Vitamin C can reduce mortality in sepsis: a systematic review and meta-analysis of animal and human evidence

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Research

Keywords: Vitamin C, Sepsis, Critical care, Mortality, Systematic review, Meta-analysis

Posted Date: September 23rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-78776/v1

Abstract

Background: The effect of vitamin C on outcomes in sepsis is unclear. This systematic review and meta-analysis included animal and human studies to evaluate the value of intravenous vitamin C as a monotherapy in sepsis.

Methods: We searched MEDLINE via PubMed, EMBASE, CENTRAL and CBM for animal studies, randomized controlled trials (RCTs), and quasi-RCTs dated up to August 10, 2020. The included studies compared the effect of intravenous vitamin C and control on outcomes in sepsis. No language restrictions were applied. Two authors independently assessed the eligibility and quality of the trials and extracted data.

Results: A total of 7 animal studies and 5 RCTs were included. Four animal studies (n=176) and all 5 RCTs (n=472) reported mortality, the primary outcome of this meta-analysis. The mortality of the vitamin C group was lower than that of the control group (odds ratio (OR) 0.22, 95% CI 0.06 to 0.81, $P = 0.02$; I^2 =60% in animal studies, and OR 0.48, 95% CI 0.33 to 0.71, $P < 0.001$; I^2 =0% in human studies). The GRADE assessment showed that the outcome was downgraded from high- to moderate-quality evidence due to imprecision. With regard to the secondary outcomes, the pooled data from animal studies showed that vitamin C had a beneficial effect on mean arterial pressure (std. mean difference (SMD) 1.36, 95% CI 0.32 to 2.41, $P = 0.01$; I^2 =78%) and capillary density (SMD 1.97, 95% CI 0.89 to 3.04, P=0.69; I^2 =0%) but had no effect on the level of lactate. The pooled data from human studies showed that vitamin C was associated with a reduction in vasopressor duration (MD -18.85, 95% CI -24.61 to -11.55, $P < 0.001$; I^2 =0%) but could not shorten the length of ICU stay or duration of mechanical ventilation. No adverse effects were reported.

Conclusions: Evidence from animal and human studies suggests that intravenous vitamin C monotherapy can reduce mortality in sepsis, with a moderate quality of evidence. We also found that vitamin C had a beneficial effect on mean arterial pressure, capillary density, and reduction of vasopressor duration in sepsis.

Introduction

Sepsis is a common disease in critically ill patients that has high morbidity, mortality and costs. It occurs when a deregulated host response to an infection results in life-threatening tissue damage and organ dysfunction [1]. The latest statistical data show that 1.7 million cases of sepsis result in more than 270,000 deaths [2], and survivors may require long-term rehabilitation care after discharge [3], so sepsis has been a hot public health issue. Recently, antioxidant therapies have emerged as potential adjunctive therapies for infectious source control and supportive care in patients with sepsis and septic shock [3–5].

Vitamin C, a water-soluble vitamin and antioxidant, is effective in ameliorating oxidative stress in animal models of sepsis and in a number of clinical trials with septic patients [6–9]. Many other physiological

effects of vitamin C are also important in sepsis, including supporting the endogenous synthesis of catecholamines [10], improving macrovascular function [11–14], inhibiting inflammatory mediators [15–17], regulating immunosuppression [18], and even exerting a direct bacteriostatic effect at high concentrations [19, 20]. As a physiological effect, increased consumption decreases the plasma levels of vitamin C in sepsis, which is accompanied by more severe organ dysfunction and worse prognosis [16, 21]. Since vitamin C cannot be synthesized in the human body, exogenous supplementation may be helpful for sepsis treatment.

The initial data on the clinical use of vitamin C were obtained in animal models, which showed that supplementation with vitamin C attenuated tissue damage, recovered organ function, and improved adverse outcomes in sepsis [22, 23]. Subsequently, several clinical trials with small sample sizes reported that the administration of vitamin C had a dose-dependent effect on the prevention of multiorgan failure, reduction of norepinephrine requirement, shortened duration of mechanical ventilation, and reduction in mortality [24–28]. Indeed, some studies have suggested that vitamin C has no beneficial effect on patients with sepsis [29, 30]. Until now, two meta-analyses have evaluated the value of vitamin C treatment in patients with sepsis [31, 32], and the results were inconsistent. Moreover, the scarcity of included randomized controlled trials (RCTs) and the use of vitamin C in combination therapies obscured the true effect of vitamin C. In 2019, two RCTs [33, 34] of intravenous vitamin C in septic patients were reported. However, neither report was included in a meta-analysis.

