Vitamin C

Since the most recent revision of this section, the results from several cohort studies, clinical trials, and meta-analyses on the use of vitamin C in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts before peer review. However, most of these studies had significant limitations, such as a small sample size or a lack of randomization or blinding. In addition, the study designs had different doses or formulations of vitamin C and different outcome measures, and the study populations included patients with varying concomitant medications and COVID-19 disease severity. The studies summarized in this section have had the greatest impact on the COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide further guidance on the role of vitamin C in the prevention and treatment of COVID-19.

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.

Recommendation for Nonhospitalized Patients With COVID-19

• There is insufficient evidence for 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. 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 40% of the planned 520 participants were enrolled (n = 214).

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) for the ascorbic acid arm, 5.9 days (SD 4.9 days) for the zinc gluconate arm, and 5.5 days (SD 3.4 days) for the arm that received both agents (overall P = 0.45). No serious adverse events were related to the treatments, although nonserious adverse events (primarily gastrointestinal) occurred more frequently in patients who received supplements than in those who did not. Zero percent of patients in the standard of care arm, 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 experienced nonserious adverse effects (overall P < 0.001).

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

- There is insufficient evidence for the Panel to recommend either for or against the use of vitamin C for the treatment of COVID-19 in hospitalized patients.

Rationale

No controlled trials have definitively demonstrated a clinical benefit of vitamin C in critically ill patients with COVID-19, and the available observational data are inconclusive. Studies of vitamin C regimens in patients with acute respiratory distress syndrome (ARDS) or sepsis not related to COVID-19 have reported variable efficacy and few safety concerns.

Clinical Data for Hospitalized Patients

Intravenous Vitamin C in Hospitalized Patients With COVID-19

In a small, prospective, open-label randomized trial of hospitalized patients with severe COVID-19 in Pakistan, patients were randomized to receive intravenous (IV) vitamin C 50 mg/kg per day plus standard therapy (n = 75) or standard therapy alone (n = 75).\textsuperscript{4} 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 (ICU) were randomized to receive vitamin C 24 g IV per day for 7 days or placebo. The study was terminated early due to a reduction of cases of COVID-19 in China.\textsuperscript{5} 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 [\(\text{PaO}_2/\text{FiO}_2\)]) 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 IV vitamin C at doses escalating from 0.3 g/kg to 0.9 g/kg over 6 days (n = 44) was compared to standard of care (n = 22).\textsuperscript{6} IV 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.

Intravenous Vitamin C in Hospitalized Patients Without COVID-19

In critically ill patients with conditions similar to COVID-19, such as sepsis and ARDS, vitamin C has been studied alone and in combination with thiamine and corticosteroids. In a randomized trial of 862 patients with sepsis who were in the ICU and required vasopressors, treatment with vitamin C 200 mg/kg IV per day for 4 days was compared to treatment with placebo.\textsuperscript{7} The vitamin C arm had more deaths (35.4% vs. 31.6%) and more cases of persistent organ dysfunction (9.1% vs. 6.9%) at 28 days. The results demonstrated a significant difference between the arms for the composite primary outcome of death or persistent organ dysfunction (44.5% vs. 38.5%; \(P = 0.01\)). For the subgroup of patients with
sepsis and COVID-19 (n = 63), there was no statistical difference between the arms for the composite primary outcome.

In a randomized trial among patients with sepsis-induced ARDS who were receiving mechanical ventilation (n = 167), patients who received vitamin C 200 mg/kg IV per day for 4 days or placebo had similar SOFA scores and levels of inflammatory markers. However, 28-day mortality was lower in the vitamin C arm than in the placebo arm (29.8% vs. 46.3%; 95% CI, 2% to 31.1%; P = 0.03). The vitamin C arm also had more days alive, ICU-free days, and hospital-free days than the placebo arm.

Several randomized trials found no consistent clinical benefit in patients who received vitamin C and thiamine, with or without hydrocortisone, for the treatment of sepsis or septic shock. Two trials observed reductions in organ dysfunction (as measured by a change in SOFA score on Day 3) or the duration of shock with no effect on clinical outcomes. Three other trials, including a large trial of 501 patients with sepsis, found no differences between the treatment and placebo arms for any physiologic or outcome measures. A meta-analysis found that in patients with sepsis not related to COVID-19, vitamin C therapy did not reduce mortality but may have improved organ dysfunction over 72 to 96 hours. However, this effect may have been mediated by thiamine and hydrocortisone rather than vitamin C. These studies on vitamin C in patients without COVID-19 have conflicting results. Therefore, there is insufficient evidence to determine whether the use of vitamin C will benefit or harm patients with COVID-19.

See ClinicalTrials.gov for a list of clinical trials evaluating the use of vitamin C in patients with COVID-19.

Other Considerations

High circulating concentrations of vitamin C may affect the accuracy of point-of-care glucometers.

References


