

A meta-analysis of randomized controlled trials

Efficacy of selenium treatment for sepsis

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Abstract

Background: To understand the clinical outcomes of selenium therapy in patients with sepsis syndrome, we conducted a meta-analysis of randomized controlled trials (RCT).

Methods: A total of 13 RCTs comparing selenium and placebo for patients with sepsis were reviewed systematically.

Results: However, we could not detect the association of selenium treatment with a decreased mortality at different time course (relative risk [RR] [95% confidence interval, CI]: 0.94 [0.82–1.06] at day 28; 0.73 [0.36–1.47] at day 90; 1.16 [0.78–1.71] at 6 months; respectively). Selenium supplementation did not show favorable efficacy in the incidence of renal failure, secondary infection or duration of mechanical ventilation (RR [95% CI]: 0.65 [0.41–1.03]; 0.96 [0.87–1.06]; standard mean difference [SMD] [95% CI]: 0.17 [–0.30–0.63]; respectively). Interestingly, we found that selenium therapy was benefit for sepsis patients with reduced duration of vasopressor therapy, staying time in intensive care unit and hospital, and incidence of ventilator-associated pneumonia (SMD [95% CI]: –0.75 [–1.37 to –0.13]; –0.15 [CI: –0.25 to –0.04]; –1.22 [–2.44 to –0.01]; RR [95% CI]: 0.61 [0.42–0.89]; respectively).

Conclusion: Based on our findings, intravenous selenium supplementation could not be suggested for routine use.

Abbreviations: CI = confidence interval, ICU = intensive care unit, RCT = randomized controlled trials, RR = relative risk, SIRS = systemic inflammatory response syndrome, SMD = standard mean difference, VAP = ventilator-associated pneumonia.

Keywords: meta-analysis, selenium, sepsis

1. Introduction

Sepsis is a life-threatening complication of an infection. During sepsis, the excessive reactive oxygen molecules and/or depletion antioxidants contribute to the dysfunction of the cells and sepsis-related deaths.^[1] Some processes are involved in the pathophysiology of sepsis and oxidative stress is suggested to play a vital role.^[1,32,33] Selenium is reported as an important trace element to this antioxidation process.^[2–4] Selenium-containing proteins, such as thioredoxin reductases and glutathione peroxidases, are essential antioxidant enzymes to remove harmful reactive oxygen species.^[3,5,6] In recent research, selenium may be involved in the immune

response and regulation of thyroid hormones.^[7,8] In addition, the selenium deficiency is often observed in a patient with sepsis, especially those accompanied with diets of inferior quality, including chronic disease, critical illness, and gastrointestinal illness.^[9,33] Selenium is seemed to be great important in some conditions of the systemic inflammatory response, and highly oxidative stress may play an essential role in the progress of complications.^[3,4,10–12]

In the current decades, series clinical trials have evaluated the effect of seleno-compounds in patients with systemic inflammation.^[13–16] They included selenious acid and sodium selenite and their combination with another antioxidant therapy was also observed. Previous evidence suggests that in patients with sepsis syndromes, a decreased selenium level may be associated with increased mortality and incidence of organ failure, with enhanced levels of reactive oxygen markers.^[7,13–14] However, published systematic reviews revealed an inconsistent conclusion about the efficacy of selenium supplementation on mortality in sepsis patients.^[17–20] Therefore, we retrieved the systematic review to investigate the clinical outcomes of selenium supplementation in the populations of the sepsis syndrome.

2. Material and methods

2.1. Identification of trials

We performed a literature search in MEDLINE (1950 to June 2018), EMBASE (1974 to June, 2018) and the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 6, 2018), using the following terms: “critical illness,” “sepsis,” “sepsis syndrome,” “septic,” “severe sepsis,” “systemic inflammatory response syndrome,” “sepsis shock,” “selenium,” “selenium compounds,” “sodium selenite.” We also screened the reference of included trials and related reviews and searched on ClinicalTrials.gov to include additional studies. A detail study protocol was uploaded on PROSPERO (CRD42018102706).

