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REPORT

Parenteral selenium for the clinical effect of sepsis: A meta-analysis of randomized controlled trials

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Abstract: Previous studies have shown that selenium and its compounds play a role in immunomodulatory, antioxidant stress and so on. If selenium can improve the prognosis of patients with sepsis, it will be another weapon in the treatment of sepsis. At present, there are some randomized controlled trials (RCTs) about parenteral selenium for the treatment of sepsis. However, the results of those studies are not consistent. Studies were searched from electronic databases including PubMed, Cochrane, and Embase. RCTs which applied the selenium to septic patients as the inference measure were collected. After data extraction and the evaluation for eventual inclusion literatures, the data were analyzed by the statistical software RevMan 5.3. A total of 11 RCTs were included, containing 1916 septic patients. Meta-analysis showed that there is no statistically significant difference between the selenium group and the control group in mortality (RR=0.95, 95%CI=0.83-1.08, *P*=0.42), ICU length of stay (MD=1.56, 95%CI=-0.66-3.79, *P*=0.17) and new infections (RR=0.95, 95%CI=0.73-1.24, *P*=0.69). The present study suggests that there is no sufficient evidence that the parenteral selenium can improve the prognosis of septic patients.

Keywords: Selenium, sepsis, intensive care union, meta-analysis.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection with completed unclear pathogenesis (Singer *et al*., 2016). Sepsis is also an important cause of death in ICU (Intensive care union) patients. With the rapid development of medical technology in recent years, a pile of novel treatment measures for sepsis are emerging and the prognosis of patients with sepsis is also improved. However, the morbidity and mortality of sepsis is still high. According to the data of the last decade, the incidence of sepsis was 437/10 million per year (95%CI =334-571) and the mortality was 17%. The incidence of severe sepsis was 270/10 million per year (95%CI =176-412) and the mortality was 26% (Fleischmann *et al*., 2016). Thus sepsis brings great threats to human health because of its high morbidity and high mortality. Therefore, it is urgent to develop new effective treatment for sepsis.

Selenium, as an important trace element in human body, is closely related to human health. Seefood, Cereals, meat and other foods are rich in selenium. *In vivo*, selenium participates in synthesis of various selenoproteins'(e.g. selenoprotein P) and play an important role in scavenging free radicals and immune regulation (Kvicala 1999; Rayman 2012; Steinbrenner 2009; Roman *et al*., 2014). Currently, many studies have shown the advantages of selenium in anti-tumor, improving viral diseases, protecting the cardiovascular, liver protection (Wadhwani *et al*., 2017; Burbano *et al*., 2002; Wang 2017 and Miller 2001).

The French scholar Forceville *et al*. (2007) revealed that the concentration of plasma selenium in patients with SIRS (systemic inflammatory response) tended to decrease by about 40% in the early stages of the disease, and was associated with higher mortality in septic patients (Forceville *et al*. 1998). Furthermore, RCTs (Randomized controlled trials) exploring whether selenium supplementation improves the prognosis of septic patients emerged in recent years, in the late 90s of the last century. The study by Angstwurm *et al*. (1999) reported that septic patients had a lower mortality after the supplement of selenium, however, this study included only 42 septic patients. In 2007, he drew a similar conclusion in a study with a larger number of cases: High doses of selenium could reduce the mortality in severe sepsis or septic shock (Angstwurm *et al*., 2007). For years, there were many other studies confirmed the

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conclusion above. However, in 2016, a study with the largest number of cases so far showed that sodium selenite failed to reduce the mortality of sepsis patients (Bloos *et al*., 2016). In order to solve these discrepancies, in this article, we made a unified standard to systematically evaluate the clinical effect of selenium on septic patients.

MATERIALS AND METHODS

Inclusion and exclusion criteria

Research type

The RCTs of parenteral selenium for the clinical effect of sepsis among adult patients (>18 years old).

Intervention measures

Patients in the control group received conventional treatment, including standard dose of selenium (<75ug/day), primary disease therapy and major organs support, such as fluid resuscitation, anti-infection therapy. The selenium group was treated with selenium preparation (higher than standard dose of selenium).

Outcomes

(1) mortality, (2) length of ICU stay, (3) new infections (such as new pneumonia).

Exclusion criteria

Excluding non RCTs, case reports, animal studies, reviews, repeated reports and Juveniles patients.

