

Adjuvant Administration of Vitamin C Improves Mortality of Patients with Sepsis and Septic Shock: A Systems Review and Meta-Analysis

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Abstract

The aim of this study was to examine whether vitamin C reduced mortality when adjuvant therapy of patients with septic shock and severe sepsis compared with placebo by meta-analysis. Eligible trials were identified from Pubmed, Embase, Ovid, and the Cochrane database. Four randomized controlled trials (RCT) and two retrospective studies were published between 2000 and 2017 met the inclusion criteria and suitable for meta-analysis. The data were analyzed with randomized-effects or fixed-effects models using Review Manager Version 5.3. Four randomized studies with a total of 109 participants were suitable for meta-analysis. The heterogeneity was assessed by calculating the Q and I^2 methods. A random-effects approach instead of a fixed-effects analysis was undertaken if $I^2 > 50\%$. Adjuvant vitamin C did not associate with a reduction in mortality as compared with placebo, it is occurred similarly in both RCT studies and retrospective studies. However, high doses of vitamin C (>50 mg/kg/day) significant reduced the mortality rate of severe sepsis patients. And administration of high doses of vitamin C to therapy severe sepsis did not significantly reduce the ICU length of stay. The results suggested a trend toward reducing mortality in severe sepsis and septic shock patients' adjuvant with vitamin C. Further multicenter large randomized controlled trials are necessary to determine the potential benefits of vitamin C in patients with severe sepsis and septic shock.

Keywords

Sepsis, Septic Shock, Vitamin C, Ascorbic Acid, Mortality

1. Introduction

Sepsis is a serious and life-threatening medical condition, affecting approx-

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imately 26 million people worldwide every year [1]. Sepsis is caused by a dysregulated host with response to infection [2] [3] [4]. Despite multiple supportive therapies, death or disability often occurs in patients. Sepsis has become a major public health issue. The mortality of severe sepsis reaches up to almost 50% in patients that presents with septic shock [5]. Over the past decades, there has been a focus on searching for a new agent that can successful in directly targeting the pathophysiologic effects of sepsis. We have researched many immunomodulators such as: anti-tumornecrosis antibodies, and anti-TNF receptor antibodies, but these immunomodulators all failed to improve 28-day mortality in sepsis patients [6]. Furthermore, we have examined human activated protein C, which can prevent microvascular dysfunction that contributes to multisystem organ failure in sepsis. However, it was found no improvement in outcomes later [7].

It is known that the pro-inflammatory mediators and oxidative stress play an important role in the pathogenesis and high morbidity and mortality associated with sepsis. When sepsis happened overwhelming oxidative stress and pro-inflammatory mediators are generated [8]. Which can increase endothelial permeability [9] and impairment of microcirculatory flow [10], contributing to organ dysfunction. However, current bundle care treatment protocols do not target the inflammatory and oxidative stress caused by sepsis [5]. Hence, there is a need for effective, targeted adjuvant therapies that reverse the inflammatory and oxidative stress present in sepsis patients.

Vitamin C, is a water-soluble vitamin that acts as an antioxidant and a cofactor for several enzymes in the body [11]. It can mitigate ROS-induced damage to endothelial and myocardial cells in ischemia/reperfusion. Therefore vitamin C might improve tissue perfusion and reduce tissue hypoxia and organ dysfunction by limiting endothelial dysfunction [12] [13]. Vitamin C also plays an important in the synthesis of catecholamines and other hormones important for the maintenance of adequate perfusion [14]. Additionally, vitamin C plays an important role in immune function, including influences macrophage activity, improves chemotaxis and supports lymphocytic proliferation [15]. Currently evidence is emerging that parenteral administration of vitamin C may be a beneficial adjuvant therapy of severe sepsis and septic shock in animal models.

