

# Vitamin C supplementation in the critically ill: A systematic review and meta-analysis

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## Abstract

**Background:** Low plasma levels of vitamin C are associated with adverse outcomes, including increased mortality, in critically ill patients. Several trials have suggested that the administration of intravenous vitamin C in this setting may have beneficial effects, such as reducing the incidence of organ failure and improving survival. However, these studies have generally involved combination therapies consisting of vitamin C along with other antioxidants, confounding the effects of vitamin C alone. The primary objective of this meta-analysis is to investigate the effects of isolated intravenous supplementation of vitamin C in adults with critical illness.

**Methods:** A database search was conducted for studies on the use of intravenous vitamin C in adult patients with critical illness. The primary outcome assessed was mortality at the longest follow-up time available. Secondary outcomes were the duration of mechanical ventilation, duration of vasopressor support, fluid requirements, and urine output in the first 24 h of intensive care unit admission.

**Results:** Five studies (four randomized controlled trials and one retrospective review) enrolling a total of 142 patients were included in this meta-analysis. Compared with controls, the administration of intravenous vitamin C was associated with a decreased need for vasopressor support (standardized mean difference  $-0.71$ ; 95% confidence interval  $(-1.16$  to  $-0.26)$ ;  $p = 0.002$ ) and decreased duration of mechanical ventilation (standardized mean difference  $-0.5$ ; 95% confidence interval  $(-0.93$  to  $-0.06)$ ;  $p = 0.03$ ), but no difference was found in mortality (odds ratio 0.76; 95% confidence interval  $(0.27$  to  $2.16)$ ;  $p = 0.6$ ). Trends were also noted toward decreased fluid requirements and increased urine output. No adverse effects were reported.

**Conclusion:** The administration of intravenous vitamin C may lead to vasopressor sparing effects and a reduced need for mechanical ventilation in the critically ill, without affecting overall mortality. However, these results should be interpreted in light of the limitations of the primary literature and should serve as a preview of upcoming trials in this area.

## Keywords

Critical care, emergency medicine, respiratory medicine, sepsis, nutrition, respiratory distress, shock, vitamin C, acute respiratory distress syndrome

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## Introduction

Vitamin C is a water-soluble vitamin with a variety of antioxidant,<sup>1</sup> anti-inflammatory,<sup>2</sup> and microvascular<sup>3</sup> effects. Widely used in over-the-counter formulations for the common cold and general well-being,<sup>4</sup> in recent years, there has been an expanding role for the use of vitamin C in the hospital setting. Although the overall prevalence of hypovitaminosis C is around 7.1% in the general population,<sup>5</sup> up to 47.3% of undifferentiated hospitalized patients are deficient in vitamin C.<sup>6</sup>

Vitamin C levels are known to be decreased in critical illness<sup>7–10</sup> and are associated with severity of illness.<sup>7,11</sup>

Although vitamin C requirements are greater in this population due to increased oxidative stress,<sup>12</sup> levels may be restored to normal,<sup>8,13</sup> or even brought to supra-normal,<sup>14</sup> with parenteral supplementation.

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Supplemental vitamin C has shown promise in both animal models of sepsis<sup>3,15–21</sup> and human trials in the intensive care unit (ICU) setting.<sup>22–31</sup> Although a simple vitamin, a variety of biological mechanisms have been postulated to account for the beneficial actions of vitamin C in the context of sepsis and organ failure. These include the prevention and restoration of micro-circulatory flow impairment due to reactive oxygen species, the preservation of vascular responsiveness to vasoconstrictors, the preservation of endothelial barrier function, and augmentation of anti-bacterial defense, leading to an overall mitigation of organ injury and dysfunction in critically ill patients.<sup>32</sup>

However, the largest studies with the most promising results have investigated vitamin C as part of combination (“cocktail”) therapies administered together with vitamin E or thiamine plus hydrocortisone.<sup>31</sup> The last study is particularly impressive, demonstrating a substantial (8.5% versus 40.4%) reduction in mortality as well as decreased Sequential Organ Failure Assessment (SOFA) scores and length of vasopressor support compared to controls, but it is unclear which, if any, of the three constituents was responsible for these effects, obscuring the true effect of vitamin C. Furthermore, questions have been raised regarding the methodology of this study with respect to its small sample size, lack of randomization, and retrospective design.<sup>33</sup>

Few studies have focused specifically on the benefits of isolated administration of vitamin C in critically ill patients. Generally, these studies have been small and have yielded few conclusive results, and a comprehensive synthesis of the data has not been conducted heretofore. Hence, we aim in this review to provide a comprehensive meta-analysis of all studies involving isolated vitamin C administration in critically ill patients and to examine the effects upon overall mortality in addition to common clinical parameters in this setting, such as vasopressor requirements, the duration of mechanical ventilation, and resuscitation fluid requirements.