Search strategy

We searched Pubmed, Cochrane and Embase database (from 1980 to August 2017). The language is not restricted. Search terms include: "randomized", "parenteral", "intravenous", "seleuim", "Selenite", "Selenious", "sepsis", "septic shock" (fig. 1).

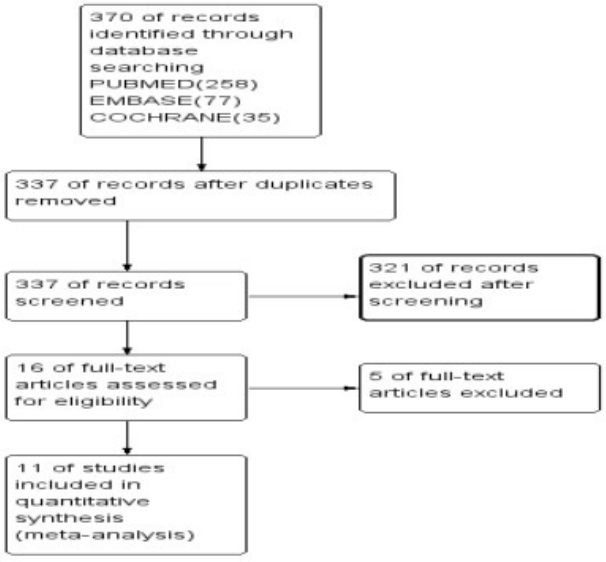

Fig. 1: Retrieval process of the studies.

Data extraction

2 researchers independently extracted data according to the inclusion and exclusion criteria. Disagreements were solved by discussions, when discussions failed to solved the disagreements, a third author was involved to make decision.

Methodological quality assessment

We used the Cochrane risk of bias tool which includes the following 7 aspects to assess the methodological quality: Random sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. The assessment criteria are as follows, high risk bias: Any aspect above be regarded as high risk; low risk bias: All the aspects were of low risk; unclear risk bias: unclear risk in any aspect while not high in other aspects.

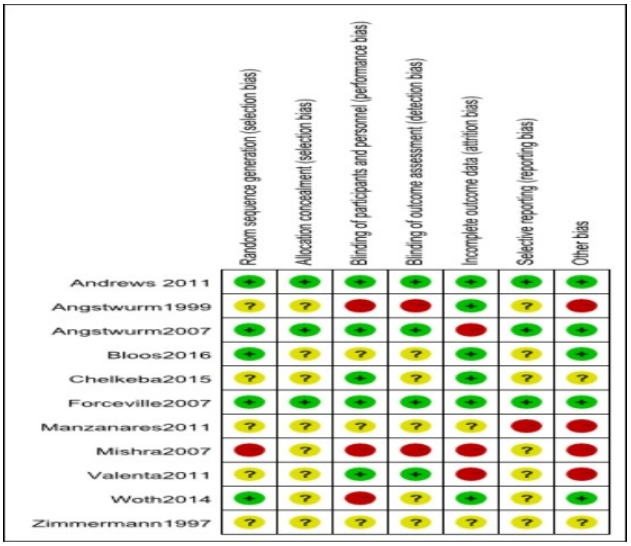

Fig. 2: Results of methodological quality evaluation

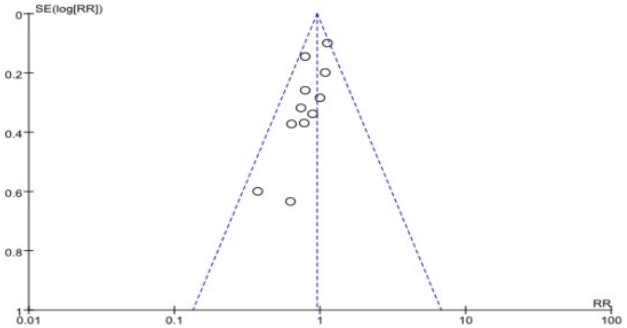

Fig. 3: The funnel plot of the publication bias analysis

STATISTICAL ANALYSIS

The RCTs were collated and checked according to the requirements of meta-analysis. Data processing was carried out by using Review Manager 5.3 software provided by the Cochrane international cooperation

organization. Using two-sided test, the level of significance was 0.05. If there was no significant heterogeneity (I^2<50%), using the Peto Mantel-Haenszel fixed effect model was used; if the heterogeneity test was significant (I^2≥50%), the Dersimonian Laird random effect model was used. And, reverse funnel plot was used to analyze potential publication bias.

