Zinc

Last Updated: December 20, 2023

Increased intracellular zinc concentrations efficiently impair the replication of a number of RNA viruses.[1] Zinc has been shown to enhance cytotoxicity and induce apoptosis when used in vitro with a zinc ionophore (e.g., chloroquine). Chloroquine has also been shown to enhance intracellular zinc uptake in vitro.[2] Zinc levels are difficult to measure accurately, as zinc is distributed as a component of various proteins and nucleic acids.[3]

The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg daily for nonpregnant women.[4] Long-term zinc supplementation can cause copper deficiency with subsequent reversible hematologic defects (i.e., anemia, leukopenia) and potentially irreversible neurologic manifestations (i.e., myelopathy, paresthesia, ataxia, spasticity).[5-7] The use of zinc supplementation for durations as short as 10 months has been associated with copper deficiency.[3] In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations (e.g., fluoroquinolones, HIV integrase inhibitors, tetracyclines).[4]

Recommendations

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of zinc for the treatment of COVID-19.
- The Panel **recommends against** using zinc supplementation above the recommended dietary allowance (i.e., zinc 11 mg daily for men, zinc 8 mg daily for nonpregnant women) for the prevention of COVID-19, except in a clinical trial **(BIII)**.

Rationale

The results from some cohort studies and clinical trials that evaluated the use of zinc in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. However, most of these studies have significant limitations, such as small sample sizes or a lack of randomization or blinding. In addition, these studies used varying doses and formulations of zinc, enrolled participants with a range of COVID-19 severities, included different concomitant medications, and measured different study outcomes. All of these factors make it difficult to compare results across studies. Because zinc has not been shown to have a clinical benefit and may be harmful, the Panel **recommends against** using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial **(BIII)**.

The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Clinical Data

In a double-blind, multicenter trial in Tunisia, nonhospitalized and hospitalized adults with COVID-19 were randomized within 7 days of symptom onset to receive elemental zinc 25 mg orally twice daily (n = 231) or matching placebo (n = 239) for 15 days.[8] Approximately 20% of these patients had received a COVID-19 vaccine prior to enrollment. During the study, none of the patients received antiviral drugs, and <40% received corticosteroids.

The primary outcome in the study was a composite of death due to COVID-19 or intensive care unit

admission within 30 days of randomization.[8] This study has several limitations. The study enrolled nonhospitalized and hospitalized patients, and comparing the results for these populations is difficult. In addition, only some patients received standard of care treatments. The data presented in the published paper had numerous and substantial inconsistencies.[9,10] Together, these limitations make it difficult to interpret the results of this study or apply these findings to the current U.S. population 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 zinc gluconate 50 mg, ascorbic acid 8,000 mg, both agents, or standard of care.[11] 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. Compared with standard of care, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the 2 supplements did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score. 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 $P = 0.45$).

Nonserious adverse effects occurred more frequently in patients who received supplements than in those who did not.[11] Nonserious adverse effects 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.

In a randomized clinical trial conducted at 3 academic medical centers in Egypt, 191 patients with laboratory-confirmed SARS-CoV-2 infection were randomized to receive either zinc 220 mg twice daily plus hydroxychloroquine or hydroxychloroquine alone for a 5-day course.[12] The primary endpoints were recovery within 28 days, the need for mechanical ventilation, and death. The 2 arms were matched for age and gender. There were no significant differences between the arms in the percentages of patients who recovered within 28 days (79.2% in the zinc plus hydroxychloroquine arm vs. 77.9% in the hydroxychloroquine alone arm; $P = 0.969$), the number of patients who required mechanical ventilation (4 in the zinc plus hydroxychloroquine arm vs. 6 in the hydroxychloroquine alone arm; $P = 0.537$), or overall mortality (2 patients in each arm; $P = 0.986$). The only risk factors for mortality were age and the need for mechanical ventilation.

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