## Methods and materials

### Data sources

This study was conducted and prepared per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.<sup>34</sup> We aimed to collect all studies which assessed the use of intravenous vitamin C in adult patients with critical illness. The following databases were searched for English language articles published from inception to September 2017: MEDLINE, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, and Elsevier. The following keywords were used along with MeSH terms: “vitamin C” or “ascorbic” or “ascorbate” and “sepsis” or “septic” or “shock” or “respiratory distress” or “ARDS” or “lung injury” or “critical” or “critically” or “intensive” or “ICU” or “trauma” or “burn.” All search terms were exploded and no restrictions or limitations were placed in our search strategy.

### Study selection criteria

We included trials with the following characteristics:

1. Type of studies: prospective and retrospective clinical trials;
2. Population: adult ICU patients;
3. Intervention: intravenous vitamin C supplementation versus placebo or no intervention, with no minimum dose.
4. Study outcome: The primary outcome examined was cause mortality in the longest duration provided by the studies. Secondary outcomes were the duration of mechanical ventilation, duration of vasopressor support, fluid requirements, and urine output in the first 24 h of ICU admission.

Trials with these characteristics were excluded:

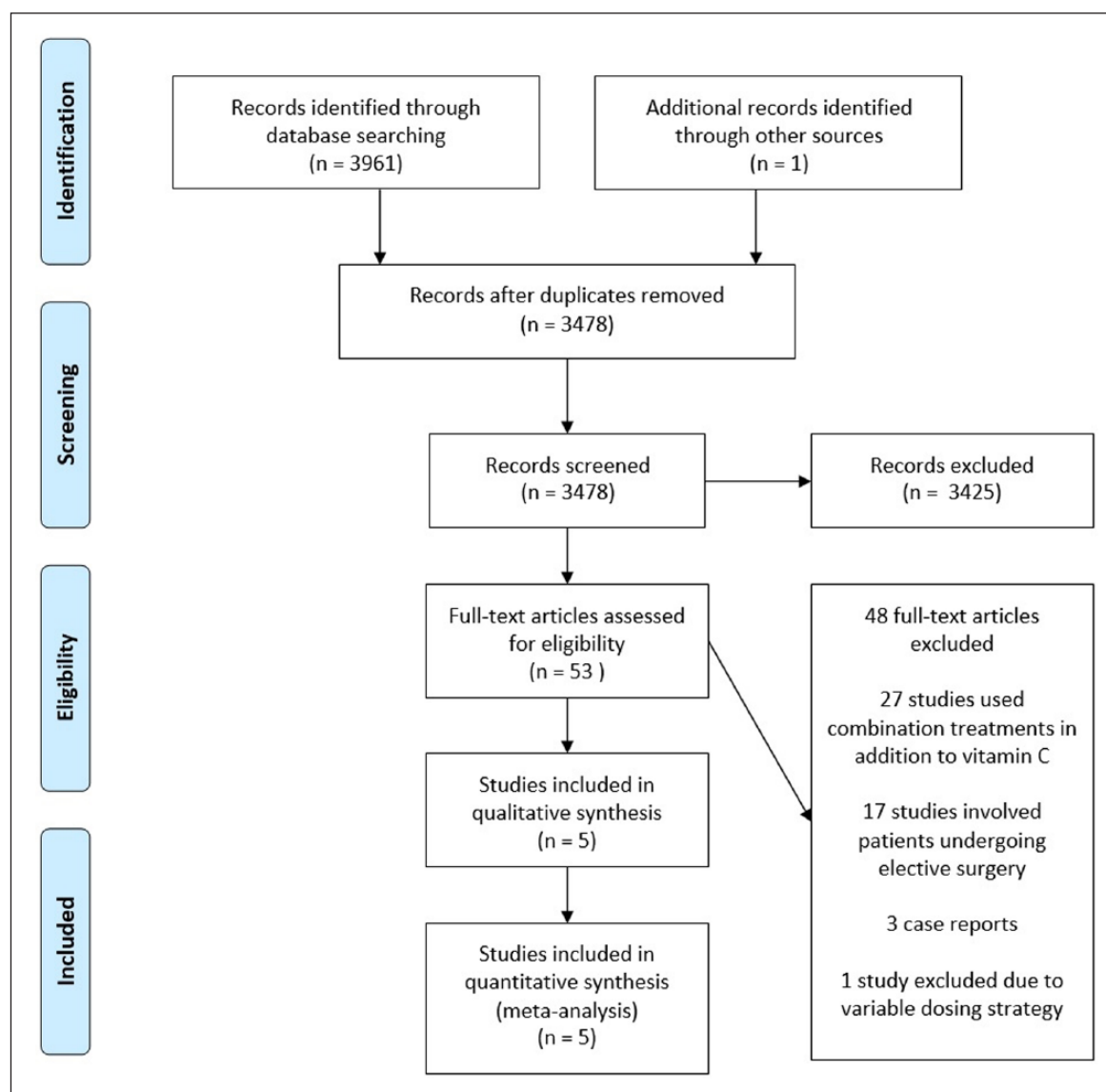
1. They were not published as original studies;
2. They were not published in English;
3. They did not use adult patients;
4. They did not use vitamin C alone without other interventions;
5. Full-text articles not available;
6. Lack of data on mortality;
7. Case reports;
8. Animal studies.

