

Vitamin C

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Vitamin C (ascorbic acid) is a water-soluble vitamin that has been considered for potential beneficial effects in patients with varying degrees of illness severity. It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity, serves as a cofactor in endogenous catecholamine generation, and has been studied in many disease states, including COVID-19.^{1,2}

Recommendation for Nonhospitalized Patients With COVID-19

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19 in nonhospitalized patients.

Rationale

Because patients who are not critically ill with COVID-19 are less likely to experience oxidative stress or severe inflammation, the role of vitamin C in this setting is unknown.

Clinical Data for Nonhospitalized Patients With COVID-19

In an open-label trial conducted at 2 sites in the United States, outpatients with laboratory-confirmed SARS-CoV-2 infection were randomized to receive either 10 days of oral ascorbic acid 8,000 mg, zinc gluconate 50 mg, both agents, or standard of care.³ The primary endpoint was the number of days required to reach a 50% reduction in the patient's symptom severity score. The study was stopped early by an operational and safety monitoring board due to futility after 214 of the planned 520 participants were enrolled.

Patients who received standard of care achieved a 50% reduction in their symptom severity scores at a mean of 6.7 days (SD 4.4 days) compared with 5.5 days (SD 3.7 days) in the ascorbic acid arm, 5.9 days (SD 4.9 days) in the zinc gluconate arm, and 5.5 days (SD 3.4 days) in the arm that received both agents (overall $P = 0.45$).³ No serious adverse events related to the treatments were reported. Nonserious adverse events were experienced by 39.5% of patients in the ascorbic acid arm, 18.5% in the zinc gluconate arm, and 32.1% in the arm that received both agents, compared with 0% of patients in the standard of care arm (overall $P < 0.001$). The most common nonserious adverse effects in this study were gastrointestinal events.

The limitations of this study include the small sample size and the lack of a placebo control. In outpatients with COVID-19, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the 2 supplements, when compared with standard care, did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score.

Recommendation for Hospitalized Patients With COVID-19

- The Panel **recommends against** the use of vitamin C for the treatment of COVID-19 in hospitalized patients (**AIIa**).

Rationale

Randomized clinical trials have failed to demonstrate benefit from vitamin C as a therapeutic

intervention for hospitalized patients with COVID-19. The data from these trials are summarized below.

Clinical Data for Hospitalized Patients With COVID-19

Two harmonized, randomized trials (LOVIT-COVID and REMAP-CAP) evaluated intravenous (IV) vitamin C versus a control in hospitalized patients with COVID-19 between July 2020 and July 2022.⁴ The studies enrolled patients from Asia, Australia, Europe, and North America, and data from the 2 studies were analyzed together. Patients in intensive care units who were critically ill and receiving organ support (1,568 patients from 90 sites) and hospitalized patients who were not critically ill (1,022 patients from 40 sites) were randomized to a vitamin C arm or a control arm. Patients in the intervention arm received IV vitamin C every 6 hours for 96 hours, for a maximum of 16 doses. Patients in the control arm received either no vitamin C or placebo. The composite primary outcome was a measure for days free of organ support up to 21 days and survival to hospital discharge. The study terminated enrollment after meeting criteria for harm and futility.

Among patients who were critically ill, the vitamin C arm ($n = 1,037$) had a median of 7 days free of organ support versus 10 days in the control arm ($n = 531$), with posterior probabilities of 8.6% for vitamin C efficacy and 99.9% for futility.⁴ Among patients who were not critically ill, both the vitamin C arm ($n = 456$) and the control arm ($n = 566$) had a median of 22 days free of organ support, with posterior probabilities of 2.9% for vitamin C efficacy and >99.9% for futility.

This study was limited by its use of combined data from 2 trials. The majority of patients enrolled were from an open-label study that used response-adaptive randomization.⁴ In addition, the precision of the treatment effect estimate in critically ill patients was limited because enrollment was stopped for harm. Data on individual vaccination status and the vitamin C product administered were unavailable. The study authors concluded that, in hospitalized patients with COVID-19, the probability that the use of vitamin C would increase the number of days free of organ support was low.

In a small, prospective, open-label randomized trial of hospitalized patients with severe COVID-19 in Pakistan, patients were randomized to receive vitamin C 50 mg/kg IV daily plus standard therapy ($n = 75$) or standard therapy alone ($n = 75$).⁵ Standard therapy included antipyretics, dexamethasone, and prophylactic antibiotics. Vitamin C recipients became symptom-free earlier (7.1 days vs. 9.6 days; $P < 0.0001$) and had a shorter duration of hospitalization (8.1 days vs. 10.7 days; $P < 0.0001$) than patients who received standard therapy alone. There were no significant differences between the arms for the outcomes of mortality and the need for mechanical ventilation. Limitations of this study include a small sample size, enrollment from only 1 hospital, and no clear method for recording symptoms.

In a pilot trial in China, 56 adults with COVID-19 who were in the intensive care unit were randomized to receive vitamin C 24 g IV daily for 7 days or placebo. The study was terminated early due to a reduction of cases of COVID-19 in China.⁶ Overall, the study found no differences between the arms for the outcomes of mortality, duration of mechanical ventilation, or change in median sequential organ failure assessment (SOFA) scores. The study reported improvements in oxygenation (as measured by the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen) from baseline to Day 7 in the treatment arm that were statistically greater than those observed in the placebo arm (+20.0 vs. -51.9; $P = 0.04$).

In a randomized trial of 66 hospitalized patients with COVID-19 who required supplemental oxygen, treatment with vitamin C at doses escalating from 0.3 to 0.9 g/kg IV over 6 days ($n = 44$) was compared to standard of care ($n = 22$).⁷ The vitamin C did not improve the primary outcome of clinical status (defined as a composite of a 50% reduction in oxygen use, a 50% reduction in bronchodilator use, or

hospital discharge) at 72 hours after randomization.

Other Consideration

High concentrations of circulating vitamin C may affect the accuracy of point-of-care glucometers.^{8,9}

References

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