And some studies have evaluated the effect of vitamin C supplementation in human severe sepsis. Fowler *et al.*, [16] and Zabet *et al.*, [17] found that intravenous infusion of vitamin C can prompt reduction of organ failure and reduce 28-day mortality. However, some experts have different opinions as follows: Ferrón-Celma *et al.*, compared infusion of the vitamin C (450 mg/day) with placebo in a small cohort of patients with sepsis. At the end of the study, the mortality rate was 40% in the placebo group and 60% in the vitamin C-treated group [18]. Heyland D *et al.*, found antioxidants (contain 1500 mg vitamin C and mineral) had no effect on 28-day mortality in critically ill patients which 32% are sepsis patients compared with placebo [19].

There have been controversial in administrate vitamin C for sepsis therapy.

And there is still no Meta analysis to declare whether Vitamin C could reduce the mortality of patients with sepsis and septic shock. Accordingly, we conducted a meta-analysis to examine the effects on the adjuvant vitamin C to treat sepsis or septic shock.

2. Methods

2.1. Study Selection

We searched Medline, Embase, Ovid and Cochrane database. All databases were searched for articles published from inception until November 2017 using the following the same keywords as searching terms: sepsis, severe sepsis, septic shock, vitamin C, ascorbic acid, ascorbic, antioxidant. Reference lists of all retrieved articles were manually searched for further studies.

2.2. Data Extraction

Two reviewers (Zhang MW and Wen Y) independently extracted the following parameters from each study: first author, year of publication, study population characteristics, study design, number of patients, sex, age, inclusion and exclusion criteria, and rate of mortality in **Table 1**. Disagreements between the two reviewers were resolved by consensus and discussion with a third reviewer. If there are confronted with the “same author” or “same data” issue, the latest published study was included.

2.3. Inclusion and Exclusion Criteria

We included trials with the following features:

- 1) Type of trials: randomized controlled clinical trials and retrospective studies.
- 2) Population: trials included adult population with sepsis or septic shock.
- 3) Intervention: patients submitted to vitamin C for sepsis therapy.
- 4) Comparison: placebo for sepsis therapy.
- 5) Outcome: the primary outcome was 28-day mortality.

Trials with the following features were excluded:

- 1) They were not published in English.
- 2) They were not published as original articles.
- 3) They did not use adult patients.
- 4) They did not administrate vitamin C for sepsis therapy.
- 5) They included no data on mortality in patients with sepsis or septic shock.
- 6) Full-text articles were not available.

2.4. Quality Assessment

The quality of each article was assessed by two reviewers independently. Disagreements were resolved by consulting a third reviewer. The five-point Jadad scale was calculated to assess the quality of the RCTs studies [20]. This scale includes the method of randomization, blinding, and loss to follow-up (**Table 2**).

Table 1. Characteristics of analysed studies. NA, non-available; RCT, randomized controlled trial; SD, standard deviation. Data are shown as mean \pm SD.

Author	Zabet <i>et al.</i>	Tanaka <i>et al.</i>	Ferrón-Celma <i>et al.</i>	Fowler <i>et al.</i>	Kahn <i>et al.</i>	Marik <i>et al.</i>
Type of study	RCT	RCT	RCT	RCT	Retrospective	Retrospective
Year	2016	2000	2009	2014	2011	2017
Country	IRAN	JAPAN	SPAIN	USA	USA	USA
Number of patients	28	37	20	24	40	94
Mean age \pm SD (years)	64 \pm 16	40 \pm 20	68 \pm 4.5	NA	42 \pm 16	54 \pm 14
Males/females (no.)	21/7	25/12	11/9	13/11	33/0	50/44
Study quality	4 stars	3 stars	4 stars	5 stars	7 stars	7 stars

NA, non-available; RCT, randomized controlled trial; SD, standard deviation.

Table 2. Clinical background of RCT studies included in the meta-analysis.