### Data extraction

Data from included studies were extracted independently by both authors, and discrepancies were resolved through discussion until consensus was reached. The primary outcome was all cause mortality in the longest duration provided by the studies. Secondary outcomes were the duration of mechanical ventilation, duration of vasopressor support, and fluid requirements and urine output in the first 24 h of ICU admission. When appropriate, standard deviations were estimated using previously described methods.<sup>35</sup> For standardized mean difference (SMD) analysis, scales of differing directionality were standardized when necessary with multiplication by  $-1$ .

### Risk of bias

We used the Cochrane Collaboration’s tool for assessing risk of bias to evaluate the quality of the included randomized controlled trials.<sup>36,37</sup> Domains assessed were random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias. The remaining observational study was similarly assessed with the ROBINS-I tool.<sup>38</sup> Studies were considered to be low risk only if every domain was individually adjudicated as such;



**Figure 1.** Study selection flow chart.

otherwise, any domain rated as unclear or high risk brought the overall risk to that respective stratification.

### Statistical analysis

Data were analyzed by Review Manager 5.3 (The Nordic Cochrane Center, Rigshospitalet, Copenhagen, Denmark). Results are presented with forest plots using odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous data and SMD with 95% CI for continuous data. The statistical heterogeneity among the studies was calculated and assessed with the  $I^2$  test based on previously recommended stratifications (low, moderate, and high to  $I^2$  values of 25%, 50%, and 75%, respectively).<sup>39</sup> A Mantel-Haenszel (MH) method was used for the dichotomous primary outcome of mortality. For all continuous outcomes, inverse variance methods were used. In addition, the random effects model of DerSimonian and Laird

was used if heterogeneity was observed; otherwise, a fixed effects model was used. The  $p$  value of  $<0.05$  was considered statistically significant. Tests for publication bias, such as the funnel plot and Egger's linear regression, were not utilized due to the low number of included studies.

## Results

### Study selection

The literature search strategy outlined above returned 3961 citations (Figure 1). After duplicates were expunged, 3478 articles were scanned by titles and abstracts, and 3425 non-relevant studies were removed. The remaining 53 articles were assessed for eligibility. Notable exclusions were due to pre- or perioperative administration for scheduled cardiac ( $n = 14$ ),<sup>40–53</sup> gastrointestinal ( $n = 1$ ),<sup>54</sup> vascular ( $n = 1$ ),<sup>55</sup> or gynecologic ( $n = 1$ )<sup>56</sup>

**Table 1.** Characteristics of included studies.

Study	Design	Setting	Patients (n intervention/n control)	Vitamin C dose in intervention group	Overall mortality n (%)	Mortality follow-up
Tanaka et al. <sup>22</sup>	Quasi-RCT	Trauma/critical care unit	Burn > 30% TBSA (total body surface area) (19/19)	66 mg/kg/h IV in Ringer's lactate (RL) for 24 h	16 (43)	Unspecified
Ferrón-Celma et al. <sup>23</sup>	RCT	Surgical	Septic patients post-abdominal surgery (10/10)	450 mg IV × 6 days post-op	10 (50)	6 days
Kahn et al. <sup>24</sup>	Observational	Burn/trauma unit	Burn > 20% TBSA (17/16)	66 mg/kg/h IV in RL for 24 h	7 (21)	2 weeks
Fowler et al. <sup>25</sup>	RCT	Medical ICU	Severe sepsis (16 (8 high dose, 8 low dose)/8)	50 mg (low dose) or 200 mg (high dose)/kg/24 h IV for 96 hours	12 (50)	28 days
Zabet et al. <sup>26</sup>	RCT	Surgical ICU	Surgical patients with septic shock (14/14)	25 mg/kg IV q6 h × 72 h	11 (39)	28 days

RCT: randomized controlled trial.

surgery, administration as part of combination therapy with other agents (n = 27),<sup>27–31,57–78</sup> or case reports (n = 3).<sup>79–81</sup> Many of the above were also excluded due to enteral administration. One study was excluded because the investigators sought to normalize plasma ascorbic acid by administering varying doses depending on baseline levels; this study also did not report clinical outcomes.<sup>82</sup> Finally, five studies (Table 1) were included in this meta-analysis.<sup>22–26</sup>