Hence, we aimed to provide a comprehensive meta-analysis of animal and human studies evaluating the value of vitamin C monotherapy in sepsis. Considering the limitation of enteral uptake, we only focused on the intravenous administration of vitamin C.

Materials And Methods

This systematic review was registered at PROSPERO with the registration number: CRD42019119436 and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [35].

Data sources

We searched the MEDLINE via PubMed, EMBASE, CENTRAL and CBM database up to August 10, 2020 using key words “Vitamin C” or “Ascorbic Acid” or “Sepsis” or “Septic Shock”. There were no language limits on eligibility. An additional file shows search strategy in more detail [see Additional file 1].

Study selection

We included studies with the primary (mortality without time limits) and secondary outcomes (such as length of ICU stay, vasopressor requirement, and organ function) of interest that were associated with the effectiveness of vitamin C on sepsis. Eligible studies were divided into two categories with the following characteristics: 1) animal studies on any model of sepsis treated with vitamin C by intravenous administration, with a placebo or other control, as well as the reported outcome; 2) human studies

including adult patients (> 18 years) with sepsis or septic shock treated with intravenous vitamin C (RCTs and quasi-RCTs were included). The exclusion criteria were as follows: participants with vitamin C deficiency or patients in human studies who were not adults; vitamin C was not used alone or not intravenously; lack of a baseline condition or control group; lack of data on any outcome; review articles, cohort studies, case reports and studies without full text; and in vitro studies.

Data extraction

The initial and full-text reviews and data extraction from the included studies were performed independently by two authors (CCZ and LNH). Any discrepancies were resolved by the third author (GJZ), and a decision was reached by consensus.

For each study, the following information was extracted: participant characteristics (including species, source and sepsis model for animal studies, and diagnosis, demographic data, clinical setting, and number of patients for human studies), details of the intervention (including vitamin C doses, route, duration and control), study design (including baseline adjustment, methods of randomization and blinding), follow-up, and outcome data.

Assessment of risk of bias

Two authors (CCZ and LNH) independently assessed the risk of bias to evaluate the quality of the included studies using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) [36] for animal studies and the Cochrane Collaboration's tool for RCTs [37]. The domain with the lowest score in the trials brought the overall risk to the respective stratification.

Statistical analysis

All analyses, except the test for asymmetry, were conducted using RevMan 5.3 (The Nordic Cochrane Center, Rigshospitalet, Copenhagen, Denmark). The results are presented with forest plots using odds ratios (ORs) for dichotomous data and the std. mean difference (SMD) or mean difference (MD) for continuous data. All estimates were provided with 95% confidence intervals (CIs). The heterogeneity was assessed by Cochran's Q statistic and the I2-test. A P value > 0.1 or I^2 statistic below 50% indicated low levels of heterogeneity. In these cases, a fixed-effects model was used. Otherwise, a random-effects model was selected. $P < 0.05$ indicated statistical significance. Publication bias was not assessed because the number of included studies was inadequate to properly assess a funnel plot.

Summary of findings

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) profiler [38] to interpret the findings and assess the quality of evidence in human studies. The "summary of findings" table (Table 1) shows outcome-specific information for the four main outcomes, namely, mortality, ICU length of stay, duration of mechanical ventilation, and vasopressor requirement.

Results

Study screening

In this systematic review, we analyzed both human and animal studies. The search strategy identified 1542 unique publications, and 2 additional records were identified from reference lists. After excluding 340 duplicates and screening 1134 titles and abstracts, 70 studies were assessed in full text for eligibility. The full-text screening excluded 58 studies for the reasons shown in Fig. 1. Finally, 12 studies (7 animal studies [39–45] and 5 human studies [26–28, 33, 34]) were included in this meta-analysis (Fig. 1). Among these, one study was reported in Chinese [33], and all the other studies were reported in English.