Author	Sequences generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Zabet, <i>et al.</i>	low	low	low	low	low	low	low
Tanaka H <i>et al.</i>	unclear	high	high	high	low	low	low
Ferrón-Celma <i>et al.</i>	unclear	low	high	high	low	low	low
Fowler <i>et al.</i>	low	low	low	low	low	low	low

And we judged retrospective studies with Newcastle-Ottawa scale [21]. We considered it to be at low risk of bias when received a score of nine or eight stars, studies that scored seven or six stars were regarded as medium risk, and scores below six were considered to be high risk of bias. This scale includes the method of randomization, blinding, and loss to follow-up which could be found in **Table 2**.

2.5. Statistical Analysis

We conducted a meta-analysis of the RCTs and retrospective studies, which were compared with clinical outcomes of septic shock patient, using either with vitamin C or placebo for therapy protocol. The primary outcomes of our analysis were mortality rate, secondary outcomes were ICU length of stay. Because of the inherent difference was significant in study design, we conducted separate meta-analyses for the RCTs and the retrospective studies. Given the inherent difference in the doses of vitamin C for adjuvant therapy of septic shock, we conducted separate meta-analyses for the low doses and high doses vitamin C. For mortality, some studies used 28-day mortality, whereas others used in hospital mortality. Given the observed heterogeneity in the study methods, we used ran-

dom effects with meta-analyses to obtain primary main clinical outcomes. Data were analyzed by Review Manager (Version 5.3, the Nordic Cochrane Centre, Copenhagen, Denmark). The pooled odds ratio (OR) for dichotomous data and mean differences for continuous data with 95% confidence intervals (CIs) were calculated. The statistical heterogeneity was explored and quantified using the Mantel-Haenszel chi-square test and the I^2 test. Heterogeneity was predefined as $P < 0.05$ with the Mantel-Haenszel chi-square test or an I^2 value $> 50\%$. The random-effects model was used when heterogeneity was observed. Otherwise, the fixed-effects model was used. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Eligible Studies

A total of 4918 reports were identified through the initial search, and 4876 reports were excluded is browsing through the abstract. The remainder of the 42 records was examined in detail. In total, six studies were included that were compared with or without vitamin C for septic adjuvant therapy. In the included trails, four RCT and two retrospective studies were published between 2000 and 2017, which met the inclusion criteria and were suitable for meta-analysis (Figure 1). The systemic inflammatory responses to septic insults and burn injury, and the main reason of cause death were multiorgan failure, thus we included two small studies in burn patients assessed the effect of high-dose vitamin C (66 mg/kg/hour). The characteristics of the included studies are summarized in Table 1.

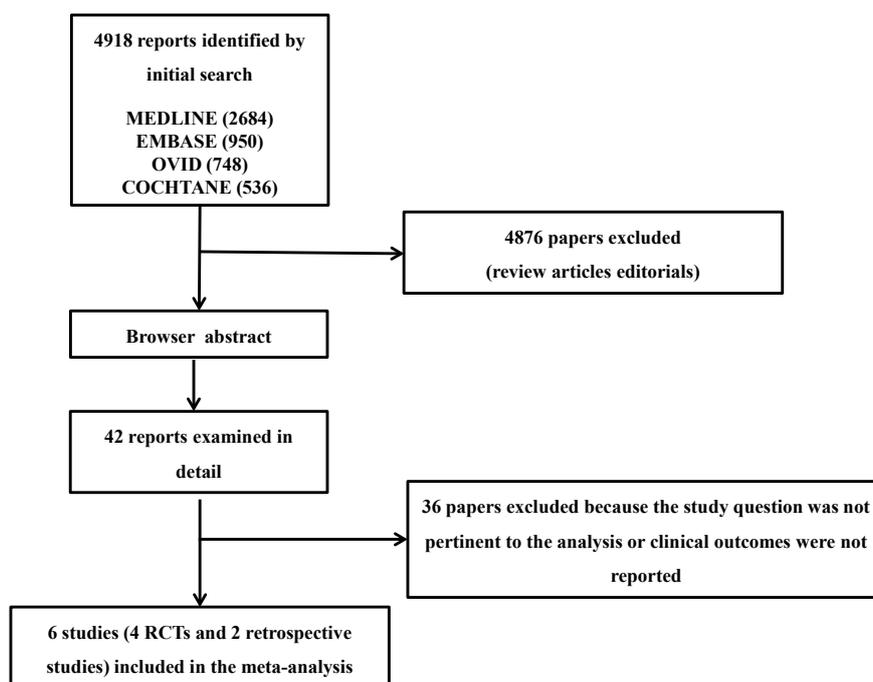


Figure 1. Selection of trials for inclusion in the meta-analysis, RCTs and randomized controlled trials.