RESULTS

The basic information of the randomized clinical trials included: a total of 370 articles about the supplement of selenium in the treatment of sepsis were found and 337 articles were collected after removing duplicates. After reading abstracts, studies belonging to animal experiments, reviews, case reports, or non- RCTs were excluded and there were 16 articles remained. Then, we read the full text of the 16 studies in detail. Finally, 11 papers containing a total of 1916 cases were included in this study, which involve 956 patients in the selenium treatment group and 960 patients in the control group (table1).

Results of methodological quality evaluation: only 2 trials belong to low-risk bias, 6 trials were judged to be high-risk bias, and the remaining 3 trials were with unclear risk of bias (fig. 2).

Publication bias analysis

In the meta analysis of the impact of selenium on the mortality of septic patients, a total of 11 studies were included, the number of studies was sufficient to conduct a funnel plot. For the funnel plot was symmetrical visually (fig. 3), we thought there was no evident publication bias.

Results of meta-analysis

Mortality

There were 11 RCTs included, 956 patients in the selenium treatment group, 960 in the control group, no

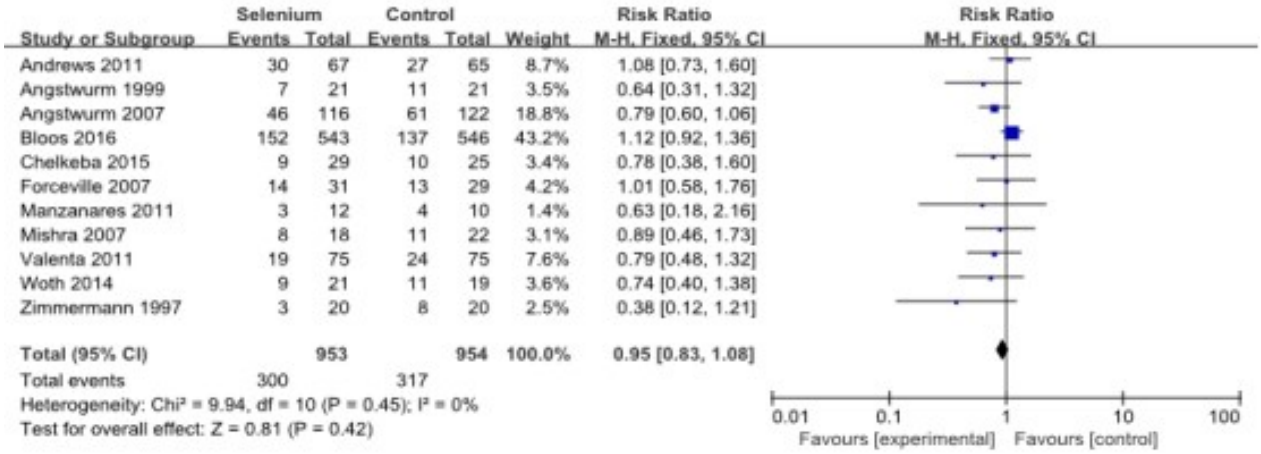

Fig. 4: Forest plot comparing mortality among selenium group to that of control group in septic patients.

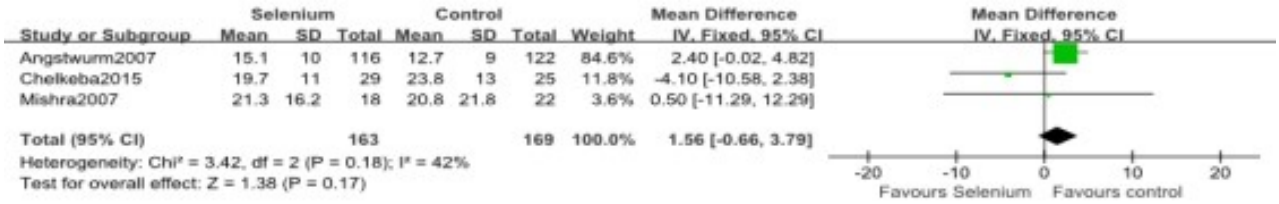

Fig. 5: Forest plot comparing the length of ICU stay among selenium group to that of control group in septic patients.