The characteristics of the animal and human studies are summarized in Table 2 and Table 3, respectively. The SYRCLE risk of bias summary for animal studies is presented in Fig. 2. The risk of bias summary figures for RCTs are presented in Fig. 2.

Primary outcome

Four [39, 42–44] of 7 animal studies (n = 176) provided mortality data. The mortality of the vitamin C group was lower than that of the control group (OR 0.22, 95% CI 0.06 to 0.81, $P = 0.02$) (Fig. 4). There was significant homogeneity (Pvalue for heterogeneity 0.06, $I^2 = 60\%$). Consistently, the pooled data from all 5 included RCTs (n = 472) revealed that vitamin C significantly reduced mortality in patients with sepsis (OR 0.48, 95% CI 0.33 to 0.71, $P < 0.001$) (Fig. 3). Data were taken from the longest available follow-up, ranging from 6 to 28 days. The heterogeneity was not significant (Pvalue for heterogeneity 0.44, $I^2 = 0\%$). The GRADE assessment showed moderate quality of evidence. This outcome was downgraded from high- to moderate-quality evidence due to the imprecision of a small number of samples (Table 1).

Secondary outcomes in animal studies

Mean arterial pressure

Of the 7 animal studies, 4 studies [39, 40, 42, 43] evaluated the effect of vitamin C on mean arterial pressure (MAP). The MAP of the vitamin C group was significantly higher than that of the control group (SMD 1.36, 95% CI 0.32 to 2.41, $P = 0.01$; Pvalue for heterogeneity 0.001, $I^2 = 78\%$) (Additional file 2).

Lactate levels

Two [39, 44] of 7 animal studies evaluated the effect of vitamin C on lactate levels. There was no significant difference between the vitamin C group and the control group (SMD 0.25, 95% CI -0.40 to 0.91, $P = 0.69$; Pvalue for heterogeneity 0.32, $I^2 = 0\%$) (Additional file 3).

Capillary density

Two [39, 43] of 7 animal studies evaluated the effect of vitamin C on capillary density. Compared with the control, vitamin C increased the densities of perfused capillaries (SMD 1.97, 95% CI 0.89 to 3.04, $P = 0.69$; Pvalue for heterogeneity 0.84, $I^2 = 0\%$) (Additional file 4).

Secondary outcomes in human studies

Length of ICU stay (days)

Of the 5 RCTs, 4 RCTs [27, 28, 33, 34] reported the length of ICU stay (n = 451). There was no significant difference between the vitamin C group and the control group (MD -3.30, 95% CI -8.94 to 2.34, *P* = 0.17) (Additional file 5). Using the GRADE approach, this outcome was downgraded from high- to low-quality evidence due to imprecision and inconsistency (Pvalue for heterogeneity < 0.001, I^2 = 87%) (Table 1).

Duration of mechanical ventilation (days)

For the evaluation of this outcome, we included 3 RCTs (n = 218) [27, 28, 34]. There was no significant difference between the vitamin C group and the control group (MD -2.34, 95% CI -7.26 to 2.4, *P* = 0.32) (Additional file 6). Using the GRADE approach, this outcome was downgraded from high- to low-quality evidence due to imprecision and inconsistency (Pvalue for heterogeneity 0.005, I^2 = 81%) (Table 1).

Vasopressor duration (hours)

For the evaluation of this outcome, we included 3 RCTs (n = 286) [27, 28, 33]. The vasopressor duration of the vitamin C group was shorter than that of the control group (MD -18.85, 95% CI -24.61 to -11.55; *P*< 0.001) (Additional file 7). Heterogeneity was not significant (Pvalue for heterogeneity 0.84, I^2 = 0%). The GRADE assessment showed a moderate quality of evidence due to imprecision (Table 1).

Adverse events

None of the trials found serious adverse events directly attributed to vitamin C supplementation.

Discussion

The present systematic review and meta-analysis provides a comprehensive understanding of the effect of vitamin C monotherapy on sepsis in animal studies and human RCTs. The primary outcome was mortality at the longest available follow-up. The results demonstrated that vitamin C was associated with decreased mortality in both septic animals and patients with sepsis. Different secondary outcomes were reported in animal and human studies. In animal studies, the pooled data showed that vitamin C had a beneficial effect on MAP and capillary density but had no effect on the level of lactate. In human studies, the results showed that vitamin C could reduce the duration of vasopressors but could not shorten the length of ICU stay or the duration of mechanical ventilation. No adverse effects were reported, which shows the safety of intravenous vitamin C administration in clinical treatment.