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2.2. Selection criteria

Among the retrieved results, only reporting clinical trials (RCT) involving humans were included. Other inclusion criteria included: study population of sepsis, severe sepsis, sepsis shock or systemic inflammatory response syndrome (SIRS); intravenous selenium supplementation (either with or without loading dose) with a placebo control; mortality at day 28, mortality at day 90 and mortality at 6 months; incidence of renal failure, duration of vasopressor therapy, duration of mechanical ventilation, staying course of intensive care unit (ICU) and hospital, secondary infection, incidence of ventilator-associated pneumonia (VAP) and serious adverse events. If the studies with other antioxidant agents' treatment, the studies about patients with burns, trauma, or undergoing major surgery, or the studies only with abstract would be excluded. No language restrictions were applied.

2.3. Data extraction and risk of bias assessment

All eligible reported were screened by 2 investigators (SL and LT) independently and abstracts, data integrity, references, and methodological quality were evaluated using a data abstraction form. If data were incomplete data, emails were sent to the authors for supplemental information. The risk of bias and methodological quality were assessed using the Cochrane risk bias tool. Any disagreement was resolved through consensus or referred to a third investigator (QL).

2.4. Statistical analysis

For dichotomous outcomes, the Mantel-Haenszel method was used to estimate the relative risk (RR) with 95% confidence interval (CI). For continuous outcomes, the inverse variance was employed to estimate standard mean difference (SMD) with 95% CI. Statistical heterogeneity was quantified by Mantel-Haenszel chi-square test and the I^2 statistic. Significant heterogeneity was suggested as $P < .10$ or $I^2 > 50\%$. The subgroup analysis was disaggregated by loading dose or not, the published years of included trials, type of participants of individual trials or set of eligible trials. Publication bias was evaluated by funnel plots, and asymmetry of funnel plot was measured by the Egger test.^[21,22] Data analyses were conducted using Review Manager Software (RevMan 5.3) and Stata (version 14, Stata Corp, College Station, TX).

3. Results

3.1. Description of studies

We retrieved a total of 291 potentially relevant reports by our electronic searches, which included 237 unique studies after deduplicating (Fig. 1). Based on the included criteria, 224 articles were excluded after the review process. Ultimately, 13 articles with 1922 individuals published from 1997 to 2017 were selected for inclusion in our meta-analysis.^[13-16,23-31] The treatment duration of studies varied from 7 days to 21 days and a loading dose of selenium was administered in 9 trials (Table 1). Four studies were conducted at a multicenter and 9 were single-center studies. The patients with septic shock and SIRS were studied in 1 and 3 studies, respectively. The others included patients with sepsis, severe sepsis or septic shock. The age of patients studied ranged from 17 years old to 83 years old and majorities (60%) were male. The sample size ranged from 35 to 1180 (mean, 161). Regarding the quality of studies, 50% of the studies were patient-

blinded, 50% had incomplete outcome data, 10% were outcome-blinded, and 25% were allocation-concealed. A high risk of bias of studied included was shown (Fig. S1 and Fig. S2, <http://links.lww.com/MD/C858>).

3.2. Mortality

Thirteen RCTs with a total population of 1922 patients with sepsis reported data on mortality at day 28,^[13-16,24-31] 2 studies with 1143 patients of sepsis reported data on mortality at day 90^[13,23] and 1 studies with 50 patients of sepsis reported data on mortality at 6 months.^[30]

At day 28, selenium treatment was not associated with a decreased mortality when compared to placebo (RR=0.94, 95% CI: 0.82-1.06) (Fig. 2). As no significant heterogeneity in the eligible trials, the fixed-effect model was used ($I^2=0\%$, $P=.47$). No matter loading dose selenium used or not, there was no significant difference on mortality at day 28 between subgroups (RR=0.94, 95% CI: 0.81-1.08; RR=0.94, 95% CI: 0.69-1.27, respectively) used fixed-effect model ($I^2=12\%$, $P=.33$; $I^2=0\%$, $P=.45$, respectively) (Fig. S3, <http://links.lww.com/MD/C858>).