3.2. Study Characteristics

The main characteristics of the included studies are shown in **Table 1**. Overall, all included studies are small cohort of patients with septic shock. Sample size ranged from 20 to 37, with a total of 109 participants.

3.2.1. Mortality

The effects of therapy with vitamin C on mortality in patients with severe sepsis were estimated from all six reports, and the heterogeneity was also determined to be significant ($P = 0.04 < 0.05$, $I^2 = 58\%$). Thus, randomized-effects were used. The mortality rates in these six studies were explored including 28 day mortality or in hospital mortality. We found that adjuvant vitamin C does not associated with a reduction in mortality as compared placebo (OR 0.46, 95% CI 0.17 - 1.24, $P > 0.05$), the similar situation was occurred in both RCT studies (OR 0.53 95% CI 0.16 - 1.73, $P > 0.05$) and retrospective studies (OR 0.39, 95% CI 0.04 - 3.64, $P > 0.05$) (**Figure 2**).

3.2.2. The Therapy Effects of the Doses of Vitamin C to Severe Sepsis

The impact of different doses of vitamin C on mortality in patients with severe sepsis was calculated from four RCTs (**Figure 3**). The heterogeneity was determined to be non-significant ($P = 0.18$, $I^2 = 36\% < 50\%$). Then fixed-effects were chosen. Compared with placebo, high doses of vitamin C (> 50 mg/kg/day) significantly reduced the severe sepsis patients' mortality rate (OR 0.39, 95% CI 0.16 - 0.94, $P < 0.05$).

3.2.3. The Effect of High Doses of Vitamin C on ICU Length of Stay

The impact of vitamin C on ICU length of stay in patients with septic shock compared with placebo was estimated from two trails (**Figure 4**). The heterogeneity was determined to be non-significant ($P = 0.56$, $I^2 = 0\%$). We found a trend toward reduced ICU length of stay in severe sepsis patients adjuvant with vitamin C compared with placebo. However, the result was not statistically significant (OR 1.46, 95% CI 4.91 - 1.98, $P > 0.05$).

3.3. Heterogeneity Analysis

Tests for heterogeneity were performed for each of the clinical endpoints using the I^2 statistic. Heterogeneity was predefined as $P < 0.05$ with the I^2 value $> 50\%$. The random-effects model was used if heterogeneity was observed. Otherwise, the fixed-effects model was used. $P < 0.05$ was considered statistically significant. A funnel plot of the studies included in the meta-analysis reporting on overall morbidity is shown in **Figure 5**. A funnel plot of the RCT studies, which was reported on overall morbidity, is shown by using the meta-analysis. None of the studies laid outside the limits of the 95% CI, and there was no evidence of publication bias.

4. Discussions

It was reported that the mortality of severe sepsis without shock was about 14%

to 30%. However, the mortality raised to 22% to 40% in septic shock [22]. As recommended by the Surviving Sepsis Campaign [23], the mainstay of sepsis

