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Meta-analysis

Daily parenteral selenium therapy in critically ill patients: An updated systematic review and meta-analysis of randomized controlled trials

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SUMMARY

Background and aim: Patients hospitalized at the intensive care unit (ICU) are more prone to oxidative stress. Antioxidants such as selenium (Se) may have beneficial effects on outcomes in these patients. Studies and systematic reviews in this field have inconclusive results.

Methods: An updated systematic search was done to find clinical trials published in PubMed, Cochrane's library, ISI web of Science, Scopus, and Ovid databases from January 1980 up to April 2020, to assess the effects of daily Se supplementation on patient's survival, hospital and ICU stay, duration of mechanical ventilation, infection, acute renal failure (ARF) occurrence and serum creatinine levels.

Results: From 1394 papers found in the first step of the search, after deleting duplicate findings, 24 studies were included in this meta-analysis. Results of the pooled random-effect size analysis of 24 trials showed no remarkable effect of daily parenteral Se administration on patient's hospital and ICU stay, duration of mechanical ventilation, infectious complications, ARF, survival and serum creatinine levels ($p > 0.05$). The subgroup analysis showed that daily parenteral Se administration (in doses higher than 1000 μg/d) increased the length of ICU stay by 4.48-folds (95%CI: −0.5, 9.46, $p = 0.07$). Parenteral Se supplementation at the first and following dose of ≤1000 μg reduced the number of ARF at the hospitalized patients by 76% and 45%, respectively ($p = 0.02$, and $p = 0.05$).

Conclusions: High doses of Se increases days of ICU stay, but low doses decreases the number of ARF occurrence in ICU patients. More trials are needed to assess its effect on ARF occurrence.

1. Introduction

Selenium (Se) is an essential nutrient with antioxidant, anti-inflammatory and immuno-regulatory properties due to its role in selenoproteins, glutathione peroxidases and thioredoxin reductases structure [1–3]. Decrease in serum levels of selenium and antioxidants is reported at the previous observational studies in critically ill patients [4–6]. Critical illness is a stress situation, with activation of the oxidant network. Balance between oxidants and antioxidants is essential for the removal of ROS, which damage "proteins, polysaccharides, nucleic acids, and polyunsaturated fatty acids", which may lead to cell death [7]. Despite the role of antioxidants for preventing oxidative stress, a pathophysiological pathway in ICU patients, routine prescribing of these supplements are controversial [8]. ASPEN guidelines recommended changes in commercially available parenteral and enteral multivitamins and trace elements [9]. Meta-analysis in this field have inconclusive results, too [8–11]. RCTs aiming the effects of Se on inflammation have inconsistent results [12–35], which are related to the doses, various compounds, and the duration of Se supplementation. The purpose of the present study is to update the systematic review and meta-analysis on efficacy of parenteral Se supplementation as monotherapy on patient's survival, duration of mechanical ventilation, number of infectious complications, ARF, serum creatinine (Cr) levels, length of hospital and ICU stay in critically ill patients.

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2. Methods

2.1. Search strategy and article selection

Two authors (SNM and MGh) searched systematically seven databases including PubMed, Ovid, Embase, Cochrane Library, Scopus, Web of Sciences, and ProQuest, independently. Keywords were as follows: "Patients" [Mesh] OR ill* OR Patient AND critic OR "Critical Illness" [Mesh] OR "critically ill" OR "critical illness" OR "Critical Illnesses" AND "Selenium" [Mesh] OR Selenium OR "selenious acid" OR "sodium selenite" OR "antioxidant cocktails". The systematically review were done from the January 1980 to April 2020 with English and Persian language. The reference list for the available papers was manually searched to complete the search process.

2.2. Article inclusion and exclusion

Controlled Clinical trials with at least one week of duration, which compared daily parenteral Se supplementation (all types of Se compounds) as intervention with the control group and reported mean or median values for ICU and hospital stay, duration of mechanical ventilation, survival, number of infectious complications, number of acute renal failure (ARF) and serum Cr levels at the baseline and end in the both groups with SD, SEM or 95% CI, were included. Observational and non-human studies, reviews, letter to editors were excluded. Also, trials including neonates and children were excluded. The crossover trials were excluded because of the potential risk of "carry-over" of treatment effect.

2.3. Data extraction and quality assessment

After the pooling of all funded articles from a systematic search of databases, duplicated references were removed and remained articles screened in titles and abstracts to find more relevant items. Then, full texts of selected articles regained and checked according to the inclusion and exclusion criteria. The data extraction was done independently by three reviewers (HS, SNM, MAM). Disagreements were solved by discussion between reviewers and we didn't need to an external referee. The excel form was designed to extract following data by the mentioned authors; the first author name, year of publication, country, the study design, APACHE score, type of Se, mean age of participants, number of participants in each group, the first and following dose of Se, type of patients, mean ± standard deviation (SD) or median (minimum–maximum) of hospital and ICU stay, ventilator dependency, percent of infection and ARF occurrence, survival, as well as, serum levels of Cr in each group at the baseline and the end of study. Cochrane tool was adopted to assess quality of included studies for meta-analysis.

2.4. Data synthesis and statistical analysis

The pooled effect size of parenteral Se therapy on outcomes estimated by use of fixed-effect model analysis; however, when significant heterogeneity existence was seen between included studies, random–effect model analysis was used. Mean changes of these variables and their SD in intervention and placebo groups were considered. To assess the existence of heterogeneity and calculate it's percent, Cochran's Q-test (at the $P < 0.05$ of significance) and the I-square (I^2) test were used, respectively. Subgroup analysis was performed according to the dose and duration of supplementation. Publication bias was evaluated by the egger's regression asymmetry test. Also, Funnel plot was painted for visual assessment. Significance was considered at the P-values below 0.05.

