INPLASY PROTOCOL

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Corresponding author:
Kai Zhang

zhangkai1993@aliyun.com

Author Affiliation:
Department of General Surgery, Lishui People's Hospital, Lishui, China.

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Conflicts of interest:
None declared.

The effect of intravenous vitamin C on clinical outcomes in patients with sepsis or septic shock: a meta-analysis of randomized controlled trials

Zhu, HY[1]; Xu, XY[2]; Zhang, K[3]; Ye, QP[4].

Review question / Objective: **Vitamin C deficiency is a common scenario in septic patients and is associated with poor outcomes. However, the effect of intravenous (IV) vitamin C for the treatment of sepsis remains controversial. Thus, we conducted a meta-analysis to evaluate the effect of IV vitamin C among patients with sepsis or septic shock.**
Eligibility criteria: **The inclusion criteria were as shown below: 1. Population: adult patients (≥18 years of age) with sepsis or septic shock. Sepsis was defined as reported by the original authors, septic shock was defined as sepsis with the need for vasopressor support; 2. Intervention: IV vitamin C as monotherapy; 3. Comparison: placebo, or no intervention; 4. Outcomes: the primary outcome was short-term mortality, including hospital, 28/30-day mortality. Secondary outcomes were the length of ICU stay, duration of vasopressor, and SOFA score after vitamin C treatment; 5. Design: randomized controlled trial.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 June 2022 and was last updated on 04 June 2022 (registration number INPLASY202260013).

INTRODUCTION

Review question / Objective: **Vitamin C deficiency is a common scenario in septic patients and is associated with poor outcomes. However, the effect of intravenous (IV) vitamin C for the treatment of sepsis remains controversial. Thus, we conducted a meta-analysis to evaluate the effect of IV vitamin C among patients with sepsis or septic shock.**

Condition being studied: **Sepsis is a life-threatening syndrome associated with physiological, pathological and biological abnormalities due to a dysregulated immune response to infections. Despite the advances in sepsis research improving the**

diagnosis and treatment, sepsis continues to be among the most common causes of intensive care unit (ICU) admissions and deaths, becomes a major global health problem. According to the Global Burden of Diseases Study, an estimated of 48.9 million incident cases of sepsis were reported worldwide in 2017, with nearly 11.0 million sepsis-related deaths, accounting for 19.7% of all global deaths. Even survivors are at high risk of developing functional limitations, cognitive impairment, and mental health problems, which significantly impair the quality of life. It is well-established that patients with sepsis have decreased levels of vitamin C (also known as ascorbic acid), and this depletion has a dose-dependent association with increased organ dysfunction and mortality. The beneficial effects and associated mechanisms of vitamin C in sepsis including its anti-inflammatory and anti-oxidant properties, acting as an enzymatic cofactor in the synthesis of vasopressin, cortisol, and catecholamine, inhibiting the nitric oxide synthase and regulating the clearance of alveolar fluid. In recent years, multiple randomized controlled trials (RCTs) evaluating the effect of intravenous (IV) vitamin C with or without hydrocortisone and thiamine have been completed. Several recently published meta-analyses assessed the combination of hydrocortisone, ascorbic acid and thiamine (HAT) treatment in patients with sepsis or septic shock. The results indicated that the HAT treatment improved the Sequential Organ Failure Assessment (SOFA) score and reduced the duration of vasopressor, but was not associated with lower short-term mortality. However, the evidence-based medical evidence for using IV vitamin C as monotherapy in patients with sepsis or septic shock are scarce. Therefore, this current meta-analysis aim to evaluate the effect of IV vitamin C alone on clinical outcomes among patients with sepsis or septic shock, and perform subgroup analyses to better understand the effectiveness of IV vitamin C in different populations and examine whether a dose-effect modified treatment effect.

METHODS

Search strategy: We systematically searched the PubMed, Embase, Scopus, and Cochrane Library for eligible studies in English from inception through May 25th, 2022. The search used broad search terms containing "sepsis", "septic shock", "vitamin C", "ascorbic acid", and "randomized".

Participant or population: adult patients (≥18 years of age) with sepsis or septic shock. Sepsis was defined as reported by the original authors, septic shock was defined as sepsis with the need for vasopressor support.

Intervention: Intervention: IV vitamin C as monotherapy.

Comparator: Comparison: placebo, or nointervention.

Study designs to be included: Design: randomized controlled trial.

Eligibility criteria: The inclusion criteria were as shown below: 1. Population: adult patients (≥18 years of age) with sepsis or septic shock. Sepsis was defined as reported by the original authors, septic shock was defined as sepsis with the need for vasopressor support; 2. Intervention: IV vitamin C as monotherapy; 3. Comparison: placebo, or no intervention; 4. Outcomes: the primary outcome was short-term mortality, including hospital, 28/30-day mortality. Secondary outcomes were the length of ICU stay, duration of vasopressor, and SOFA score after vitamin C treatment; 5. Design: randomized controlled trial.

Information sources: We systematically searched the PubMed, Embase, Scopus, and Cochrane Library for eligible studies in English from inception through May 25th, 2022.

Main outcome(s): The primary outcome was short-term mortality, including hospital, 28/30-day mortality.

Additional outcome(s): Secondary outcomes were the length of ICU stay,

duration of vasopressor, and SOFA score after vitamin C treatment.

Data management: Two authors (Huiyan Zhu, Qiaoping Ye) independently retrieved relevant studies, extracted characteristics of studies (first author, years of publication, population, intervention and control methods, vitamin C level) and predefined outcomes from included studies.

Quality assessment / Risk of bias analysis: The Cochrane risk of bias tool was utilized for assessing the methodological quality of including studies by two authors (Huiyan Zhu, Qiaoping Ye), any differences in opinion were resolved by a third adjudicator (Xiaoya Xu).

Strategy of data synthesis: We computed the pooled odds ratio (OR) with 95% confidence interval (CI) for dichotomous outcomes, and mean difference (MD) with 95% CI for continuous outcomes. The heterogeneity between studies was assessed by the Higgins inconsistency (I2) statistics. Substantial heterogeneity was identified when I2 value>30% and a random-effects model was employed to perform the analysis, otherwise a fixed-effects model would be used. Publication bias was assessed by using the funnel plot and Egger's regression test.

Subgroup analysis: A prespecified subgroup analysis stratified by the types of disease (sepsis versus septic shock), dose (high dose as daily dose of ≥100 mg/kg or 10000 mg/day) and duration (<5 days versus ≥5 days) of IV vitamin C treatment.

Sensitivity analysis: A sensitivity analysis was conducted to explore the effect of individual study by consecutive exclusion of each study at one time.

Language: English.

Country(ies) involved: China.

Keywords: Key words: Vitamin C; Ascorbic acid; Sepsis; Septic shock; Meta-analysis.

Contributions of each author:
Author 1 - Huiyan Zhu - conceived the idea, performed the analysis, and drafted the initial draft writing of this paper.
Author 2 - Xiaoya Xu - contributed to the collection and interpretation of data.
Author 3 - Kai Zhang - helped to frame the idea of the study and provided technical support.
Author 4 - Qiaoping Ye - conceived the idea, performed the analysis, drafted the initial draft writing of this paper, contributed to the revision of this paper, and the final approval of the version to be published.