### Study characteristics and quality

These five studies (four RCTs and one retrospective review) enrolled a total of 142 patients, of whom 76 received intravenous vitamin C, compared to 66 controls. Isovolumic placebo was administered in three studies,<sup>23,25,26</sup> while in the remaining two studies, vitamin C was incorporated into resuscitation fluids in the intervention group.<sup>22,24</sup> The average age was 54 years, and 72% of participants were male. Study settings were medical,<sup>25</sup> surgical,<sup>23,26</sup> and burn/trauma.<sup>22,26</sup> All studies were single-center. The risk of bias summary figure is presented in Figure 2. Three of the four RCTs described some type of random sequence allocation, and these same three were also double-blinded. The Tanaka trial, despite its heading, should more accurately be considered as a quasi-randomized control trial, as the study participants therein were allocated per month of admission.<sup>22</sup> Because blinding of outcome assessment was not specified, no trial was considered low risk. Across all domains, three studies were considered to be of unclear risk and the remaining two as high risk.

## Meta-analysis results

### Intravenous vitamin C administration and ICU/hospital mortality

Meta-analysis of the five included trials totaling 142 patients shows that intravenous vitamin C administration does not significantly reduce ICU and hospital mortality in critically

ill patients (OR 0.76; 95% CI (0.27 to 2.16); p = 0.6) (Figure 3). Data were taken from the longest available follow-up, ranging from 6 to 28 days.<sup>23,25,26</sup> Because study heterogeneity was moderate ( $I^2 = 50\%$ ), a random effects model was used for this analysis. A sensitivity analysis was performed by removing each study singly and reanalyzing the remaining studies; no change in the effect size was noted.

### Duration of vasopressor support

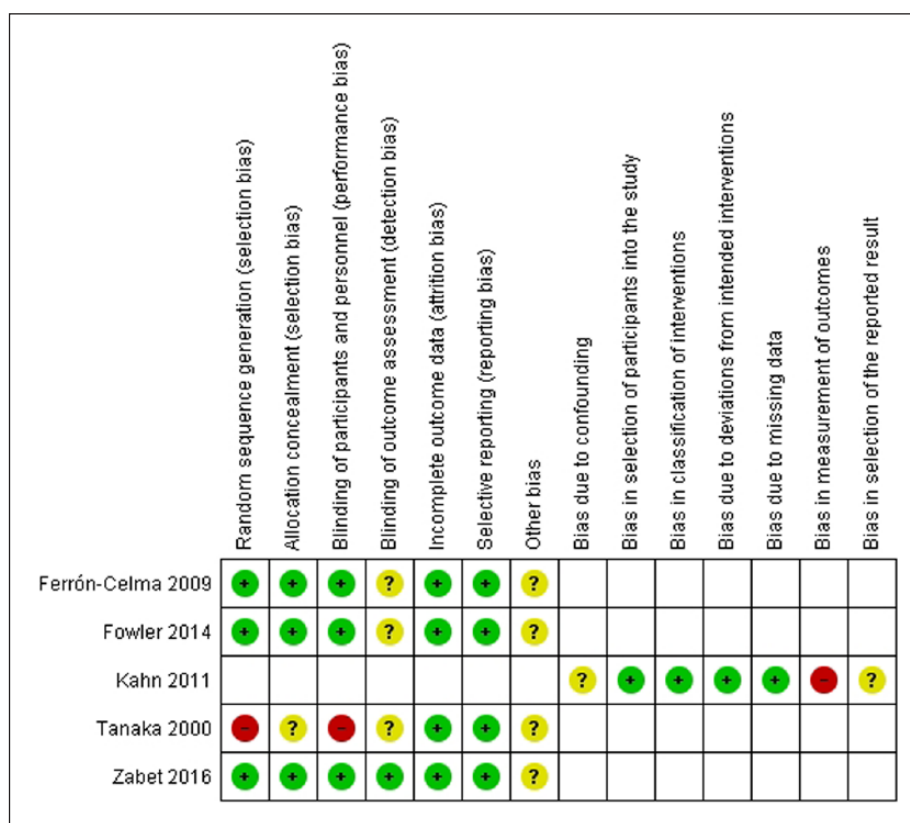
Three studies<sup>24–26</sup> enrolling a total of 85 patients evaluated the requirements for vasopressor support needed to maintain adequate hemodynamics. Compared to controls, the administration of intravenous vitamin C was associated with a reduced duration of vasopressor use (SMD  $-0.71$ ; 95% CI  $(-1.16$  to  $-0.26)$ ; p = 0.002) (Figure 4). Vasopressors administered include norepinephrine,<sup>26</sup> vasopressin, dopamine, and phenylephrine.<sup>24</sup> Because the data among these studies were homogeneous, a fixed effects model was used.