At day 90, pooled analyses showed similar mortality between the selenium and control group (RR=0.73, 95% CI: 0.36-1.47) (Fig. S4, <http://links.lww.com/MD/C858>). The random-effect model was used due to significant heterogeneity in the eligible trials ($I^2=83\%$, $P=.01$).

At 6 months, meta-analyses showed no significant effect of the selenium treatment, when compared with placebo (RR=1.16, 95% CI: 0.78-1.71) with a fixed-effect model (Fig. S5, <http://links.lww.com/MD/C858>).

3.3. Other clinical outcomes

Five trials^[16,23,27,29,30] with 227 patients with sepsis reported data on the incidence of renal failure, and selenium supplementation were not associated with reduced incidence of renal failure compared with control group (RR=0.65, 95% CI: 0.41-1.03), used a fixed effect model ($I^2=0\%$, $P=.59$) (Fig. 3).

A pooled analysis of 4 trials^[13,16,23,30] with 1246 sepsis patients shown that selenium treatment was associated with reduced duration of vasopressor therapy (SMD=-0.75, 95% CI: -1.37 to -0.13; Fig. 4) with the random effect model ($I^2=87\%$, $P<.0001$). When data from 5 trials about mechanical ventilation^[13,16,24,27,30] were included, selenium supplementation showed similar effect with placebo (SMD=0.17, 95% CI: -0.30 to 0.63) using a random effect model ($I^2=80\%$, $P=.0005$) (Fig. S6, <http://links.lww.com/MD/C858>).

The aggregated results of the 6 trials^[13,15,16,24,27,29] with 1445 patients shown that selenium supplementation was associated with reduced the staying time in ICU (SMD=-0.15, 95% CI: -0.25 to -0.04) with a fixed effect model ($I^2=57\%$, $P=.04$) (Fig. S7, <http://links.lww.com/MD/C858>). Four trials^[13,16,24,28] with 1253 patients on staying time in hospital, and selenium supplementation was not associated with reduced this time (SMD=-1.22, 95% CI: -2.44 to -0.01) (Fig. S8, <http://links.lww.com/MD/C858>) and the random effect model was used ($I^2=96\%$, $P<.0001$).

A meta-analysis of 5 trials^[13,15,24,27,30] with 1472 patients shown that selenium treatment was not associated with reduced secondary infection compared with placebo (RR=0.96, 95% CI: 0.87-1.06), used the fixed effect model ($I^2=38\%$, $P=.17$) (Fig. S9, <http://links.lww.com/MD/C858>).