3. Results

3.1. Study selection

Of 1394 articles that were found in a systematic search of databases, 510 items were excluded because of being duplicated and 884 reports screened in tiles and abstracts to find more relevant articles to the topic. After this step, 39 articles were selected to assess for eligibility. Finally, 24 trials remained and included in the meta-analysis. Figure 1 shows the diagram of the article selection process.

3.2. Study characteristics

Of 4071 participants in the meta-analysis, 1900 were in the Se supplemented and 2190 were in the control group. Publication year of the included studies was recorded from 1983 to 2018. The duration day of the supplementation was between 5 and 28 days. The amount of Se was 60–4000 μg at the first dose and 60–1500 μg at the following dose. The characteristics and quality assessment of the included articles were summarized at Tables 1 and 2.

3.3. Effects of Se supplementation on hospital and ICU stay

A meta-analysis for the effect of daily Se supplementation on hospital and ICU stay was carried out in 8 and 11, respectively. The overall weighted mean differences [WMD] were estimated for hospital stay [WMD (0.84) (95% CI -6.92 to 13.05), $p = 0.5$] (Fig. 2), and ICU stay [WMD (0.19) (95% CI -0.33 to 0.71), $p = 0.43$] (Fig. 3). Cochran's Q-test showed statistically significant heterogeneity between the trials for hospital stay ($p < 0.001$, $I^2 = 97.52\%$), as well as for ICU stay ($p < 0.001$, $I^2 = 97.97\%$).

3.4. Effect of Se supplementation on number of days on ventilator

The effect of daily Se supplementation on days of ventilator dependency was carried out in 5 trials. The overall WMD for days of ventilator dependency was as follows: WMD (0.84) (95% CI -2.79 to 0.59), $p = 0.2$ (Fig. 4). Cochran's Q-test showed no statistically significant heterogeneity between the trials for days of ventilator dependency ($p = 0.86$, I^2=<0.001%).

3.5. Effect of Se supplementation on number of infectious complications and ARF

The effect of daily Se supplementation on the number of infectious complications and ARF was carried out in 6 and 5 trials, respectively. The odds ratio for percent of infection was 0.88 (95% CI 0.67 to 1.16, $p = 0.37$) (Fig. 5). The odds ratio for percent of ARF occurrence was 0.59 (95%CI 0.34 to 1.03, $p = 0.06$) (Fig. 6). Cochran's Q-test showed no statistically significant heterogeneity between the trials for infection ($p = 0.3$, $I^2 = 11\%$) and ARF ($p = 0.5$, I^2<0.001%) occurrence.

3.6. Effect of Se supplementation on serum Cr levels

Four trials were assessed the effect of daily Se supplementation on serum Cr levels. The overall WMD for serum Cr levels was 3.06 (95% CI -6.9 to 13.05), $p = 0.55$ (Fig. 7). Cochran's Q-test showed statistically significant heterogeneity between the trials for serum Cr levels ($p = 0.01$, $I^2 = 71.9\%$).