### Duration of mechanical ventilation

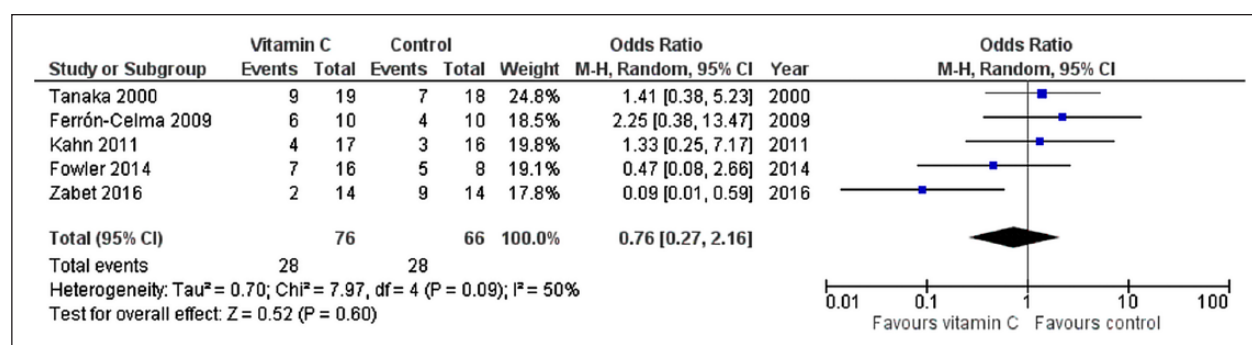
Administration of vitamin C was associated with a reduction in the duration of mechanical ventilation in the three studies totaling 89 patients which investigated this outcome (SMD  $-0.5$ ; 95% CI  $(-0.93$  to  $-0.06)$ ; p = 0.03) (Figure 5). Data were reported as either time spent on ventilator support<sup>22,26</sup> or ventilator free time.<sup>25</sup> Again, a fixed effects model was used for this analysis.

### Fluid requirements and urine output

Trends were noted toward both decreased fluid requirements (SMD  $-0.9$ ; 95% CI  $(-1.86$  to  $0.06)$ ; p = 0.07) and urine output (SMD  $-0.5$ ; 95% CI  $(-1.12$  to  $0.12)$ ; p = 0.11) in the three studies which investigated this outcome in the first 24 h of ICU admission<sup>22,24,26</sup> (Figure 6). A random effects model was used due to high study heterogeneity. Also, in Zabet



**Figure 2.** Risk of bias summary for RCTs (left) and the remaining observational study (right).



**Figure 3.** Forest plot of the effect of intravenous vitamin C administration on mortality at the longest available follow-up of all studies.

et al.<sup>26</sup> study, while there was no difference in the first 24 h, there was a trend toward increased urine output when the entire duration of the study is considered, and this would result in overall statistical significance.

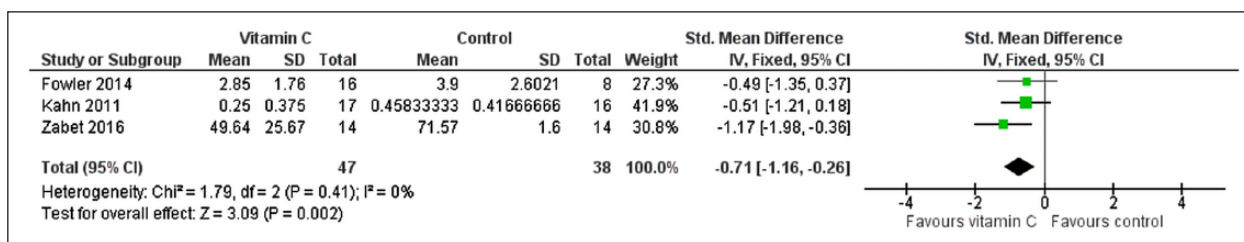
## Discussion

Although several meta-analyses have explored the effect of combination antioxidants in critical illness, our study is the first to focus exclusively on the role of vitamin C. The main results from our analysis of five studies are that vitamin C administration is not associated with decreased mortality but

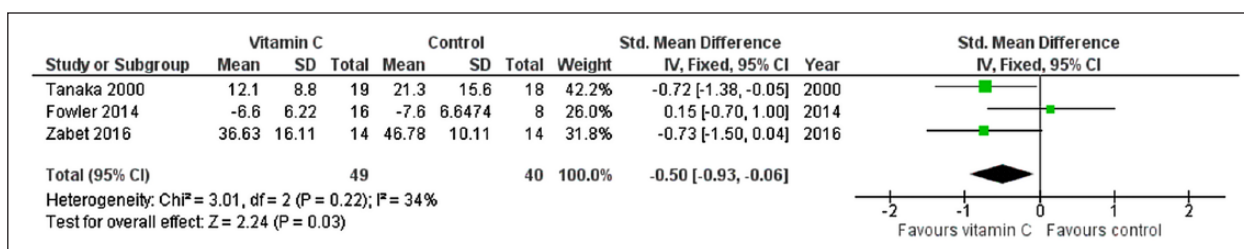
is associated with decreased vasopressor requirements and duration of mechanical ventilation.