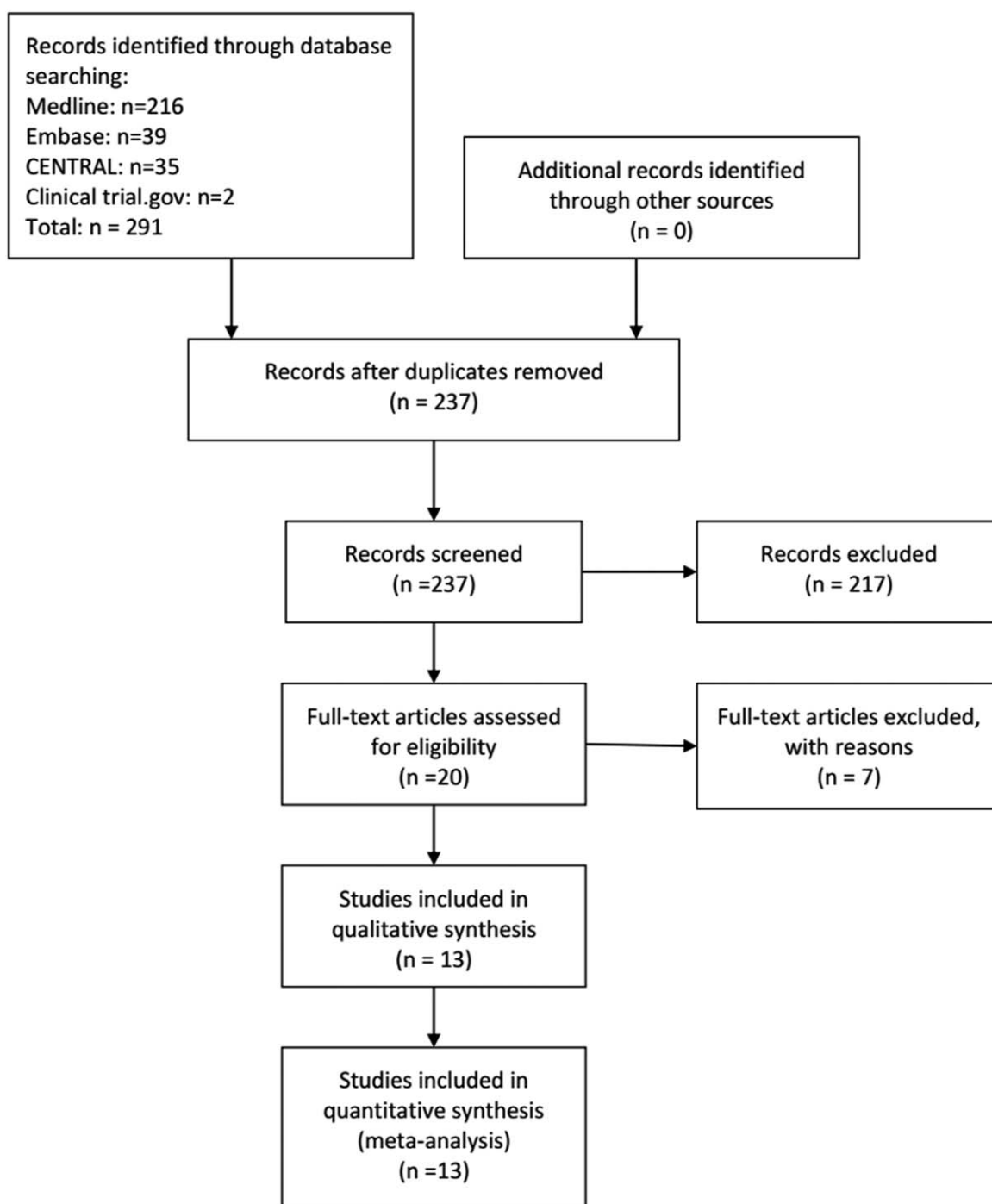


Figure 1. Selection process of trials.

The aggregated results of the 2 trials^[24,27] with 85 patients shown that selenium supplementation was associated with reduced incidence of VAP compared with placebo (RR=0.61, 95% CI: 0.42–0.89), and the fixed effect model was used ($I^2=0%$, $P=.53$) (Fig. S10, <http://links.lww.com/MD/C858>).

Two RCTs^[27,30] with a total population of 91 patients with sepsis reported data on serious adverse events, included respiratory failure, refractory shock, and acute kidney injury. The aggregated results shown, between the selenium and control group, that there were no significant different on incidence of respiratory failure, refractory shock or acute kidney injury

(RR=3.45, 95% CI: 0.75–15.90; RR=0.85, 95% CI: 0.34–2.14; RR=0.84, 95% CI: 0.41–1.72; respectively) (Fig. S11, <http://links.lww.com/MD/C858>). The fixed effect model was used ($I^2=0%$, $P=.62$; $I^2=0%$, $P=.77$; $I^2=0%$, $P=.52$; respectively).

3.4. Sensitivity analyses and Publication bias

Based on the published years of included trials, we conducted a subgroup analysis and showed that before 2001 selenium supplementation was associated with reduced mortality at day