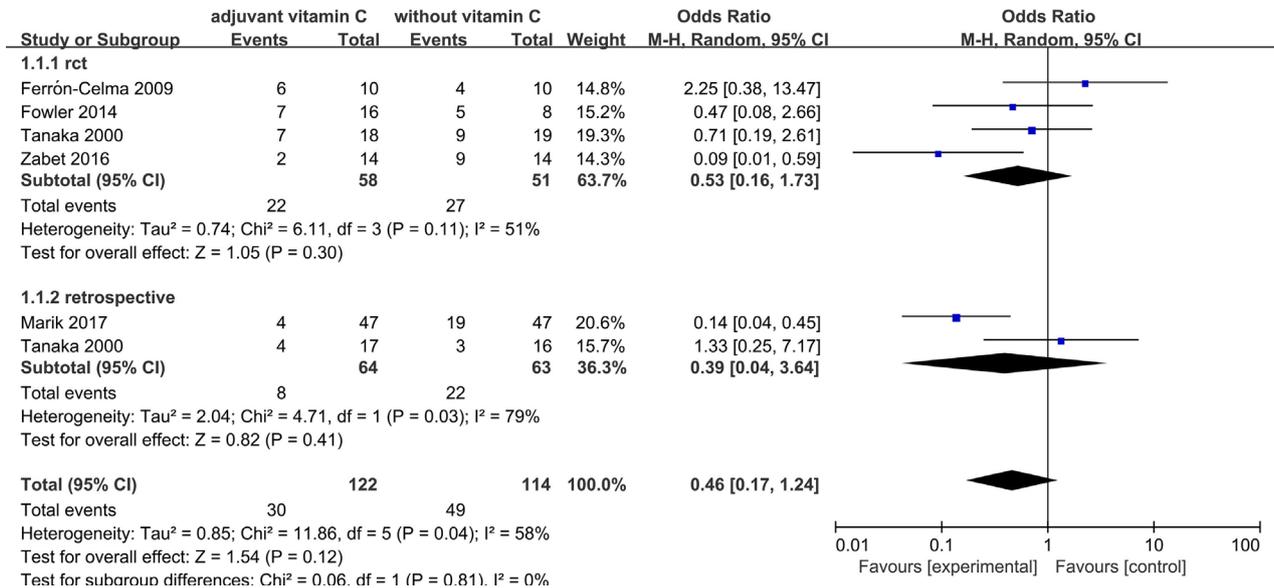


Figure 2. Results of the meta-analysis on mortality.