Vitamin C is an essential vitamin with a variety of physiological actions, including antioxidant, the synthesis of steroids and catecholamine, regulation of the function of immune and endothelial cells, and promotion of wound healing [46]. In sepsis, vitamin C depletion dramatically increases, and its concentration decreases, which is accompanied by more severe organ dysfunction and worse prognosis. Therefore, vitamin C may be an important therapeutic option in sepsis. Animal and human studies have supported a scientific basis for vitamin C having beneficial and therapeutic effects on the host response to sepsis. Our systematic review focused on whether intravenous vitamin C monotherapy could improve prognosis, especially mortality in sepsis.

As shown in Table 2, 4 of the 7 included animal studies reported mortality, with different available follow-up times, including 24 h[39, 42], 48 h [43], and 7 days [44]. We found that the mortality of the vitamin C group was significantly lower than that of the control group. This finding is closely related to the improvement of the secondary outcomes (MAP and capillary density) by vitamin C. Our study further reviewed the mechanisms underpinning the protective effects of vitamin C supplementation in sepsis, including the prevention of microvascular dysfunction [39, 40, 42], regulation of vaso-regulatory gene expression[41], and inhibition of iNOS expression[40, 42].

Several factors influenced the quality of the animal studies. The first was the different animal species. Two animal species were used in the included studies: rats in 4 studies and mice in 3 studies. Generally, it is thought that rat models have a higher clinical relevance than mouse models [47]. Second, the type of sepsis model was different. Cecal ligation and perforation were chosen in all the studies except one, which used the method of E-coil endotoxin or cecal ligation and incision. Third, there were large variations in the time, frequency and dosage of vitamin C administration. It seems that pre-septic administration is better than post-septic administration, and large doses are better than small doses. In addition, the SYRCLE risk bias of all animal studies was high due to selection bias, performance bias, detection bias and other bias. These factors increased the heterogeneity and decreased the quality of the animal studies. Therefore, we could not obtain definitive conclusions from animal evidence.

Human studies have provided more evidence for individual vitamin C strategies. Five RCTs met the standards of this meta-analysis. Among these, two recent RCTs by Fowler (CITRIS-ALI trial) and Jing-jing Niu et al. investigating the role of intravenous vitamin C in septic patients were included in this meta-analysis for the first time. The CITRIS-ALI trial reported in 2019 was a randomized, double-blind, placebo-controlled, multicenter trial with 167 patients. The Jing-jing Niu et al. study was a randomized, double-blind, placebo-controlled, single-center trial with 234 patients. The other three RCTs were all single-center trials with small sample sizes. All the trials observed 28-day mortality, except one that observed 6-day mortality [26]. The conventional analysis showed that the mortality in the vitamin C group was significantly decreased compared with that in the control group. Consistently, a previous meta-analysis, including 2 RCTs and 1 retrospective study with 146 septic patients, reported a marked reduction in mortality in the vitamin C group [31]. In contrast to our results, a meta-analysis conducted by Zhang and Jativa [48] with 5 studies (4 RCTs and 1 retrospective study) enrolling a total of 142 adults with critical illness was performed, and the result showed no difference in mortality between the control and vitamin C groups. Moreover, an updated meta-analysis [32] reevaluated the value of vitamin C treatment in patients with sepsis, and the data from 10 studies (4 RCTs and 6 retrospective studies) involving 1671 patients did not show any beneficial effect of vitamin C on mortality. We presume that this discrepancy might be explained by the following aspects. First, unlike the two previous meta-analyses, all human studies included in the present meta-analysis were RCTs, and retrospective studies were excluded. Second, the populations of our meta-analysis (patients with sepsis) and the previous one conducted by Zhang and Jativa (adults with critical illness) were different. Third, we only focused on the isolated intravenous administration of vitamin C in the treatment group, while vitamin C was prescribed along with thiamine and steroids in most of the included studies in the updated meta-analysis. The beneficial effects of

vitamin C as a part of combination therapy in sepsis have been reported by previous studies, but the effect of the isolated administration of vitamin C is unclear. This meta-analysis revealed that intravenous vitamin C as a monotherapy was associated with an obvious reduction in mortality in sepsis. For the primary outcome, heterogeneity was not significant, and the GRADE assessment showed a moderate quality of evidence.