Table 1**Descriptive characteristics of studies included in the meta-analysis.**

Study	Country	Study set	Time frame	Cases (N)	Age, yr	Sex (M/F)	Patients	Interventions	Study outcomes	Duration of follow-up	Attrition (%)
Chelkeba, 2017	Ethiopia	ICU, single-center	2012–2014	54	17–82	44/10	Sepsis, severe sepsis, or septic shock	Loading dose 2000 µg of sodium selenite followed by 1500 µg continuously for 14 d versus placebo	Mortality, duration of vasopressor therapy, incidence of renal failure	90 d	0
Bloos, 2016	Germany	Thirty three ICUs, multi-center	November 2009 to June 2013	1180	65.7 ± 13.7	691/398	Severe sepsis or septic shock	Loading dose 1000 µg of sodium selenite followed by a continuously 1000 µg/d until discharge from the ICU but not longer than 21 d versus placebo	Mortality, duration of vasopressor therapy, duration of mechanical ventilation, length of stay ICU, length of stay hospital, secondary infection	90 d	8
Chelkeba, 2015	Iran	ICU, single-center	2012–2014	54	17–82	46/8	Sepsis, severe Sepsis and septic shock	Loading dose 2000 µg of sodium selenite followed by 1500 µg of sodium selenite for 14 d versus placebo	Mortality, duration of mechanical ventilation, length of stay ICU, length of stay hospital, secondary infection, VAP, Mortality	90 d	0
Woth, 2014	Hungary	ICU, single-center	NR	40	54–78	23/17	Severe septic	1000 µg/30min loading dose of sodium selenite and 1000 µg/d treatment for a maximum of 14 d versus control group (not described)	Mortality	7 d	0
Valenta, 2011	Czech Republic	ICU, single-center	March 2004 to April 2009	150	Adult, mean age 60	97/53	SIRS, sepsis, or septic shock	Sodium selenite loading dose 1000mg then 500 mg/d IV for 5–14 d versus placebo	Mortality	28 d	0
Manzanarates 2011	Uruguay	ICU, single-center	December 2006 to January 2008	35	Adult, mean age 54–58	15/16	SIRS	Selenite loading 2000mg then 1600 mg/d for 10 d versus placebo	Mortality, incidence of renal failure, duration of mechanical ventilation, length of stay ICU, secondary infection, VAP, Serious adverse events	28 d	11
Andrews, 2011	United Kingdom	Ten ICUs, multi-center	June 2004 to November 2008	132	Adult, mean age 64	66/66	Sepsis	Sodium selenite 500 mg/d for 7 d versus placebo	Mortality	6 mo	0
Montoya, 2009	Mexico	ICU, single-center	October 2007 to Febrer 2008	68	Adult, mean age 65–67	38/30	Septic	Selenium 1000mg IV on day 1 then 500mg on the day 2 then 200 mg/d for 7 d versus selenium 100 mg/d for 9 d	Mortality, length of stay hospital	28 d	0
Mishra, 2007	United Kingdom	ICU, single-center	2002–2004	40	Adult, mean age 65–67	19/21	Septic	Sodium selenite 474mg IV for 3 d then 31 mg/d for 3 d then 158 mg/d for 3 d then 31.6 mg/d versus placebo	Mortality, incidence of renal failure, length of stay ICU	28 d	0
Forceville, 2007	France	Seven ICUs, multi-center	February 2002 to March 2004	60	Adult, mean age 66–69	38/22	Septic shock	Sodium selenite 4000 mg IV loading dose on day 1 followed 1000 mg/d for 9 d versus placebo	Mortality, incidence of renal failure, duration of vasopressor therapy, duration of mechanical ventilation, secondary infection	12 mo	0
Angstwuerm, 2007	Germany	Eleven ICUs, multi-center	December 1999 to October 2004	238	Adult, 64.6 ± 14.0	162/76	SIRS, sepsis, or septic shock	Sodium selenite 1000mg IV loading dose followed 1000 mg/d for 14 d versus placebo	Mortality, length of stay ICU, secondary infection,	28 d	20
Angstwuerm, 1999	Germany	ICU, single-center	March 1995 to August 1996	42	18–83	29/13	Patients with SIRS	Sodium selenite 500 mg/d for 3 d followed 250 mg/d for 3 d then 125 mg/d for 3 d then 35 mg/d versus maintenance dose 35 mg/d	Incidence of AKI, in-hospital mortality, length of stay ICU, length of stay hospital, duration of mechanical ventilation, duration of vasopressor therapy	28 d	0
Zimmermann, 1997	German	NR	NR	40	NR	NR	SIRS	Sodium selenite 1000mg IV loading then 1000 mg/d infusion versus placebo	Mortality	28 d	0

AKI = acute renal failure, ICU = intensive care unit, NR = not reported, RCT = randomized controlled trial, SIRS = systemic inflammatory response syndrome, VAP = ventilator-associated pneumonia.