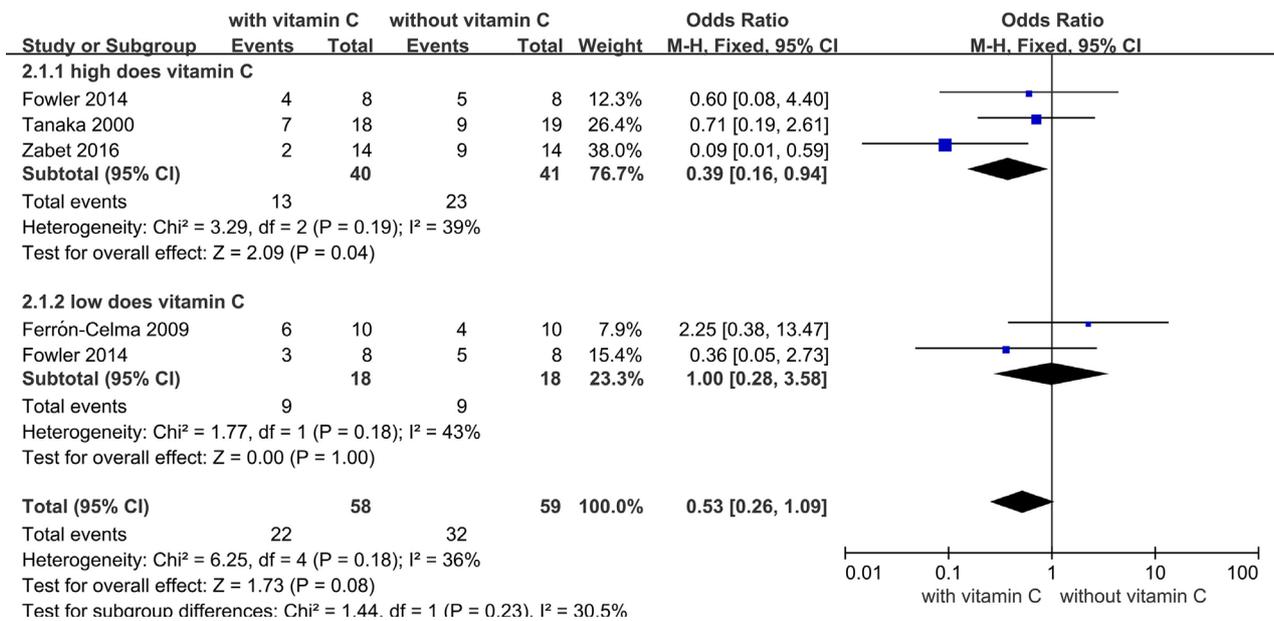


Figure 3. Results of the meta-analysis on the mortality of different doses vitamin C to treat severe sepsis.

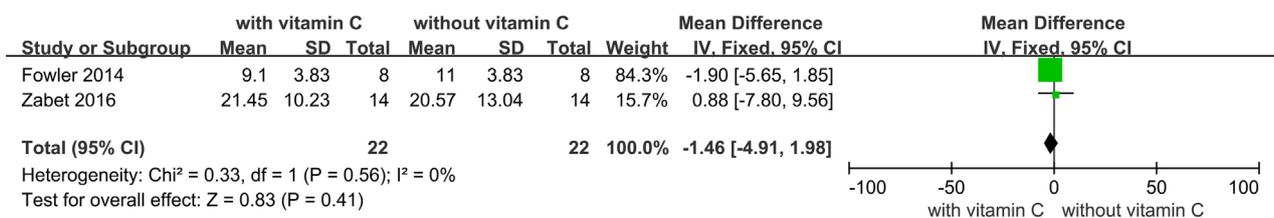
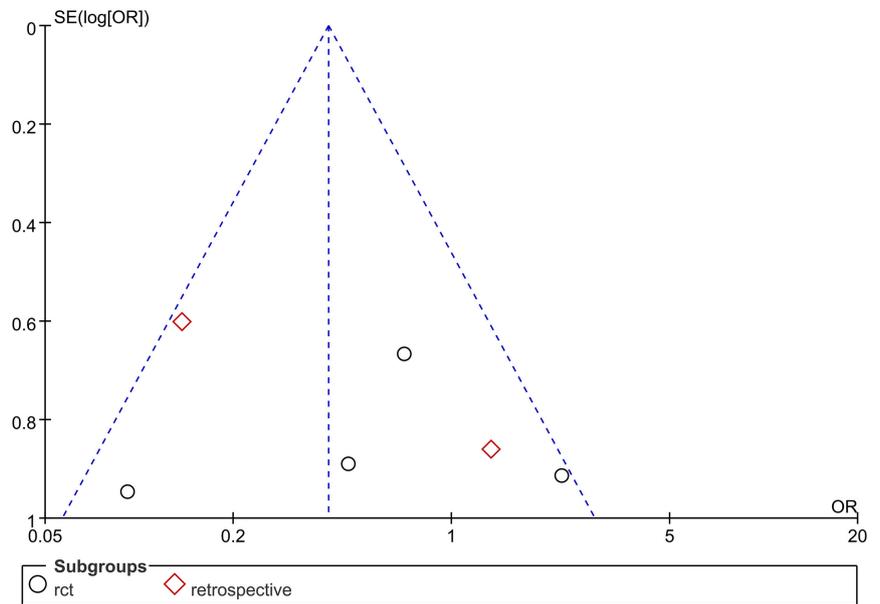
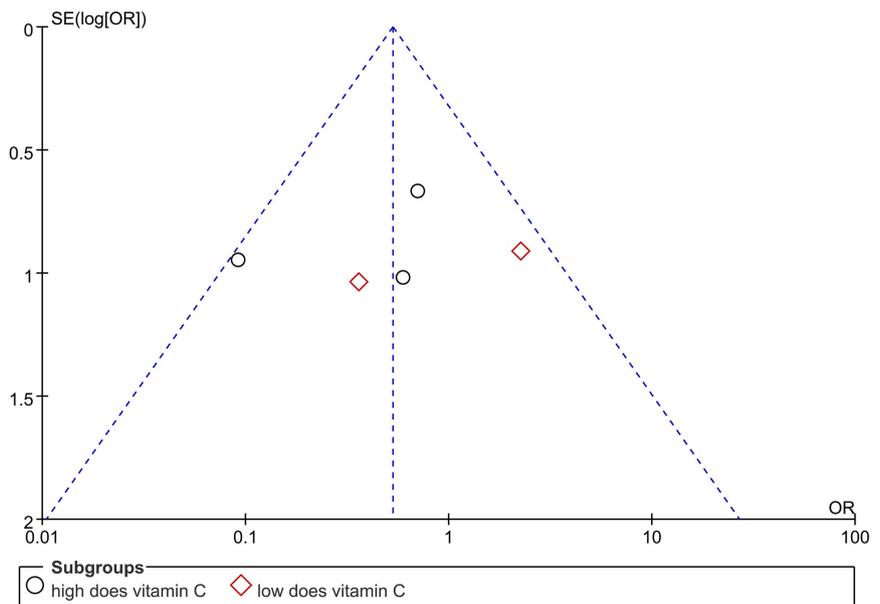