In addition, intravenous vitamin C was significantly associated with a decreased need for vasopressor support in patients with sepsis. Because vitamin C can synthetize catecholamines, exogenous supplementation increased the plasma concentrations of vitamin C to dozens of times the physiological level, which enriched endogenous catecholamines so that vascular tension and reactivity were improved, resulting in a reduction in exogenous vasoconstrictive drugs. Consistently, a series of studies reported that vitamin C might reduce the duration of vasopressor support in sepsis or septic shock [24, 49]. A recent meta-analysis of human studies revealed that intravenous vitamin C supplementation was associated with a decreased demand for vasoconstrictive drugs in critically ill patients [48]. However, it is noteworthy that vitamin C was not associated with the length of ICU stay or duration of mechanical ventilation in our systematic review. The reason might be attributed to the limited number of studies, small sample sizes and high heterogeneity. For these two outcomes, the GRADE assessment showed a low quality of evidence.

It is well known that oral and intravenous administration lead to substantially different plasma concentrations of vitamin C. The maximal saturation of vitamin C is approximately 500–1000 mg by oral administration, while intravenous vitamin C administration can achieve 70-fold higher plasma concentrations than oral administration [50]. Since the capacity of vitamin C is dose-dependent, intravenous vitamin C was used and investigated by more physicians. In this review, one study used a lower dose of intravenous vitamin C (450 mg/day), while the other four studies used higher doses ranging from 50 mg/kg/day to 200 mg/kg/day. The duration of treatment was more than 3 days. No adverse effects were reported, even in the group administered the highest dose of intravenous vitamin C. Although the optimal dose of vitamin C is unknown, an adequate dose of intravenous vitamin C for at least 3 days is needed to normalize plasma concentrations and improve outcomes in patients with sepsis.

A major strength of this meta-analysis is that we investigated the effect of intravenous vitamin C as a monotherapy on outcomes in sepsis. As opposed to studies of vitamin C in combination therapies and/or via different routes of administration, our study results can show the effect of vitamin C more clearly. Moreover, we reviewed both animal and human studies with clearly reported outcomes, which makes the results more comprehensive and compensates for the lack of human research. Additionally, all the included human studies were RCTs, and two recent RCTs with larger sample sizes had not been included in any previous meta-analyses. Findings from RCTs are considered to be more transparent and consistent. Finally, GRADE assessment was conducted in this meta-analysis to estimate the external validity of the evidence in human studies. We appraised that it is helpful for clinical decision making.

There are several limitations in this systematic review. First, the SYRCLE risk of bias summary showed that all animal studies had high bias, so the overall effects might be spurious. Second, publication bias could not be assessed due to the limited number of included studies. Third, low plasma levels of vitamin C are associated with adverse outcomes, including severity of organ failure, disease and mortality. However, we excluded populations with vitamin C deficiency and ignored the plasma levels of vitamin C in the enrolled patients. Therefore, no assessment was performed in the ascorbate-deficient population. Fourth, because only five human studies were included, the subgroup analyses of different doses to find the optimal dose of vitamin C were limited. Finally, focusing on the isolated administration of vitamin C may exaggerate its effect because some of the included patients received hydrocortisone, one recommended treatment in sepsis, especially in septic shock. However, hydrocortisone and vitamin C have several common functions, which will increase the effect of vitamin C.

Conclusions

This meta-analysis, including animal and human studies, found that intravenous vitamin C as a monotherapy reduced mortality in sepsis. During sepsis, vitamin C was associated with a decrease in vasopressor duration, an elevation in MAP, and increased densities of perfused capillaries. However, vitamin C could not shorten the length of ICU stay or duration of mechanical ventilation. In summary, our review highlights the beneficial effect of intravenous vitamin C on the outcome of sepsis.

Declarations

Acknowledgments

Not applicable.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

CCZ and LNH searched the scientific literature, analysed and interpreted the data; CCZ also drafted the manuscript; GJZ helped to collect the data and performed statistical analyses; ZQL contributed to the conception and design; ZJH contributed to the conception, design and revised the manuscript. All authors read and approved the final version of the manuscript.

