angstwurm 2007	46/122	61/124		45.6 %	0.77 [0.57, 1.02]
Berger 2001	2/9	1/12		2.3 %	2.67 [0.28, 25.04]
Kuklinski 1991	0/8	8/9		1.6 %	0.07 [0.00, 0.98]
Mishra 2007	8/18	11/22		19.5 %	0.89 [0.46, 1.73]
Zimmermann 1997	3/20	8/20		7.8 %	0.38 [0.12, 1.21]
Subtotal (95% CI)	**177**	**187**		**76.9 %**	**0.71 [0.43, 1.17]**
Total events: 59 (Treatment), 89 (Control)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 6.30$, df = 4 (P = 0.18); I^2 =36%					
Test for overall effect: Z = 1.36 (P = 0.18)					
2 Selenium 90 day					
Angstwurm 1999	7/21	11/21		17.0 %	0.64 [0.31, 1.32]
Lindner 2004	5/35	3/35		6.1 %	1.67 [0.43, 6.45]
Subtotal (95% CI)	**56**	**56**		**23.1 %**	**0.87 [0.35, 2.14]**
Total events: 12 (Treatment), 14 (Control)					
Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 1.57$, df = 1 (P = 0.21); I^2 =36%					
Test for overall effect: Z = 0.30 (P = 0.76)					
Total (95% CI)	**233**	**243**		**100.0 %**	**0.75 [0.53, 1.06]**
Total events: 71 (Treatment), 103 (Control)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 7.67$, df = 6 (P = 0.26); I^2 =22%					
Test for overall effect: Z = 1.62 (P = 0.11)					

Analysis 1.2. Comparison 1 Selenium versus no selenium, Outcome 2 Selenium mortality ICU and pancreatitis (sodium selenite).

Review: Selenium supplementation for critically ill adults

Comparison: 1 Selenium versus no selenium

Outcome: 2 Selenium mortality ICU and pancreatitis (sodium selenite)