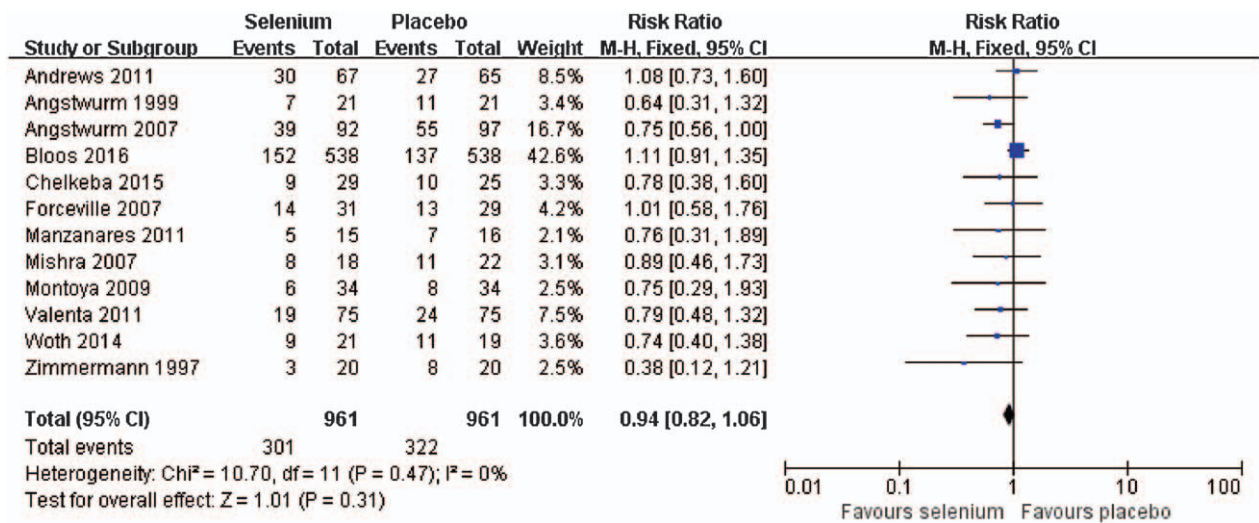


Figure 2. Effect of selenium versus placebo on the mortality at day 28.

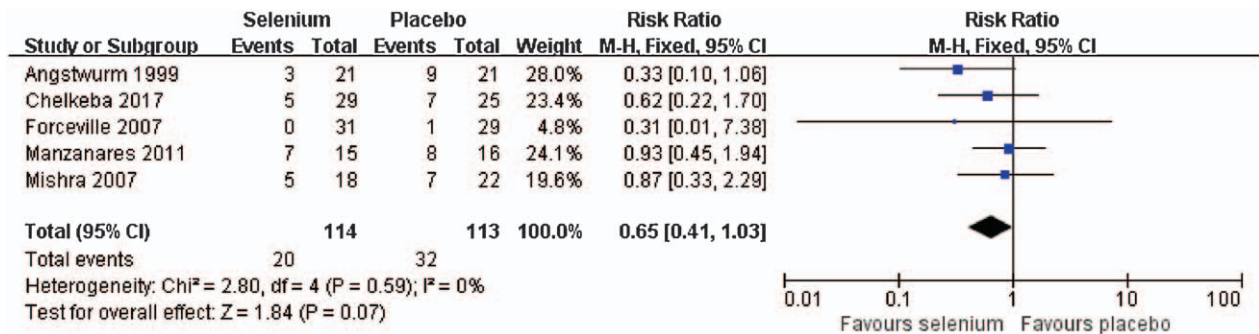


Figure 3. Effect of selenium versus placebo on the incidence of renal failure.