Funding

This research received no external funding.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

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Tables

Due to technical limitations the Tables are available as download in the Supplementary Files.

Figures

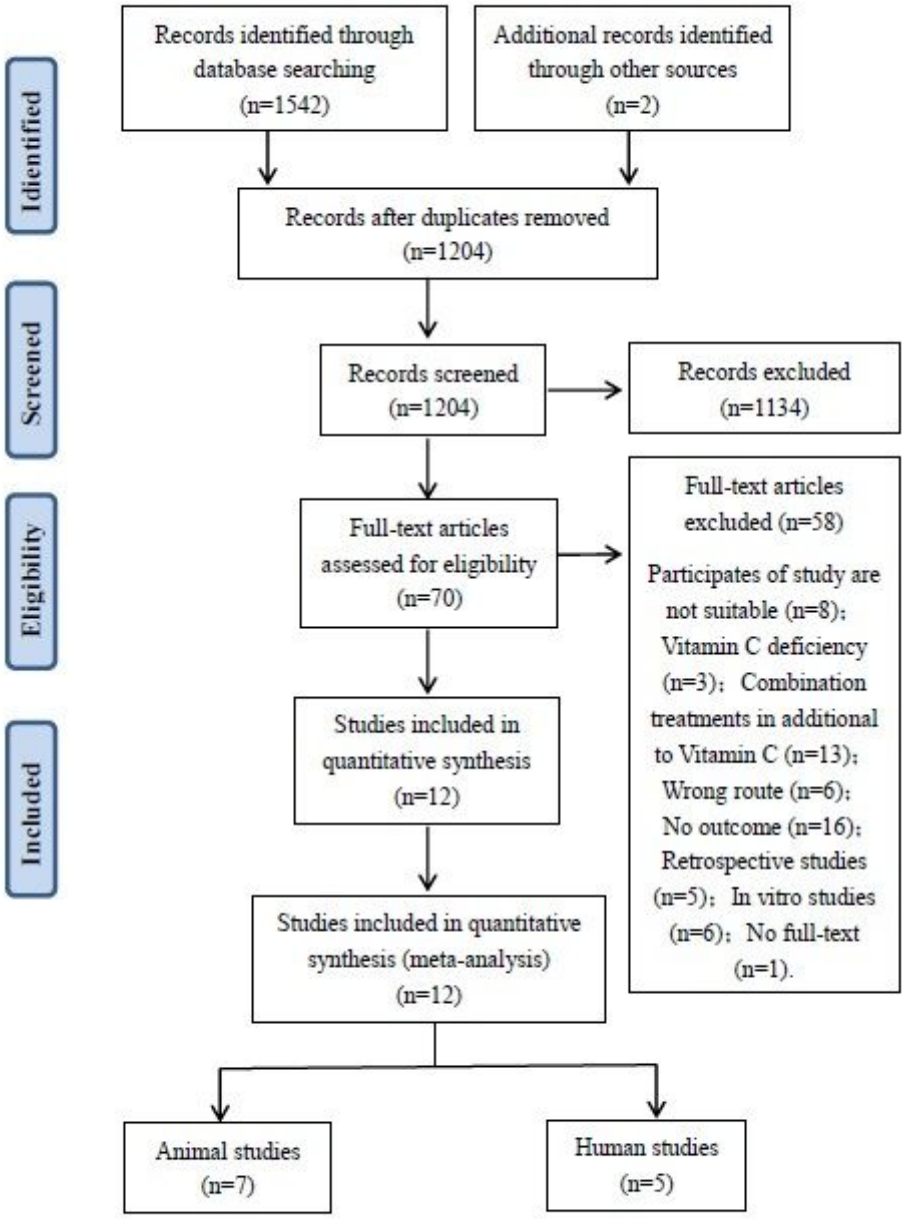

Figure 1

Study selection flow diagram according to the PRISMA guidelines.