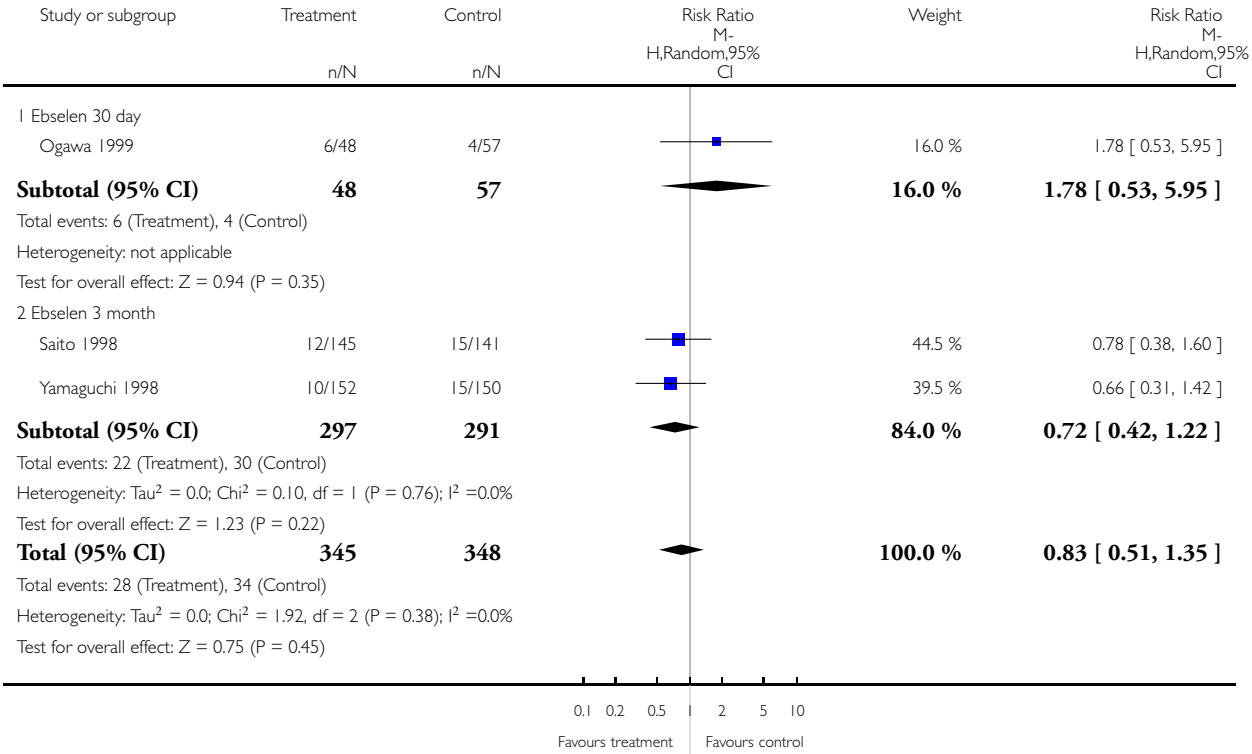


Analysis 1.3. Comparison 1 Selenium versus no selenium, Outcome 3 Mortality by duration (ebselen).

Review: Selenium supplementation for critically ill adults

Comparison: 1 Selenium versus no selenium

Outcome: 3 Mortality by duration (ebselen)

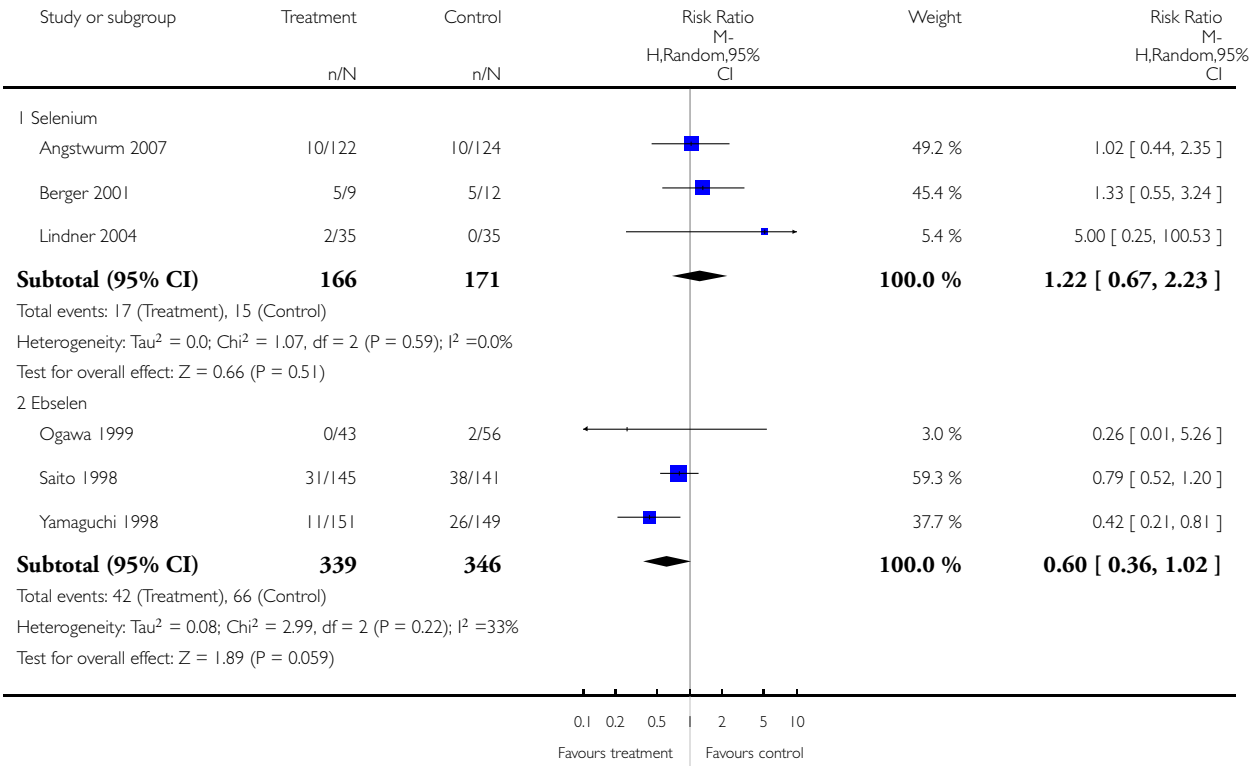


Analysis 2.1. Comparison 2 Selenium versus no selenium, Outcome 1 Number of infected participants.