28 (RR=0.36, 95% CI: 0.14–0.95), while this associate could not be observed from 2012 to 2011 and from 2012 to recently (RR=0.76, 95% CI: 0.55–1.04; RR=1.09, 95% CI: 0.84–1.40; respectively) (Fig. S12, <http://links.lww.com/MD/C858>). Moreover, selenium treatment decreased mortality at day 28 in the subgroup of patients with SIRS than placebo (RR=0.43, 95% CI: 0.19–0.96). But, no significant inter-group difference in mortality was found among the subgroup patients with sepsis shock or with sepsis, severe sepsis and sepsis shock at day 28 (RR=0.95, 95% CI: 0.77–1.16; RR=1.01, 95% CI: 0.37–2.80; respectively) (Fig. S13, <http://links.lww.com/MD/C858>). In addition, pooled analysis of trials of single-center shown that

selenium treatment was associated with reduced mortality at day 28 compared with placebo (RR=0.62, 95% CI: 0.41–0.92), but not in multi-center trials (RR=1.02, 95% CI: 0.82–1.28) (Fig. S14, <http://links.lww.com/MD/C858>).

No evidence of potential publication bias was shown by Egger test and Begg test ($P = .133$ and $P = .837$, respectively, Fig. 5).

4. Discussion

Our analysis included 13 trials, with 1922 individuals with sepsis and randomly assigned to selenium or placebo group. Generally, selenium supplementation shows no effect on decreased mortality

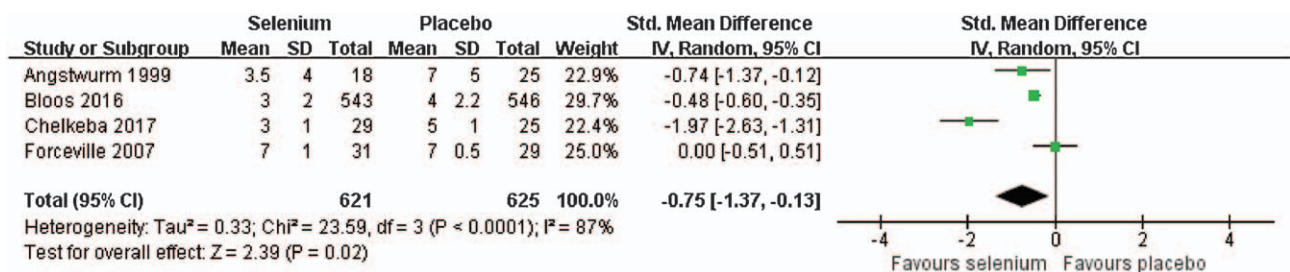


Figure 4. Effect of selenium versus placebo on the duration of vasopressor therapy.

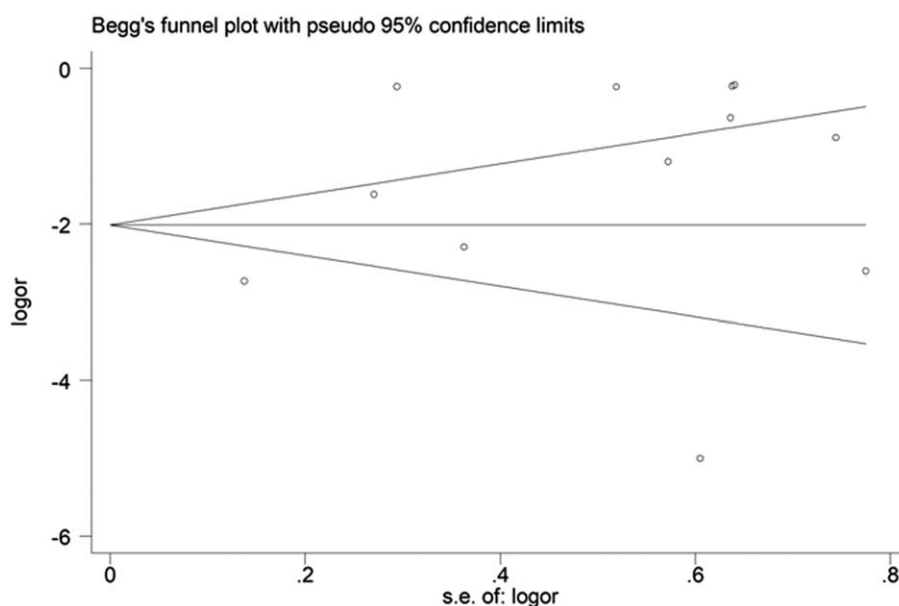


Figure 5. Begg funnel plot.