Vitamin C is an essential cofactor for the production of endogenous vasopressors.<sup>83</sup> Through its actions on tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis,<sup>84,85</sup> and its role as a cofactor for dopamine  $\beta$ -hydroxylase,<sup>86</sup> vitamin C is involved in the biosynthesis of norepinephrine at physiologic concentrations.<sup>84</sup> Vitamin C also acts as a cofactor for peptidylglycine  $\alpha$ -amidating monooxygenase (PAM),<sup>87</sup> an enzyme that catalyzes the formation of arginine vasopressin.<sup>88</sup> On the basis of these observations, Carr et al.<sup>89</sup> hypothesized that “the administration of

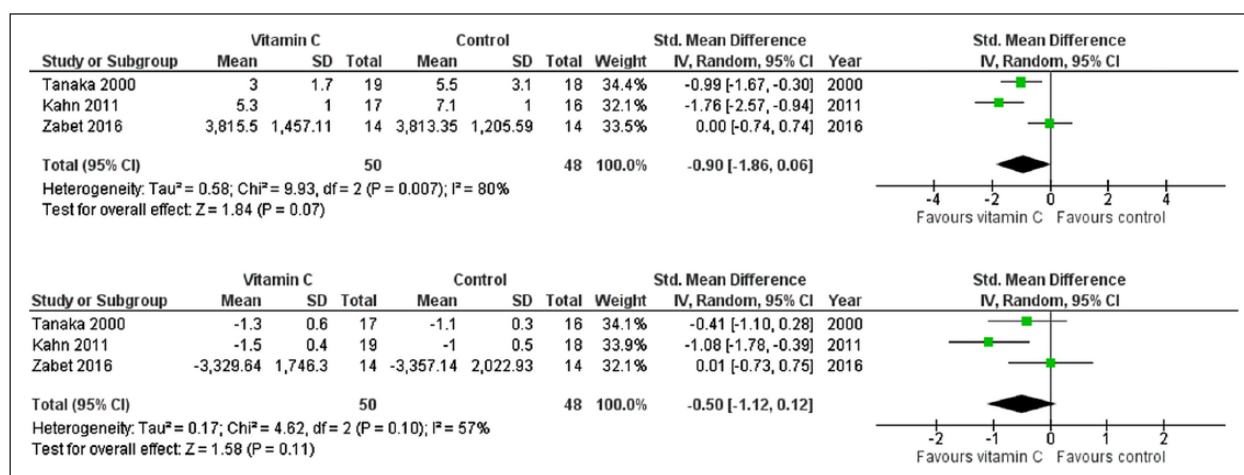




**Figure 4.** Forest plot of the effect of intravenous vitamin C administration on vasopressor requirements.



**Figure 5.** Forest plot of the effect of intravenous vitamin C administration on the duration of mechanical ventilation.



**Figure 6.** Forest plots of the effect of intravenous vitamin C administration on fluid requirements (top) and urine output (bottom) in the first 24 h of ICU admission.

high-dose ascorbate in conditions of hypovitaminosis C (e.g. severe sepsis and septic shock) may support the endogenous synthesis of these vasoactive compounds and thus ameliorate the need for exogenously administered vasopressors.”

It is noteworthy that, although we were able to demonstrate decreased vasopressor requirements and trends toward reduced fluid resuscitation needs and increased urine output, we did not find an overall difference in mortality. One possible reason for this discrepancy is the variance in baseline patient characteristics across the included studies. In general, the studies which did not demonstrate a numerically less mortality rate in the treatment group featured patients with relatively less severe hemodynamic derangements upon study commencement. In Tanaka et al.’s<sup>22</sup> study, the average

mean arterial pressure of enrolled patients was around 90 mm Hg, and all deaths occurred after the 96-h fluid resuscitation phase, by which time plasma vitamin C levels in the treatment group had already declined to match controls. In Kahn et al.’s study, only 4 of 17 patients in the treatment group required vasopressors compared to 9 of 16 controls. The authors note that “because one group had more than 50% more patients on vasopressors, the results would have been misleading.” In Ferrón-Celma et al.’s<sup>23</sup> study, only 5 of 20 patients even required vasopressor support. Conversely, Zabet et al.<sup>26</sup> did demonstrate decreased mortality with vitamin C administration, but the average mean arterial pressure (MAP) upon enrollment was under 70 mm Hg. Taken together, these observations support the hypothesis that

vitamin C indeed exerts a vasopressor sparing effect, but the magnitude of this effect may depend upon the initial need for vasopressor support. The benefits of supplemental vitamin C would be expected to be more pronounced in those with refractory vasopressor-dependent shock compared to patients with stable hemodynamics with little or no need for vasopressor support, and this difference in expected benefit might explain the difference in mortality among the analyzed studies. A similar line of reasoning applied to the VASST (Vasopressin and Septic Shock) trial, where the administration of supplemental vasopressin reduced the need for norepinephrine support without affecting mortality; the authors therein speculated that the reason for this was due to the high average MAP of enrolled patients (72–73 mm Hg).<sup>90</sup>