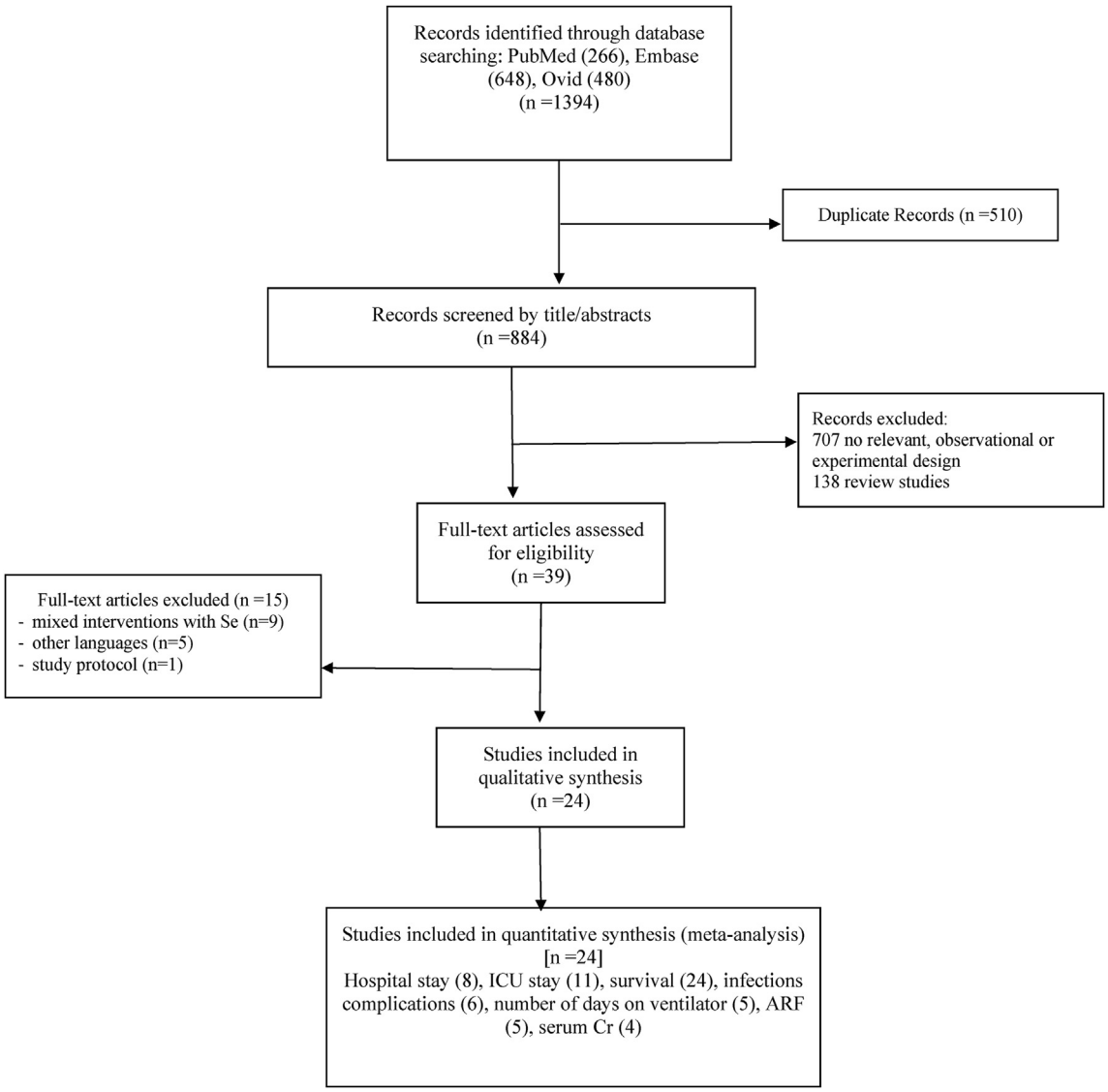

Fig. 1. Flowchart of study selection for inclusion trials in the systematic review.

3.7. Effect of Se supplementation on survival

The effect of daily Se supplementation on survival up to 28 days, 3 month and 6 month was carried out in 19, 3 and 2 trials, respectively. Daily Se supplementation had no effect on survival. The odds ratio for survival were as follows: up to 28 days 1.08 (95% CI 0.87 to 1.34, $p = 0.47$), 3month 1.18 (95% CI 0.68 to 2.04, $p = 0.54$) and 6month 1.29 (95% CI 0.89 to 1.86, $p = 0.17$) (Figs. 8–10). Cochran's Q-test showed no statistically significant heterogeneity between the trials for survival up to 28 days ($p = 0.16$, $I^2 = 24\%$), 3month ($p = 0.06$, $I^2 = 63.4\%$) and 6month ($p = 0.3$, $I^2 = 75\%$).

3.8. Subgroup analysis

Subgroup analysis showed no significant effect of Se supplementation on hospital stay, as well as number of das on ventilator, number of infectious complications, and survival at the first dose of $\leq$1000 and > 1000 μg/day, following dose of $\leq$1000 and > 1000 μg/day, and duration of $\leq$10 and > 10 days ($p > 0.05$). Parenteral Se supplementation at the first and following dose of $\leq$1000 μg reduced the number of ARF at the hospitalized patients by 76% and 45%, respectively ($p = 0.02$, and $p = 0.05$). Length of ICU stay was increased 4.48-folds at the patients received parenteral Se at the doses more than 1000 μg per day (95%CI: −0.5, 9.46, $p = 0.07$). The results of the subgroup analysis are shown in Tables 3 and 4.

3.9. Publication bias

The funnel plot showed no Visual evidence of publication bias for the assessed outcomes (Fig. 11). No publication bias was found using the egger test ($p > 0.05$ for all outcomes).

4. Discussion

This is an updated systematic review and meta-analysis on the effects of parenteral Se supplementation on outcomes of ICU patients. No beneficial effect of parenteral Se was found at the present study on the duration of hospital stay, days on ventilator, serum Cr levels and survival. Only at the subgroup analysis, we found that parenteral Se supplementation at the first and following doses lower than 1000 μg reduces number of ARF by 76% and 47%.

Table 1
Characteristics of the included trials at the meta-analysis.

Author	Country	Study design	APACHE score Int/P	Sex	Duration day	Sample size Int/P	Mean age Int/P	Type of Selenium	First-dose (μg) Following (μg)	Patients
Andrews (2011) [13]	UK	Double blinded randomized parallel trial	II:20/20	F/M	7	127/125	64.5/63.1	Selenium	500 500	GI bleeding
Angstwurm M.W. (2007) [12]	Germany	Prospective randomized, placebo-controlled, multiple-center trial	III: 92.2/91.2	F/M	14	92/97	63.9/65.3	Sodium selenite	1000 1000	sepsis
Bloos F. (2016) [14]	Germany	Double blinded randomized parallel trial	II:24.7/24.4	F/M	21	293/300	65.8/65.6	Sodium selenite	1000 1000	sepsis
H. Brodska (2015) [15]	Czech Republic	prospective, randomized, open-label study	II:30/28	F/M	14	75/75	60/60	sodium-selenite pentahydrate	1000 500	SIRS or sepsis
L. Chelkeba (2017) [16]	Iran	prospective, single-blinded, randomized control clinical trial	II:17/16.4	F/M	14	29/25	35/41	Sodium selenite	2000 1500	sepsis
L. Chelkeba (2015) [17]	Iran	prospective, single-blinded, randomized control clinical trial	II:17/16.4	F/M	14	29/25	35/41	Sodium selenite	2000 1500	sepsis
X. Forceville (2007) [18]	France	prospective, placebo controlled, randomized	N	F/M	10	31/29	N	Sodium selenite	4000 1000	septic shock
F. RGBON (2017) [19]	Brazil	Double blinded randomized parallel pilot trial	N	F/M	14	8/12	51.1/49.7	selenious acid	60 60	Inflammatory process
Gärtner R. (1983) [20]	Germany	Double blinded randomized parallel trial	II:≥15/≥15	F/M	9	21/21	N	Sodium selenite	500 250	SIRS
Heyland D.K. (2007) [21]	Canada	open-label, phase I, dose-escalating, clinical trial	II:20.6/21.9	F/M	28	7/7	71.8/65.6	selenium	500 500	needed mechanical ventilation
Kazda (2006) [22]	Czech Republic	Double blinded randomized parallel trial	N	F/M	14	26/35	N	Sodium selenite	1000 500	ICU patients
Khalili H. (2017) [23]	Iran	clinical trial	N	F/M	10	125/182	32/39	Sodium Selenite Pentahydrate	1000 500	TBI
Ladislav Kočan (2014) [24]	Slovak Republic	clinical trial	II:24/25.5	F/M	6	31/34	53/60	sodium selenite	750 750	sepsis
Mahmoodpoor (2018) [25]	Iran	pilot double-blind placebo-controlled randomized clinical trial	II:24/23.2	F/M	10	20/20	57/58	sodium selenite	4000 2000	ARDS
Mahmoodpoor (2018) [26]	Iran	clinical trial	II:21/23	F/M	10	47/52	55/54.5	sodium selenite	3000 1500	mechanically ventilated SIRS
W. Manzanares (2010) [27]	Uruguay	randomized, pilot study	II:21/23	F/M	10	10/10	54/41	selenious acid	2000 1600	SIRS
W. Manzanares (2011) [28]	Uruguay	placebo-controlled, randomized study	II:24/22	F/M	10	15/16	58/54	selenious acid	2000 1600	SIRS
V. Mishra, 2007 [29]	UK	double-blind controlled trial	II:17.6/19.8	F/M	9	18/22	65.8/67.1	sodium selenite	474 316	sepsis
M. Moghaddam (2017) [30]	Iran	double-blinded controlled trial	III:49.91/49.34	F/M	14	57/56	40.07/42.93	selenium	500 500	TBI
J. Reisinger (2009) [31]	Austria	clinical trial	SAPSII:59/59	F/M	5	124/102	64/66	Sodium selenite	200–1000	cardiac arrest after CPR
S. Yasser (2014) [32]	Germany	retrospective clinical study	SAPSII:50.8/ 47.7	F/M	8	413/627	67/67	selenium	any dose of Se supplementation	sepsis
Schmidt T (2018) [33]	Switzerland	Randomized, placebo-controlled, double-blinded clinical trial	SAPSII:28/29	F/M	13	206/205	66/68	sodium selenite	4000 1000	cardiac surgery
J. Valenta (2011) [34]	Czech Republic	randomized clinical trial	II:30/28	F/M	9.5	75	60/60	Sodium Selenate Pentahydrate	1000 500	SIRS
G'abor Wot (2014) [35]	Hungary	randomized clinical trial	SAPSII:50/56	F/M	14	21	62/66	sodium selenite	1000 1000	multiple organ failure