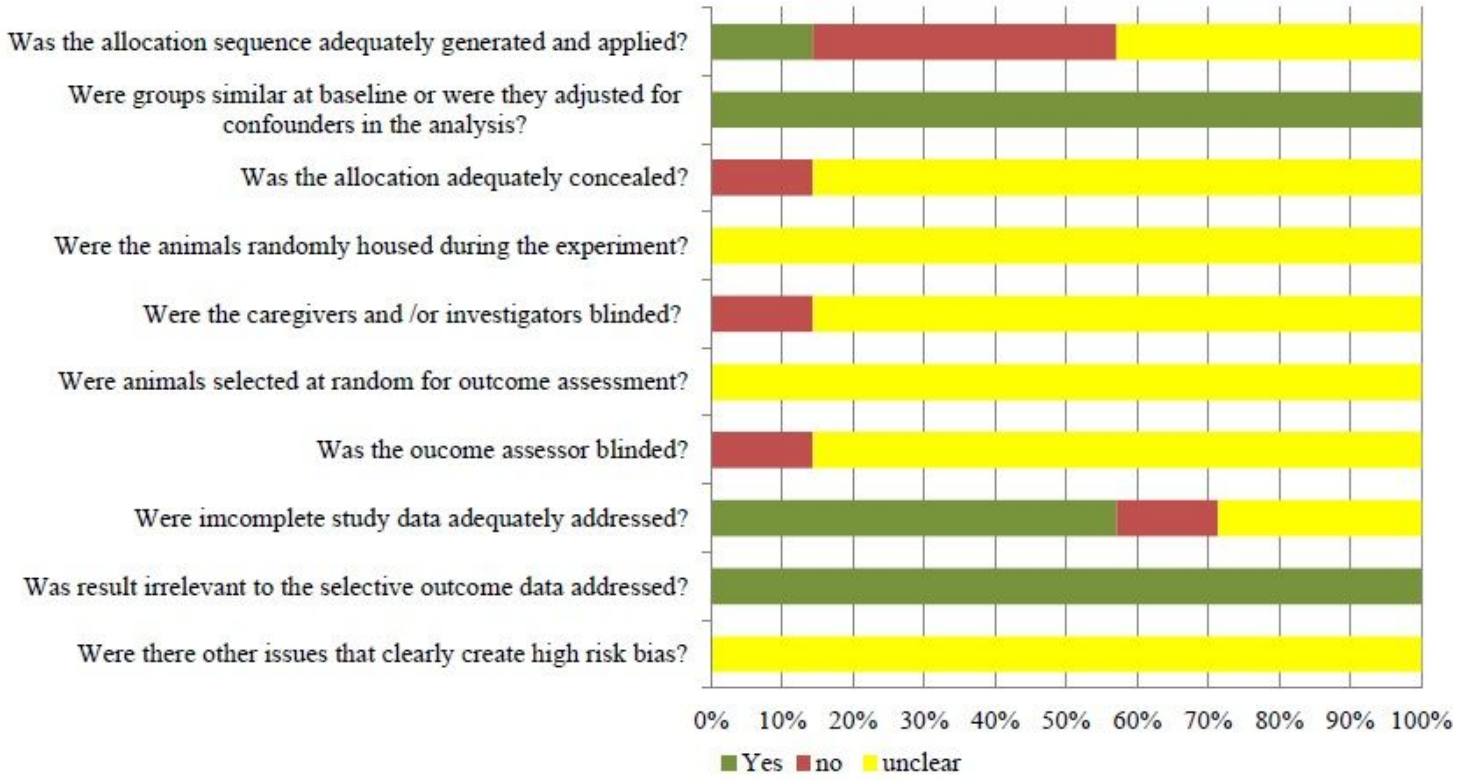

Figure 2

SYRCLE's risk of bias tool shows the quality of animal studies included in the meta-analysis, score (%) per risk of bias item. Yes = low risk of bias, no = high risk of bias, unclear = unclear risk of bias.