The significance of the decreased requirements for mechanical ventilation is unknown, as is the question of whether this is actually reflective of a real improvement in pulmonary status. Across all studies, only Tanaka et al.<sup>22</sup> demonstrated an improvement in any parameter of pulmonary function (increased PaO<sub>2</sub>/FiO<sub>2</sub> ratio in the treatment group), but the average duration of mechanical ventilation in the treatment group was 12.1 days, far longer than the initial 24-h period of vitamin C administration. Furthermore, it is unclear whether this effect is dependent upon a decreased need for resuscitation fluids and hence a concomitant reduction in the incidence and severity of pulmonary edema or is an independent effect upon the lung parenchyma. Animal research has demonstrated that vitamin C exerts a protective effect upon the pulmonary tissues in both ischemia–reperfusion<sup>91</sup> and lipopolysaccharide-induced models of lung injury<sup>15,92,93</sup> through a variety of mechanisms, including increased alveolar fluid clearance, enhanced epithelial barrier function, and the attenuation of pro-inflammatory and pro-coagulant states accompanying sepsis.<sup>94</sup> The same group has reported encouraging results in a recent series of case reports in the setting of acute respiratory distress syndrome (ARDS)<sup>79–81</sup> and has recently concluded a phase II multicenter trial investigating Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury (CITRIS-ALI, NCT02106975).<sup>95</sup> This study should further clarify the possible role of vitamin C in the treatment of acute lung injury and ARDS.

The optimal dose and target plasma concentration of vitamin C in the setting of critical illness are unknown. The recommended daily oral dose in healthy subjects needed to maintain normal plasma levels above 50  $\mu\text{mol/L}$  is 95–110 mg/day.<sup>96</sup> However, physiological requirements are increased during times of increased oxidative stress and metabolic turnover,<sup>12</sup> and plasma levels have been found to be correspondingly lower in the ICU population.<sup>7</sup> Intravenous dosing has been shown to produce higher plasma concentrations than oral administration<sup>97</sup> due to saturable intestinal absorption,<sup>98</sup> and 3 g/day is required to maintain plasma levels in the normal range in ICU patients.<sup>8</sup>

The five studies included in this meta-analysis featured doses as low as 450 mg/day<sup>23</sup> to 1584 mg/kg/day,<sup>22,24</sup> a 250-fold difference in a 70 kg subject. The difference in dosages

given may result in differing effects. As previously mentioned, vitamin C is an essential cofactor for the production of endogenous vasopressors.<sup>83</sup> It has been suggested that vitamin C is released from the adrenal cortex in response to adrenocorticotrophic hormone (ACTH) to ensure that “norepinephrine synthesis [in the medulla] always proceeds at maximum velocity ( $V_{\text{max}}$ ).”<sup>99</sup> Indeed, this study noted that vitamin C levels in the adrenal veins of patients with hyperaldosteronism who were administered ACTH were found to be  $176 \pm 71 \mu\text{mol/L}$ , over four times higher than concentrations within plasma. The authors speculated that this allows vitamin C to act locally as a paracrine mediator to stimulate norepinephrine and epinephrine synthesis. If the Carr hypothesis<sup>89</sup> is correct, and given the suppression of corticotropin and the overall dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis during critical illness,<sup>100,101</sup> it can be surmised that the minimum plasma concentration of vitamin C required in critical illness to support endogenous norepinephrine synthesis should be at least as great as the maximum intraadrenal concentration needed for this function in healthy controls. Analogous reasoning with hypophyseal vein concentrations can be extended for endogenous vasopressin synthesis in the setting of sepsis-related endocrine dysfunction. This level might be slightly higher given the higher pituitary concentrations of vitamin C.<sup>102</sup>

In the Fowler study, patients administered “low-dose” vitamin C at 50 mg/kg/24 h achieved an average steady-state plasma concentration of 331  $\mu\text{mol/L}$ ,<sup>25</sup> above what would be expected to support endogenous norepinephrine synthesis. However, there was a further reduction in SOFA scores among patients given a higher dose of vitamin C at 200 mg/kg/24 h. Patients in this latter group achieved an average steady-state plasma concentration of 3082  $\mu\text{mol/L}$ . This may suggest additional, non-hemodynamic benefits at higher, supra-physiologic doses, possibly through the antioxidant, anti-inflammatory, and microvascular actions of vitamin C, and these may be responsible for the aforementioned pulmonary benefits. Furthermore, serum levels of C-reactive protein,<sup>25</sup> procalcitonin,<sup>25</sup> poly(ADP-ribose) polymerase,<sup>23</sup> and malondialdehyde<sup>22</sup> were decreased in the intervention groups across multiple studies. Several of these markers of cellular damage have been found to correlate with organ failure beyond the cardiovascular and pulmonary systems, suggesting an overall bodily cytoprotective effect in the context of systemic inflammation.<sup>103,104</sup>