APACHE: acute physiology and chronic health evaluation; SPAS: simplified acute physiology score; N: not mentioned; F: female; M: male; Int: intervention group; P: placebo; SIRS: Systemic inflammatory response syndrome; TBI: traumatic brain injury; ARDS: Acute respiratory distress syndrome; CPR: Cardiopulmonary Resuscitation.

Table 2
Quality assessment.

Study	Random Sequence Generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting
P. Andrews et al. (2011)	L	H	H	U	L	H
M.W. Angstwurm et al. (2007)	L	H	H	H	L	H
F. Bloos et al. (2016)	L	H	H	H	L	H
H. Brodska et al. (2015)	L	L	L	L	L	H
L. Chelkeba et al. (2017)	L	L	L	U	L	H
L. Chelkeba et al. (2015)	L	L	L	U	L	H
X. Forceville et al. (2007)	L	H	H	U	L	H
F. Rgbon et al. (2017)	L	L	L	U	L	H
R. Gärtner et al. (1983)	L	H	H	H	L	H
D.K. Heyland et al. (2007)	L	L	L	U	L	H
Kazda (2006)	L	L	L	U	L	H
H. Khalili et al. (2017)	L	L	L	U	L	H
K. Ladislav et al. (2014)	L	L	L	U	L	H
Mahmoodpoor et al. (2018)	L	H	H	H	L	H
Mahmoodpoor et al. (2018)	L	L	L	U	L	H
W. Manzanares et al. (2010)	L	L	L	U	L	H
W. Manzanares et al. (2011)	L	H	H	U	L	H
V. Mishra et al. (2007)	L	H	H	U	L	H
M. Moghaddam et al. (2017)	L	H	H	U	L	H
J. Reisinger et al. (2009)	L	L	L	U	L	H
S. Yasser et al. (2014)	L	L	L	U	L	H
T. Schmidt et al. (2018)	L	H	H	H	L	H
J. Valenta et al. (2011)	L	L	L	U	L	H
G. Wot et al. (2014)	L	L	L	U	L	H

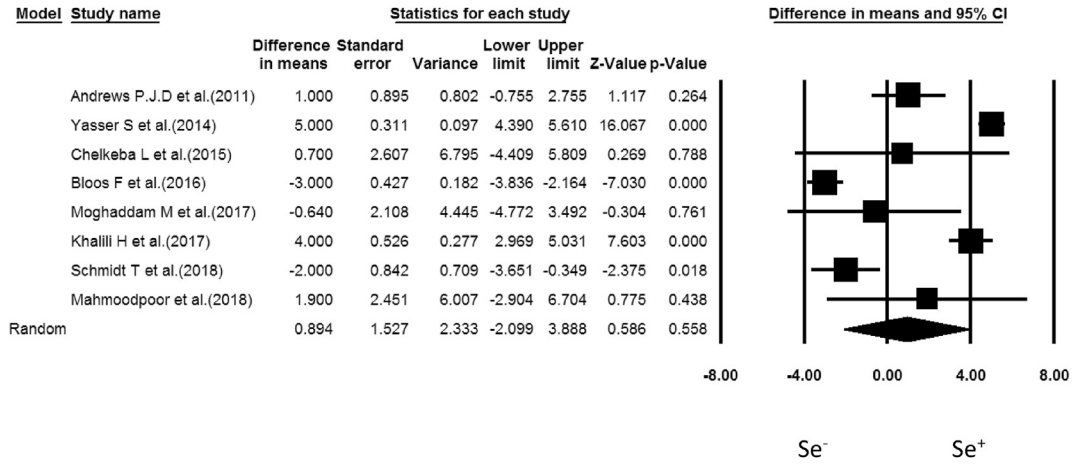

Fig. 2. Forest plot of the random-effects model meta-analysis of parenteral selenium therapy on hospital stay. WMD, weighted mean difference.