of adult's patients with sepsis. Interestingly, some subgroups, such as the study published before 2001, SIRS patients, single-center studies, show that selenium can reduce mortality in patients with sepsis. Additionally, patients may benefit from selenium treatment with less duration of vasopressor therapy and shorter staying time in ICU and hospital, but not in the incidence of renal failure and serious adverse events, duration of mechanical ventilation or secondary infection. In addition, our results show that the safety of selenium is acceptable.

In contrast to previous systematic reviews, this meta-analysis included 4 additional RCTs and 1 of them was a multi-center large sample trial. We analyzed overall mortality based on the follow-up period, and reversed the secondary clinical outcomes including safety data. But, a previous systematic review showed that selenium treatment reduced in day 28 mortality, and less secondary clinical outcomes were defined.^[19] Another published meta-analysis focused population of critically ill patients included 21 RCTs with 4044 patients. It showed that selenium does not improve clinical outcomes.^[17] The applicability of our results is only for adults with sepsis, and there is inadequate evidence to support this intervention for routine use. It is well known that the RCT is the strictest method because it is usually used to determine the causal relationship between treatment and outcome. The randomization process is the strength of RCT. None of the included studies was reported with overall low bias risk. Nine of the 13 studies were at high bias risk in the generation of random sequence. Only 4 studies registered in the database and only 2 trials published the study protocol, and we had deemed 9 of 13 studies at high reporting bias risk. Therefore, we should interpret the results with prudence as the overall high bias risk of included studies. From what has been discussed above, the evidence quality of this study was low.

Some limitations of existing evidence should be acknowledged. First, this report included patients with sepsis syndrome at few countries and regions, and with different study set, with different baseline characteristics; all of which could have resulted in the heterogeneity. Second, methodologic quality was low or unclear in most of the eligible studies. The published years of included

trials or the study setting of single-center or multi-center revealed different results, suggesting that the possible benefit is unclear among different study time or different setting, even though difference of this subgroup was statistically significant. Thirdly, the diagnosis of all trials is based on sepsis 1.0 or 2.0. It is worth to expect whether there will be a different clinical outcome based on the new diagnostic criteria of sepsis. Fourth, most of the eligible trials were small sample-size studies, and few trials reported more outcomes in relation to a clinical endpoint. Although it is needed to carry out high-quality RCTs recruiting a larger number of patients with sepsis syndrome, and reporting more outcomes in connection with a clinical endpoint, for made stronger conclusions, performing RCTs in critically ill patients may be faced with ethical challenges. Moreover, on account of the limited availability of data, relevant adverse effects associated with treatment could not be fully evaluated. Additionally, there is a need to conduct longer follow-up trial to evaluate the influence on mortality and other clinical outcomes. Last, most of the eligible trials did not access the cost-effectiveness of selenium supplementation, which is important to identify feasibility, specifically in developing countries.

5. Conclusion

In conclusion, our analyses shown the effect of selenium supplementation on duration of vasopressor therapy, staying time in ICU and hospital, incidence of VAP, but we failed to find the effect on mortality, either with loading does or not, and on a reduction in the incidence of renal failure, duration of mechanical ventilation, and incidence of secondary infection. And, there was not obvious harmful effect of the treatment among sepsis patients. Thus, intravenous selenium supplementation could not be suggested to routine use for serious sepsis patients. Moreover, well-designed, large-sample studies of selenium therapy, with low bias risk, according to the CONSORT statement, should be conducted. Detail clinical outcomes, longer period follow-up period, and life quality of patient and cost-effectiveness should be assessed.

Author contributions

Every author was responsible for the content of this manuscript and approved to submit. The study was designed by SL and LT. The search strategies were conducted by QZ. The selection of study, assessment of validity, and extraction of data were done by PG and XA. TT and LH entered and analyzed the data.

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