High-dose intravenous vitamin C is generally regarded as safe even in gram doses.<sup>105</sup> No significant side effects were reported across any of these five studies. Nevertheless, caution should be exercised in patients with renal impairment.<sup>106</sup> Although rare, oxalate nephropathy has been documented in burn patients using the same 66 mg/kg/h dose used in the Tanaka and Kahn studies.<sup>107</sup> Patients with glucose 6-phosphate dehydrogenase deficiency and paroxysmal nocturnal hemoglobinuria should be excluded from treatment due to the risk of intravascular hemolysis.<sup>13</sup> Although not studied in the critically ill population, potential pro-oxidant effects are

largely of academic interest only and do not appear to be of concern in noncancerous cells.<sup>108</sup> Interestingly, one recent study in the outpatient setting suggests that intravenous vitamin C administered at gram doses may cause an acute decrease in MAP of around 7 mm Hg.<sup>109</sup> Although this effect was limited to patients with prehypertension at baseline, vitamin C does indeed have acute vasodilatory properties;<sup>110</sup> whether this may precipitate a paradoxical collapse in hemodynamic function in the setting of critical illness is unknown.

A major strength of this meta-analysis is that we investigated only the administration of isolated vitamin C on clinical outcomes in the critically ill, as opposed to vitamin C in combination with other agents as part of an antioxidant cocktail, the effects of which cannot be attributed properly to any particular agent. Also, a varied mix of medical, surgical, and burn patients were included, and each study contributed relatively equally in weight.

This meta-analysis has several weaknesses that should be kept in mind. First, only five studies were included due to the paucity of research on isolated vitamin C administration. Study sizes were small, with the largest study consisting of only 37 subjects, the doses used between studies was disparate, and the risk of bias was generally judged to be uncertain or high. Sample sizes for secondary outcomes were even sparser. Heterogeneity among the studies and the patient populations therein was not insignificant. In particular, mortality data had to be taken from the longest available time point in each study due to the non-uniform duration of follow-up across studies. In addition, through the inclusion of patients across many diverse settings, the gain in statistical power resulting therefrom must be weighed against the weakening association between the fixed intervention and the growing list of conditions, all under the umbrella of “critical illness,” on which the agent acts in thematic relation to. Whereas the mechanisms by which vitamin C exerts its actions have been studied mostly on animal models of sepsis and septic shock, such pathways may not pertain in likewise fashion to the hypovolemic shock of burn patients; the inclusion of the latter population and the application of meta-analytic techniques thereto may result in a conclusion that dilutes or otherwise obfuscates the effects of vitamin C when applied only to sepsis. One study utilized a dose of vitamin C far below the others, and this was not adjusted for patient weight;<sup>23</sup> however, the exclusion of this study did not affect the primary outcome of mortality. Finally, focusing on the isolated administration of vitamin C ignores any summative or synergistic benefits to be had when used in combination with other agents. Without even knowing the specific nature of vitamin C, it does seem a priori implausible that a single substance would have a substantial effect upon a parameter as global as mortality given the complex biochemical and pathophysiological milieu of critical illness. Many essential vitamin and mineral deficiencies can occur in this setting, including iron, selenium,<sup>111</sup> magnesium,<sup>112</sup> thiamine,<sup>113</sup> and vitamin D,<sup>114</sup> and repletion of several of these may be required before substantial clinical improvements are seen.

In view of these deficiencies in the primary literature, this meta-analysis should be considered as an orienting endeavor to guide future studies. Indeed, further trials are in various stages of completion in this area, exploring the role of vitamin C within the context of acute lung injury,<sup>95</sup> severe sepsis,<sup>115,116</sup> and septic shock.<sup>117,118</sup> In addition, spurred by the promising results of the Marik study, trials are underway to explore the effects of vitamin C combined with thiamine and hydrocortisone.<sup>119–123</sup> Taken together, these studies should elucidate both the role of isolated vitamin C and its synergistic effects.

## Conclusion

Vitamin C deficiency is common in the context of critical illness and is associated with negative outcomes. Based on the current available evidence, the intravenous administration of vitamin C produces vasopressor sparing effects, possibly through the support of endogenous vasopressor synthesis, and reduces dependency on mechanical ventilation, possibly through the amelioration of lung injury, without affecting overall mortality. However, these conclusions should be tempered by the inherent limitations of the primary literature, particularly with respect to study heterogeneity, and forthcoming trials should further clarify the role of vitamin C in the management of the critically ill.

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