Parenteral Se supplementation in the doses higher than 1000 μg increased the length of ICU stay by 4.48-folds.

Se, is an important mineral playing various physiologic roles. It incorporated in enzymes and proteins which have antioxidant effects in inflammatory and oxidative situations such as sepsis, along with other pathological conditions [36]. Serum levels of Se decrease early in inflammation due to destruction of the enzymes as well as redistribution of Se, and its consumption [37]. Previous studies on the effects of Se on outcomes in ICU patients had ineffectiveness results due to various doses (under dosing), lack of an initial loading dose, short-term treatment or inclusion of patients with normal selenium plasma concentrations at the baseline, as well as route of administration. One systematic review resulted that Se supplementation in critically ill patients reduces mortality (risk ratio 0.84 (0.67–1.05)) but has little effect on infectious complications (risk ratio 0.93 (0.70–1.23)) [38]. Another meta-analysis revealed a tendency toward mortality reduction ($Z = 1.70$; $p = 0.09$), at the high doses of sodium-selenite [39]. Studies reported that intravenous Se administration, as an adjunctive sepsis therapy, restores activity of antioxidants, reduces oxidative stress, and improve survival [12,28,34,40,41]. A recent meta-analysis on 19 RCTs involving 3341 critically ill patients resulted intravenous Se

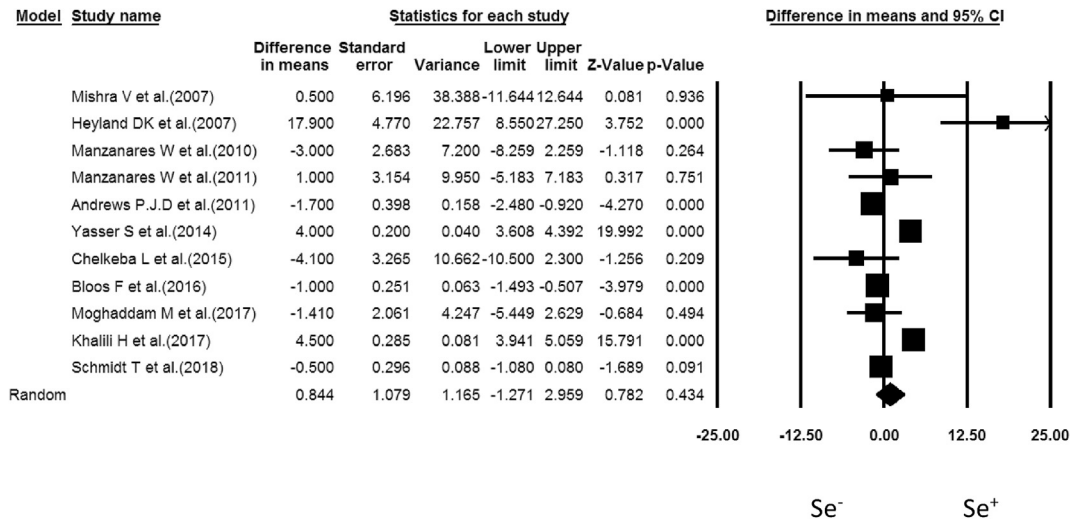

Fig. 3. Forest plot of the random-effects model meta-analysis of parenteral selenium therapy on ICU stay. WMD, weighted mean difference.

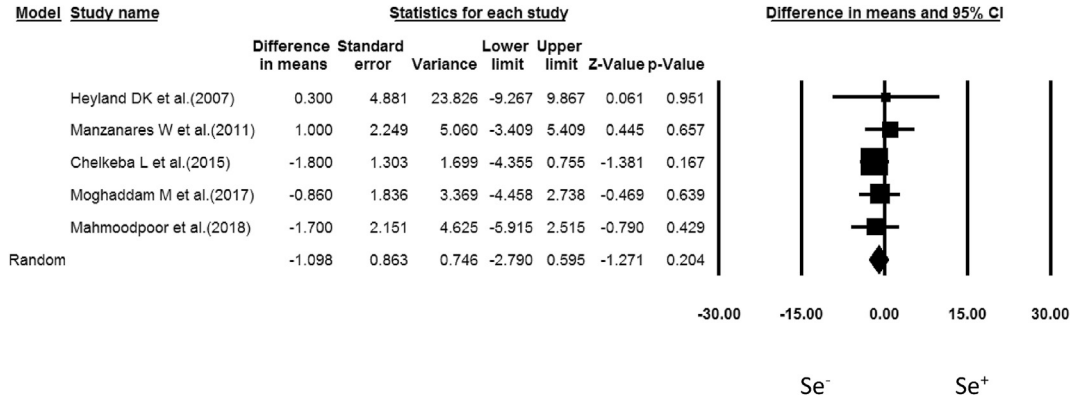

Fig. 4. Forest plot of the random-effects model meta-analysis of parenteral selenium therapy on number of days on ventilator. WMD, weighted mean difference.