Figure 4. Results of the meta-analysis on the ICU length of stay.



(a)



(b)

Figure 5. (a) Funnel plot of the all studies reporting on overall morbidity is shown included in the meta-analysis; (b) Funnel plot of the RCT studies reporting on overall morbidity is shown included in the meta-analysis.

treatment is directed at early identification and treatment of infection through antibiotic administration and source control, as well as reversing hemodynamic instability through fluid resuscitation and using vasopressors. However, sepsis remains a major cause of death and long-term disability despite multiple supportive therapies. Poor outcome is associated with ascorbate depletion, ROS, microvascular endothelial cells, and microvascular dysfunction [5]. Some researchers suggested that microvascular dysfunction plays the most important

role in the deaths of septic patients [24]. As such, vitamin C was promoted as adjuvant therapy in conditions characterized by prevents or even reverses these pathological changes.

Evidences are emerging that administration of vitamin C may be a beneficial adjuvant therapy of severe sepsis and septic shock in animal models. For example, Fisher *et al.*, found vitamin C deficient mice were easy to develop sepsis-induced multiple organ dysfunction and parenteral infusion, and ascorbic acid can reverse these injuries [25]. For example, injection of ascorbate or dehydroascorbic acid (DHAA, the oxidized state of vitamin C, 200 mg/kg) increases the survival in mice that occurred with septic shock by exposure to lipopolysaccharide (LPS) [26]. Similarly, injection of DHAA (200 mg/kg) also significantly ameliorated survival in fecal stem solution injection into peritoneum (FIP) mice [27]. Moreover, in an animal study, mice with vitamin C deficiency had an three folds mortality from *Klebsiella pneumoniae* infection versus those administrated with ascorbate [28]. Additionally, vitamin C has shown to attenuate LPS mediated lung injury during sepsis in mouse model [26].

These robust experimental benefits are only derived from studies of mice but not human beings. There are little controlled studies on the effects of vitamin C on sepsis and septic shock patients. Fowler *et al.*, studied the intravenous supplemented of 50 or 200 mg/kg/day ascorbic acid in patients with severe sepsis. As compared with placebo, patients who received ascorbic acid prompted reduction of organ failure, exhibited less inflammation and ameliorated 28-day mortality [17]. Zabet *et al.*, studied infusion of 25 mg/kg ascorbic acid every 6 hours for 72 hours compared with placebo in the patients with septic shock who required norepinephrine treatment. The results have shown that mean dose of norepinephrine, duration of norepinephrine infusion and 28-day mortality were significantly decreased in the ascorbic acid than in the placebo [16]. Recently, Marik *et al.*, examined the role of vitamin C combined with hydrocortisone and thiamine in patients with sepsis. The mortality of the treatment group significantly reduced compared with matched controls. Patients who received vitamin C have lower rates of acute kidney injury and a more rapid reduction in sequential organ failure assessment (SOFA) scores [29].