Review: Selenium supplementation for critically ill adults

Comparison: 2 Selenium versus no selenium

Outcome: 1 Number of infected participants



Analysis 3.1. Comparison 3 Selenium versus no selenium, Outcome 1 Number of participants with adverse event.

Review: Selenium supplementation for critically ill adults

Comparison: 3 Selenium versus no selenium

Outcome: 1 Number of participants with adverse event

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Selenium					
Angstwurm 1999	3/21	9/21		11.9 %	0.33 [0.10, 1.06]
Angstwurm 2007	110/122	119/124		72.1 %	0.94 [0.88, 1.01]
Mishra 2007	5/18	7/22		16.0 %	0.87 [0.33, 2.29]
Subtotal (95% CI)	**161**	**167**		**100.0 %**	**0.75 [0.40, 1.43]**
Total events: 118 (Treatment), 135 (Control)					
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 4.67$, df = 2 (P = 0.10); $I^2 = 57\%$					
Test for overall effect: Z = 0.87 (P = 0.38)					
2 Ebselen					
Saito 1998	15/145	20/141		67.0 %	0.73 [0.39, 1.37]
Yamaguchi 1998	11/152	5/150		33.0 %	2.17 [0.77, 6.10]
Subtotal (95% CI)	**297**	**291**		**100.0 %**	**1.16 [0.40, 3.36]**
Total events: 26 (Treatment), 25 (Control)					
Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 3.15$, df = 1 (P = 0.08); $I^2 = 68\%$					
Test for overall effect: Z = 0.28 (P = 0.78)					

APPENDICES

Appendix 1. Medline and Healthstar search strategy

1. selenium compounds.mp
2. selenium.mp
3. selen$.tw
4. ebselen.tw
5. 1 or 2 or 3 or 4

Appendix 2. CAB abstracts search strategy

1. random$.tw
2. trials$.tw
3. placebo$.tw
4. 1 or 2 or 3
5. selen$.tw
6. ebselen.tw
7. 5 or 6
8. 4 and 7

Appendix 3. BIOSIS search strategy

1. TI=random*
2. TI=trial*
3. TI=placebo*
4. 1 or 2 or 3
5. TI=selen*
6. TI=ebselen
7. 5 or 6
8. 4 and 7

Appendix 4. Cochrane Central Register of Controlled Trials

1. selen* (all fields)
2. ebselen (all fields)
3. 1 or 2

WHAT'S NEW

Last assessed as up-to-date: 16 August 2007.

Date	Event	Description
20 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2002

Review first published: Issue 4, 2004

Date	Event	Description
17 August 2007	New search has been performed	Three new trials are included. Two of these were previously classified as ongoing trials (Mishra 2005, Angstwurm 2006). The conclusions of the review are unchanged
16 August 2007	New search has been performed	Search strategies reran until 17th August 2007
16 August 2007	New search has been performed	Search reran

CONTRIBUTIONS OF AUTHORS

All four reviewers were involved in protocol development, literature searching, quality assessment and data abstraction of trials, and production of the review.

DECLARATIONS OF INTEREST

Alison Avenell and David Noble are grantholders in the ongoing SIGNET trial.

SOURCES OF SUPPORT

Internal sources

- University of Aberdeen, UK.
- Grampian University Hospitals NHS Trust, UK.

External sources

- Chief Scientist Office of the Scottish Executive Health Department, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Antioxidants [adverse effects; *therapeutic use]; Azoles [adverse effects; *therapeutic use]; Critical Illness [mortality; *therapy]; Organoselenium Compounds [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Selenium [adverse effects; *therapeutic use]

MeSH check words

Adult; Humans