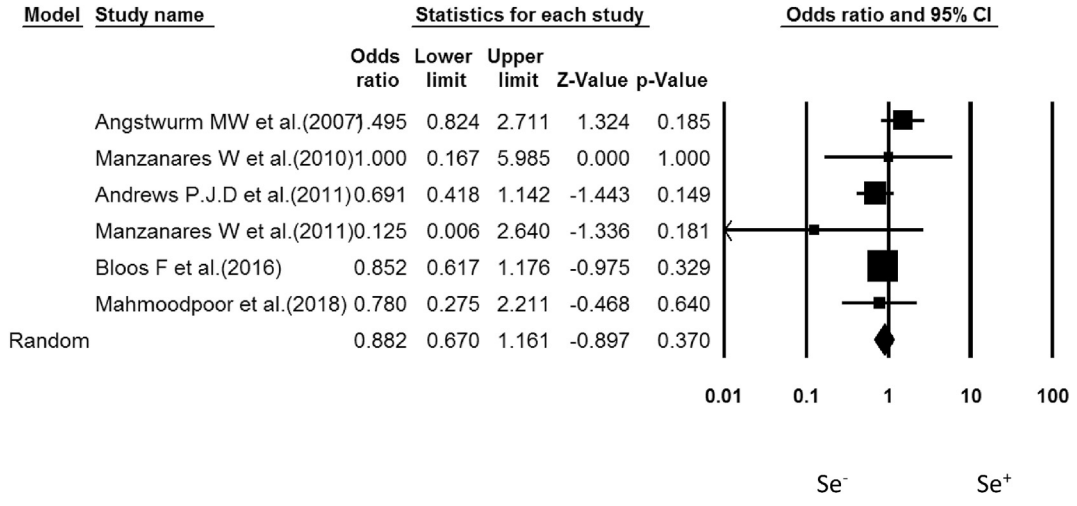

Fig. 5. Forest plot of the random-effects model meta-analysis of parenteral selenium therapy on number of infectious complications.

supplement decreased the total mortality (*RR* = 0.86, 95% CI: 0.78–0.95, p = 0.002) and shorten the length of stay in hospital (WMD: −2.3, 95% CI −4.03 to −0.57, p = 0.009), but had no significant effect on 28-days survival (RR = 0.96, 95% CI: 0.85–1.09, p = 0.54), and could not shorten the length of ICU stay (WMD: −0.15, 95% CI −1.68 to 1.38, p = 0.84) [44]. Studies in this field have inconclusive results. It may be because of various doses and types of Se, route of administration (enteral or parenteral), and

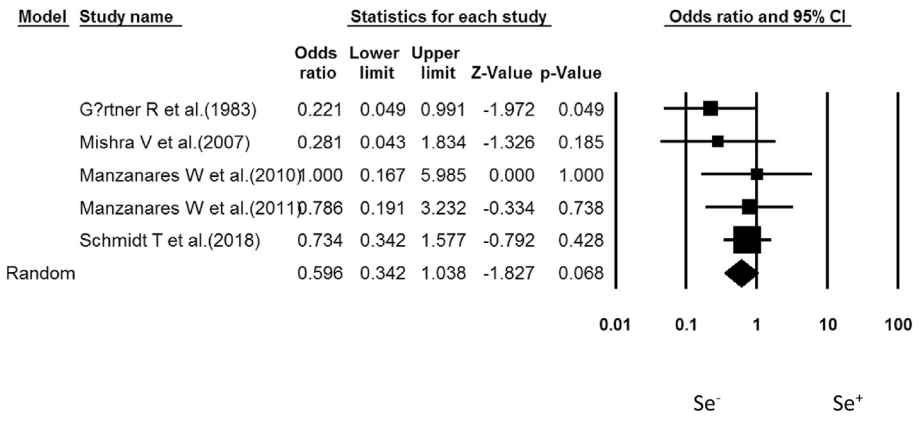

Fig. 6. Forest plot of the random-effects model meta-analysis of parenteral selenium therapy on number of ARF (acute renal failure).

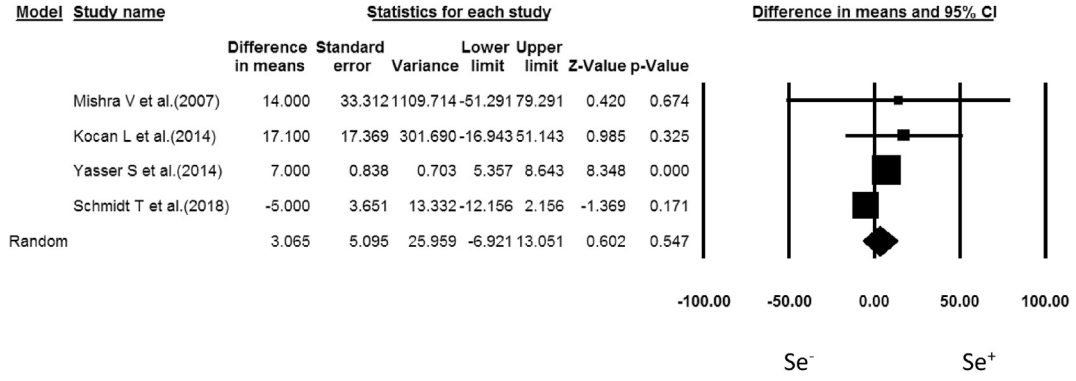

Fig. 7. Forest plot of the random-effects model meta-analysis of parenteral selenium therapy on serum Cr (creatinine).