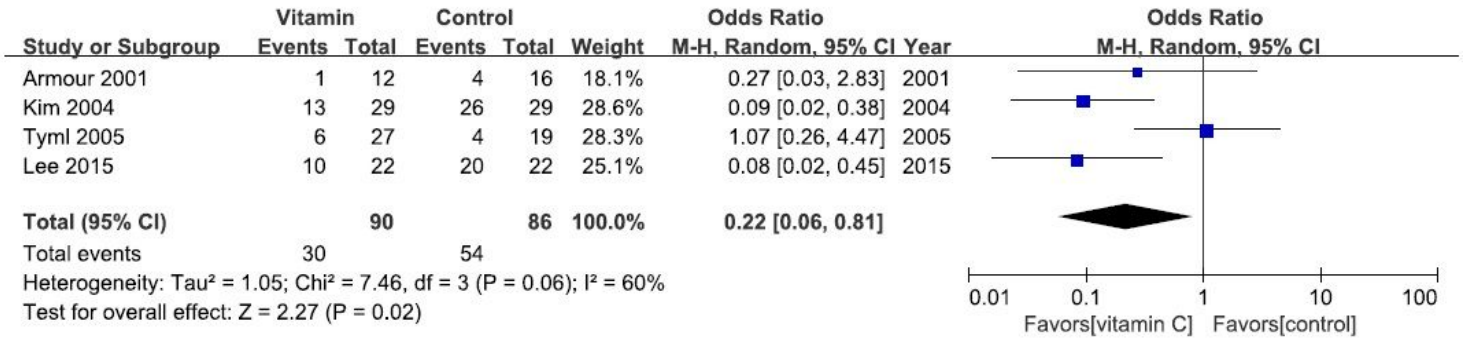

Figure 3

Forest plot for mortality in animal studies. df = degrees of freedom, M-H = Mantel-Haenszel.

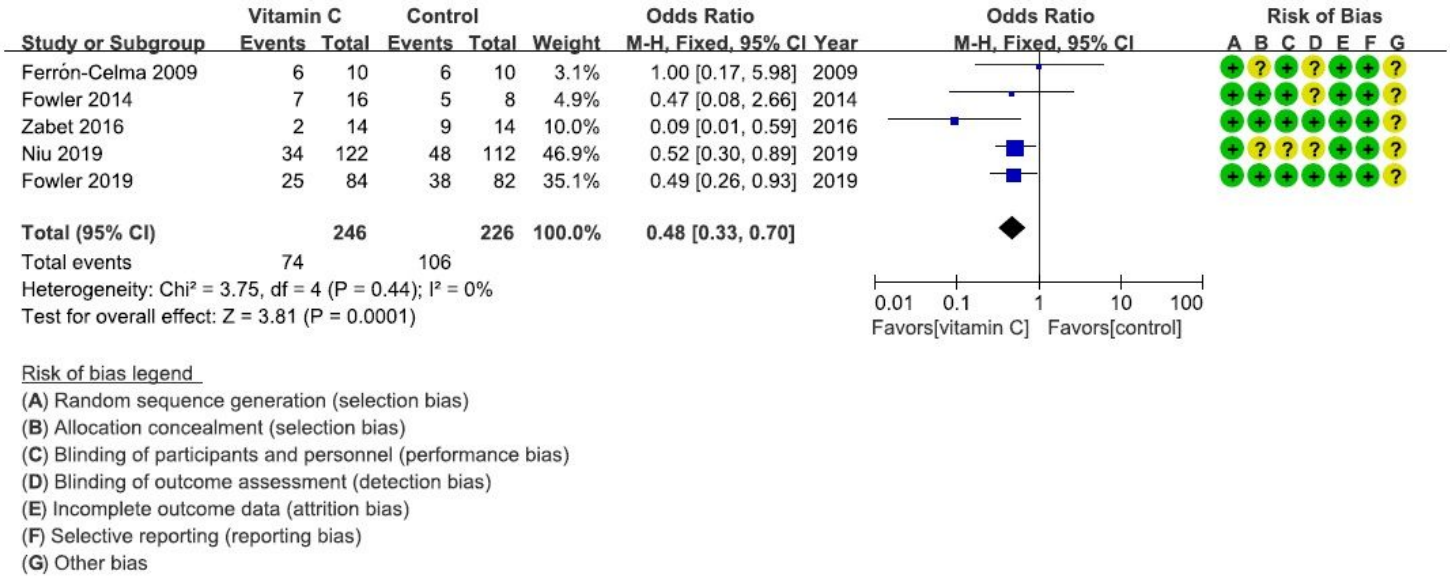

Figure 4

Forest plot for mortality in human studies, and risk of bias summary for human studies included in the meta-analysis. df = degrees of freedom, M-H = Mantel-Haenszel.

Supplementary Files

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