Fig. 6: Forest plot comparing the new infections among selenium group to that of control group in septic patients.

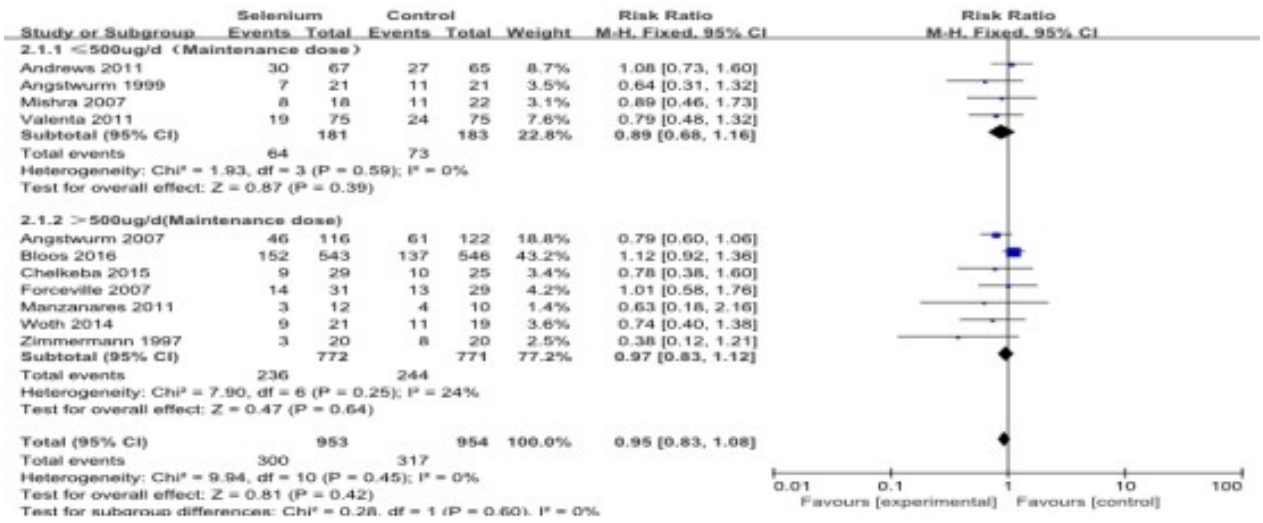

Fig. 7: Forest plot comparing the mortality among high maintenance dose selenium group to that of low maintenance dose in septic patients.

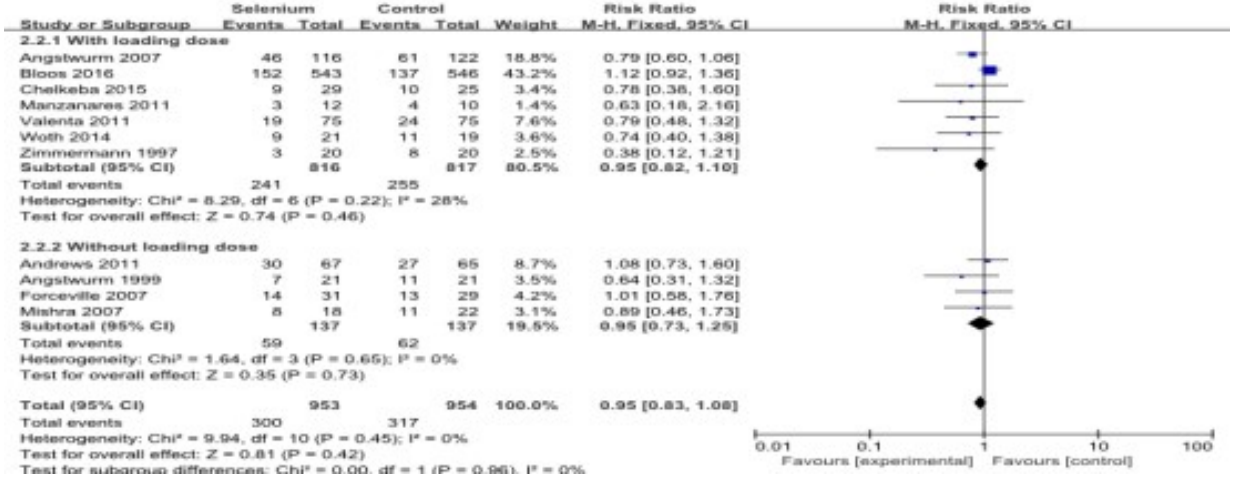

Fig. 8: Forest plot comparing the mortality among with loading dose group to that of without loading dose group in septic patients.

statistical heterogeneity was found between the two groups (P=0.45 I^2=0%), thus we used the fixed effect model. The results showed that there was no statistical difference in the mortality (RR=0.95, 95%CI=0.83-1.08, P=0.42) (fig. 4).