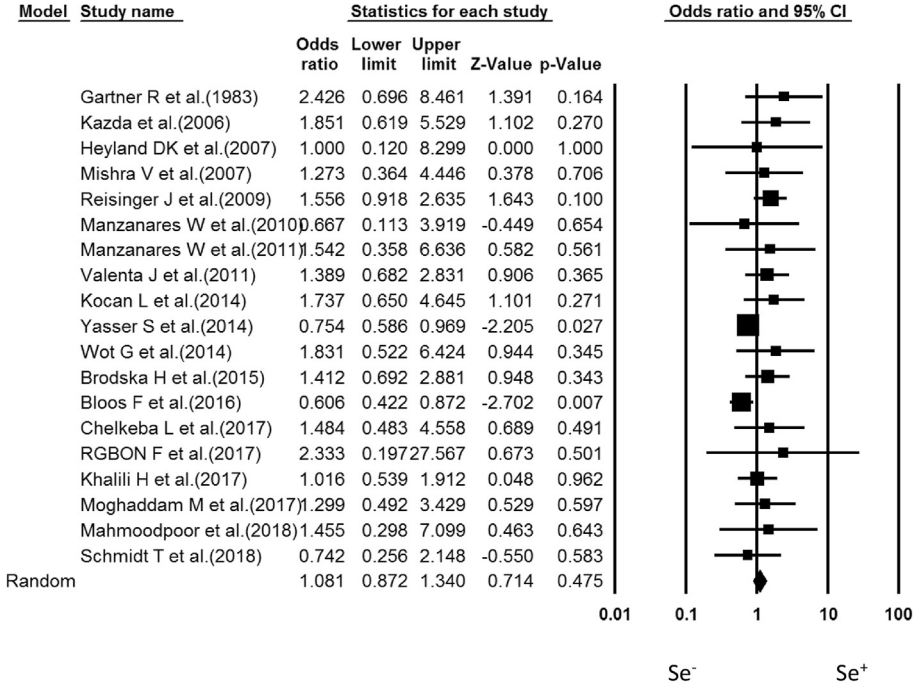

Fig. 8. Forest plot of the random-effects model meta-analysis of parenteral selenium therapy on survival, up to 28 days.

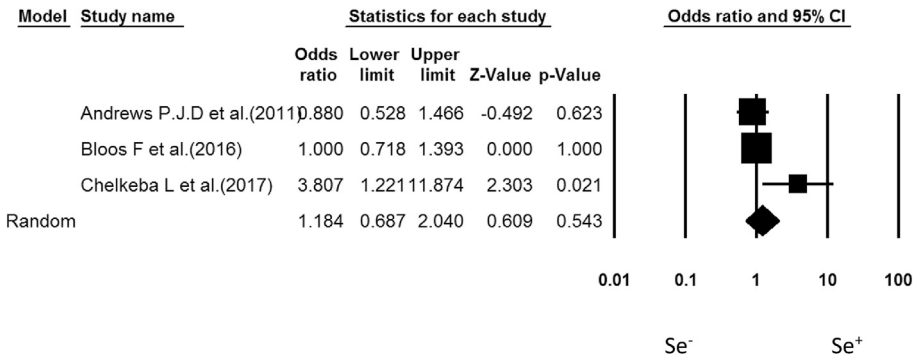

Fig. 9. Forest plot of the random-effects model meta-analysis of parenteral selenium therapy on 3 month survival.

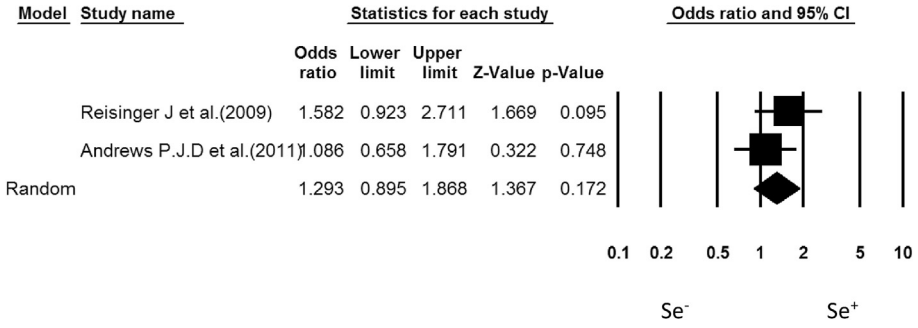

Fig. 10. Forest plot of the random-effects model meta-analysis of parenteral selenium therapy on 6 month survival.

Table 3
Subgroup analyses of daily parenteral Se supplementation on number of days on ventilator, hospital and ICU stay.

	NO	WMD (95%CI)	P within group	P heterogeneity	I^2
Subgroup analyses of daily parenteral Se supplementation on number of days on ventilator					
Trial duration (days)					
≤10	3	−1.1 (−3.7, 1.5)	0.4	0.9	0.0%
>10	2	−1.09 (−3.3, 1.1)	0.33	0.28	13.79%
First intervention dose (μg)					
≤1000	2	-0.011 (−2.9, 2.67)	0.93	0.52	0.0%
>1000	3	−1.67 (−3.8, 0.45)	0.12	0.91	0.0%
Following intervention dose (μg)					
≤1000	1	1 (−3.4, 5.4)	0.65	1	0.0%
>1000	3	−1.67 (−3.8, 0.45)	0.12	0.91	0.0%
Subgroup analyses of daily parenteral Se supplementation on hospital stay					
Trial duration (days)					
≤10	5	1.32 (−2.55, 5.2)	0.5	<0.001	98.3%
>10	3	0.17 (−4.86, 5.2)	0.9	0.03	71.1%
First intervention dose (μg)					
≤1000	2	1.31 (−5.4, 8.05)	0.7	0.7	0.0%
>1000	5	1.35 (−2.4, 5.1)	0.5	<0.001	98.3%
Following intervention dose (μg)					
≤1000	4	1.96 (−2.36, 6.28)	0.37	<0.001	87.9%
>1000	2	0.49 (−5.25, 6.2)	0.86	<0.001	99.06%
Unknown	2	−0.85 (−7.08, 5.4)	0.79	0.32	0.0%
Subgroup analyses of daily parenteral Se supplementation on ICU stay					
Trial duration (days)					
≤10	6	1.16 (−1.38, 3.72)	0.37	<0.001	98.7%
>10	5	0.2 (−3.37, 3.77)	0.91	0.002	77.1%
First intervention dose (μg)					
≤1000	6	−0.13 (−3.72, 3.45)	0.94	0.001	75.75%
>1000	4	2.4 (−1.34, 6.23)	0.2	<0.001	98.89%
Following intervention dose (μg)					
≤1000	6	−0.02 (−3.72, 3.67)	0.99	<0.001	97.1%
>1000	3	4.48 (−0.5, 9.46)	0.07	<0.001	99.1%
Unknown	2	−1.84 (−7.97, 4.28)	0.5	0.27	17.05%

Se. Selenium; CI, confidence interval; WMD, weighted mean differences.