Schorah *et al.*, found that plasma ascorbic concentrations keep at a very low level though supplement of low doses ascorbic (200 mg/day) in sepsis or traumatic injury patients [30]. And we found blood ferritin, redox-reactive iron, and ascorbate oxidation rate are significantly elevated in septic patients, and then reflected the accelerated destruction of ascorbate [31] [32]. Supplementation of the high dose of ascorbate can restore plasma ascorbate concentrations to normal level in septic patients. The results of our meta-analysis also shown that high doses of vitamin C can reduce the mortality of septic patients, but this effects did not occur in low doses vitamin C group. However, the high doses of vitamin C remain undetermined. Under normal physiological conditions, 100 to 300 mg vitamin C per day can normalize plasma ascorbate [33]. Infusion 1000 mg/day,

but not 300 mg/day of vitamin C can restore plasma ascorbate concentrations to normal in critically ill patients [34]. Because of the ascorbate repletion in septic patients, up to 3 g (50 mg/kg/day) daily is needed to restore normal plasma concentrations [34]. Thus, we defined the dose of 50 mg/kg/day as a cutoff point for low and high doses in our meta-analysis.

What needs to be pointed out that there is a main potential adverse effect with a long time of using high-dose vitamin C, that is formation of calcium-oxalate stones in the kidneys [35]. However, this adverse effect never mentioned in our included six studies. The reason maybe is septic patients only require high-dose vitamin C therapy for a few days until source control and hemodynamic stability. And there has reported that it is scarce formation of calcium oxalate stones in the kidneys if you with a normal renal function [36]. And we recommend intravenous injection vitamin C to replacement oral for high oral intake causes diarrhea [37]. Additionally, in patients with glucose-6-phosphate dehydrogenase deficiency infusion high-dose ascorbate may cause intravascular hemolysis [38]. Therefore, it is wise to avoid administration of high doses of vitamin C in patients with renal dysfunction or glucose-6-phosphate dehydrogenase deficiency. Do not use vitamin C for a long time in patients, and the best way to administer vitamin C is intravenous injection.

The results of this meta-analysis should be interpreted with caution for several reasons. Firstly, all of the data in the present study come from low sample size of studies, and the overall level of clinical evidence is not sufficient. Secondly, the most trials included were severe sepsis or septic shock patients, whereas one trial was burn injury patients. Even though there existed similarities between the systemic inflammatory responses to septic insults and burn injury, and the main reason cause death were multiorgan failure, the results were potentially heterogeneity i [18]. Moreover, different doses of vitamin C were used, oral and intravenous vitamin C regimens were mixed. Thus, those results related with vitamin C were potentially overstated. Finally, some of the trials included 28-day mortality values, whereas one trial only reported mortality, thus various time points may influence the overall results extrapolation.

5. Conclusion

To our knowledge, no meta-analysis has compared with vitamin C or placebo to treat sepsis patients up to now. In this meta-analysis, the treatment of vitamin C as a novel adjuvant therapy on mortality in severe sepsis and septic shock was investigated. The result has shown that high doses of vitamin C (>50 mg/kg/day) significant reduce the mortality rate of severe sepsis patients. However, low doses of vitamin C have no effect on the mortality. Administration of high doses vitamin C was not significant reduce ICU length of stay in septic patients. In the future, a large multicenter randomized controlled trial is necessary to determine the potential benefits of vitamin C in patients with severe sepsis and septic shock.

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Declaration of Conflict of Interest

The remaining authors have no financial relationships to disclose and no conflicts of interest to report.

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