Length of ICU stay

In terms of the Length of ICU stay, only 3 RCTs were included, with 163 patients in the selenium treatment group and 169 in the control group. We used the fixed effect model because of no statistical heterogeneity (P=0.18 I^2=42%) and revealed that there was no difference in the length of ICU stay between the two groups (MD=1.56, 95%CI=-0.66-3.79, P=0.17) (fig. 5).

New infections

4 RCTs enrolling 719 patients in the selenium treatment group and 722 in the control group reported the new infections. There is no statistical heterogeneity between 2 groups either (P=0.18 I^2=38%) and we found no difference between the two groups in the risk of developing new infections (RR=0.95, 95%CI=0.73-1.24, P=0.69) (fig. 6).

Subgroup analysis

As the forest plot shows, there was no statistical difference in the mortality between subgroups of RCTs using high maintenance dose (>500ug per day) versus low maintenance dose (≤500ug per day) when we carried out the subgroups analysis (with loading dose versus without loading dose), no difference was found either (fig. 7,8).

DISCUSSION

Our meta-analysis of 11 RCTs (1916 patients) showed that intravenous use of selenium did not improve patients' outcomes, including near-term mortality, length of ICU stay and new infections.

Table 1: The basic information of the randomized clinical trials included

Study	The patients'		Interventions		Outcomes	Funding
	Seleniu	Control	Selenium	Control	28-day mortality	No funding source mentioned
Valenta (2011)	75	75	1,000 μg on day 1, 500μg/ d on days 2–14	a standard Se dose (＜75 ug/day)		
Woth （2014）	21	19	1000μg/30 minutes loading dose and 1000μg/d treatment for a maximum of 14 days	not described	mortality	No funding source mentioned
Chelkeba (2015)	29	25	2 mg IV bolus followed by 1.5 mg continuous infusion for 14 days	standard therapy without selenium	28-day mortality; Length of ICU stay； new infections	Tehran University of Medical sciences, International campus
Bloos （2016）	543	546	1,000 μg on day 1,1000 μg/ day until discharge from the ICU	Placebo	28-day mortality; new infections	German Federal Ministry of Education and Research
Forceville （2007）	31	29	4,000 μg on the first day, 1,000 μg/day on the 9 following days	Placebo	28-day mortality; new infections	Ministry of Health, France
Mishra (2007)	18	22	(474, 316,158 mg/day), each for 3 consecutive days followed by a standard dose of 31.6 mg/day of Se	the standard dose of Se	28-day mortality; Length of ICU stay	Royal Liverpool NHS trust
Angstwurm （2007）	116	122	1000μg/30 minutes loading dose and 1000μg/d treatment for 14 days	Placebo	28-day mortality; Length of ICU stay; new infections	Biosyn Arzneimittel GmbH
Angstwurm （1999）	21	21	500 μg/d for 3 d then 250 μg/d for 3 d then 125 μg/d for 3 d then 35μ g/d	Placebo	28-day mortality	No funding source mentioned
Zimmermann (1997)	20	20	1,000 μg IV loading then 1,000 μg/d infusion	Placebo	28-day mortality	No funding source mentioned
Andrews (2011)	67	65	500ug/d for 7d	Placebo	mortality	Chief Scientist Office, Fresenius-Kabi Oxford Nutrition
Manzanares (2011)	12	10	2000μg loading dose and 1600μg/d treatment for 10 days	Placebo	mortality	CSIC grant in Uruguay