Table 4
Subgroup analyses of daily parenteral Se supplementation on survival, number of infectious complications and ARF.

	NO	OR (95%CI)	P within group	P heterogeneity	I^2
Subgroup analyses of daily parenteral Se supplementation on survival (up to 28 days)					
Trial duration (days)					
≤10	10	1.16 (0.86, 1.56)	0.3	0.19	27.2%
>10	9	1.03 (0.73, 1.47)	0.85	0.2	27.11%
First intervention dose (μg)					
≤1000	12	1.08 (0.84, 1.39)	0.56	0.18	27.36%
>1000	6	1.31 (0.86, 2)	0.2	0.83	0.0%
Following intervention dose (μg)					
≤1000	12	1.13 (0.84, 1.54)	0.42	0.18	27.37%
>1000	4	1.3 (0.61, 2.79)	0.50	0.88	0.0%
Unknown	3	1.03 (0.68, 1.56)	0.89	0.04	69.53%
Subgroup analyses of daily parenteral Se supplementation on number of infectious complications					
Trial duration (days)					
≤10	4	0.7 (0.45, 1.08)	0.11	0.7	0.0%
>10	2	0.98 (0.72, 1.31)	0.87	0.1	62.33%
First intervention dose (μg)					
≤1000	3	0.91 (0.65, 1.28)	0.6	0.14	49.56%
>1000	3	0.71 (0.29, 1.75)	0.45	0.49	0.0%
Following intervention dose (μg)					
≤1000	3	0.91 (0.65, 1.28)	0.6	0.14	49.56%
>1000	3	0.71 (0.29, 1.75)	0.45	0.49	0.0%
Subgroup analyses of daily parenteral Se supplementation on number of ARF					
Trial duration (days)					
≤10	4	0.47 (0.21, 1.06)	0.07	0.48	0.0%
>10	1	0.73 (0.34, 1.58)	0.43	1	0.0%
First intervention dose (μg)					
≤1000	2	0.24 (0.08, 0.78)	0.02	0.84	0.0%
>1000	3	0.77 (0.41, 1.45)	0.42	0.95	0.0%
Following intervention dose (μg)					
≤1000	3	0.53 (0.28, 1)	0.05	0.3	17.98%
>1000	2	0.86 (0.28, 2.61)	0.79	0.84	0.0%

Se. Selenium; CI, confidence interval; OR, odds ratio.

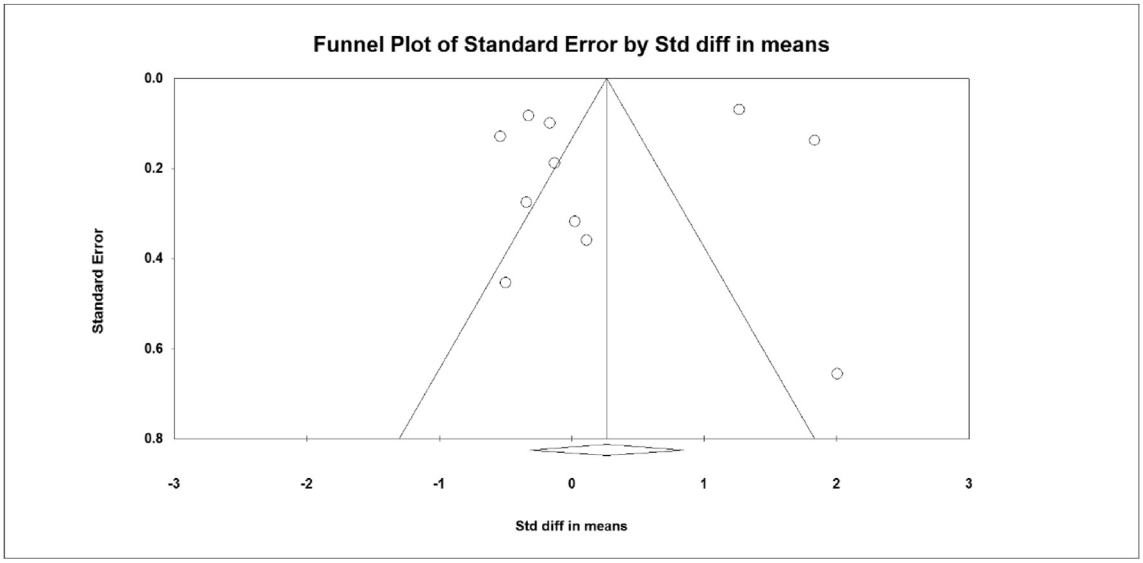

Fig. 11. Funnel plot.

duration of therapy. On the other hand, there is no systematic review and meta-analysis to compare the effects of Se in doses lower or higher than 1000 μg per day and the duration lower or higher than 10 days, as mentioned at the ASPEN guidelines [7,8]. In addition, the previous meta-analysis resulted that Se supplementation has no effect on renal failure [9]. Moreover, they concluded that using high-dose of Se showed beneficial effect on 28-day mortality in ICU patients, which are in contrast with our results. Our results showed that at the doses higher than 1000 μg/day, length of ICU stay increases by 4.48-folds.

5. Conclusions

Parenteral Se administration had no effect on hospital stay, days of ventilator dependency, number of infectious complications and patient's 28-days, 3-month and 6-month survival. Interestingly, low doses of parenteral Se decreases the number of ARF at the critically ill patients but high doses increases length of ICU stay. According to the present updated systematic review and meta-analysis, Se supplementation in ICU patients must be revised according to the dose of supplementation. More trials are needed to assess its effect on ARF occurrence.

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Declaration of competing interest

There is no conflict of interest.

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