Studies have shown that immune dysfunction and oxidative stress play an important role in the pathogenesis of sepsis (Mantzarlis and Tsolaki 2017 and Hotchkiss *et al*., 2013). In septic patients, immunecells can produce proinflammatory and anti-inflammatory cytokines. In the early stage, the former is dominant, but it is on the contrary in the end stage of sepsis, the imbalance of those two types of cytokinecauses multiple organ dysfunction (Hotchkiss *et al*., 2013). In addition, oxidative stress can cause DNA damage, mitochondrial dysfunction, and lipid per oxidation at the cellular level, thus participating in the occurrence of multiple organ damage (Valko *et al*., 2007). Seleniumis is involved in the synthesis of glutathione peroxidase (GPx) and thioredoxin reductase (TR) (Kvicala 1999; Rayman 2012; Steinbrenner 2009; Roman *et al*., 2014). These substances can scavenge lipid peroxides, hydrogen peroxide. to maintain the intracellular redox state, thereby avoiding cell damage by oxidative stress (Lewin *et al*., 2001 and Thomas *et al*., 1990). In immunomodulatory, a study has shown that selenium can regulate the inflammatory response by inhibiting the activity of nuclear factor kappa B (NF-κB) induced by cytokines (Tolando *et al*., 2000). Animal experiments have shown that selenium can improve phagocytosis of the macrophages and total complement hemolytic activity (HC (50)) of murine (Guo *et al*. 2013). A randomized controlled study by Valenta J *et al*. showed that plasma selenium level in sepsis patients was negatively related to the levels of inflammatory markers like CRP and PCT(CRP: r=-0.172, P=0.035; PCT: r=-0.187, P=0.022) (Valenta *et al*., 2011). In spite of those advantages mentioned above, our meta analysis failed to find the benefit of selenium in improving the prognosis of septic patients. The reasons may be as follows, except for the shortcomings of our study (see below) may have Influence on the outcomes, the following reasons should also be considered, Firstly, The pathogenesis of sepsis is complex, immune dysfunction and oxidative stress are only 2 of the aspects of sepsis, no benefits of selenium in other aspects of sepsis was found. Furthermore, When selenium is applied to the septic patients, its appropriate dose is still controversial.

In recent years, meta-analysis about selenium's clinical effect on sepsis have emerged from time to time, but the results of those meta-analysis are inconsistent. In 2013, a meta-analysis showed that parenteral selenium supplementation in septic patients could reduce the mortality (Huang *et al*., 2013) (RR 0.83, 95% CI 0.70-0.99, P=0.04, I^2 =0%). A meta-analysis by Alhazzani (2013) in the same year also came to a similar conclusion (Alhazzani *et al*., 2013) (OR, 0.73; 95% CI, 0.54, 0.98; P=0.03; I^2=0%). However, a meta-analysis by Kong *et al*. (2013) published in 2013 found no significant reduction in the mortality of septic patients with selenium. In addition, another meta-analysis published in 2016 also showed that intravenous selenium cannot improve the prognosis of critically ill patients; in the subgroup analysis, the mortality of the septic patients didn't decrease either (RR 0.99, 95% CI 0.90-1.1, P=0.90, I^2=0%), but the subgroup analysis contained only two RCTs with septic patients (Manzanares *et al*., 2016). Although our meta-analysis did not suggest the benefit of selenium for the septic patients, a recent research conducted by Kwon *et al*. (2016) found that the combination therapy of niacin and selenium can decrease the mortality of septic rats, however, individual therapies of either niacin or selenium failed to exert similar effects, which suggests that selenium preparations in the treatment of sepsis may still have some potential benefits through combining with other drugs or changing dosages and administration approaches.

Our meta-analysis has the following strengths: (1) the three databases were screened and the quality of the RCTs was carefully evaluated by two researchers independently; (2) we used the Cochrane risk of bias tool to assess the methodological quality (3) there is no evident publication bias; and (4) to date, this is the largest meta-analysis that examined the clinical effect of selenium supplementation in septic patients.

This meta-analysis also has some limitations: (1) most of the methodological quality assessment of RCTs belong to high-risk bias; (2) most RCTs are not double-blind and (3) the dosages of selenium in these studies are quite different. These limitations may affect the outcomes, therefore, it still needs to be cautious when referring to the results of this study and patients' actual situation must be taken into consideration.

CONCLUSION

To sum up, take together with 15 RCTs, it can be concluded that the routine uses of selenium to improve prognosis of septic patients should be avoided, however, because the quality of most RCTs' is not high, RCTs with higher quality should be conducted to further clarify the clinical effects of selenium in the treatment of sepsis in the future.

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