Zinc treatment of outpatient COVID-19: A retrospective review of 28 consecutive patients

Previous research has shown that zinc can interfere with proteolytic processing of polyproteins in RNA viruses, and the RNA polymerase of SARS-CoV-1. Coronaviruses frequently cause the common cold. A recent meta-analysis of seven randomized controlled trials showed that zinc lozenges shortened the mean duration of the common cold by 33% (95% confidence interval: 21%–45%). Hospitalized COVID-19 patients taking supplemental zinc in addition to standard therapy were reported to have lower death rates, and patients with lower zinc levels on admission had higher mortality. We recently reported that four outpatient COVID-19 patients taking high dose oral zinc appear to recover shortly after initiation of zinc.

We retrospectively reviewed consecutive cases of laboratory confirmed COVID-19 (26 cases), or CDC case definition (two cases), who were started on zinc gluconate/citrate lozenges (23 mg of elemental zinc, 21 patients) or zinc acetate lozenges (15 mg of elemental zinc, seven patients), at a total dosage of 2–2.5 mg/kg/day. Patients were instructed to place one lozenge on their tongue q2–4 h while awake, for a minimum of 10 days. Depending on weight, patients took between 6 and 12 lozenges daily. Written or verbal consent was obtained before treatment. The median number of days between symptom onset and initiation of zinc was 4 days, ranging from 1 to 21 days after onset of symptoms. The mean age was 40: 17 female, 11 male, 3 Hispanic, 3 Asian, 1 African-American, and 21 Caucasian. Patients were contacted daily for symptom evaluation, and for side effects.

Ten symptoms were scored according to a COVID-19 symptom checklist, categorized on a 3-point scale: 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe. Fever and shortness of breath were further defined as follows: Fever 0 = ≤98.6, 1 = ≥98.6–100.0, 2 = ≥100.0–102.0, 3 = ≥102.0. Shortness of breath (SOB) 1 = moderate intensity exercise, 2 = with walking on flat surface, 3 = with any movement or at rest.

Cough, nausea/vomiting, diarrhea, sore throat, headache, muscle/body aches, fatigue and loss of smell/taste were also assessed.

All 28 patients were improved after 7 days of zinc. Symptomatic improvement began a mean of 1.6 days after zinc treatment. Patients 40 or older took an average of 2.1 days to improve versus 1.4 days for those under 40 (p < .05, t test). The mean COVID score at 7 days was not different for more than 40 aged patients, versus less than 40. The time to improvement did not correlate with the number of days since the onset of symptoms. Nine patients were symptomatic with fever, cough and SOB, before zinc. The mean COVID-19 symptom score pretreatment was 8.6, versus 1.6 posttreatment, p ≤ .001, Wilcoxon signed-rank test. No patients were hospitalized after zinc treatment. A comparison of COVID-19 checklist scores before and after 7 days of zinc is seen in Table 1. Three weeks after zinc two patients were still fatigued: otherwise, all were asymptomatic.

| Case number | Age | Days to improvement | Pre zinc covid score | Post zinc covid score |
|-------------|-----|--------------------|---------------------|----------------------|
| 1           | 25  | 1                  | 6                   | 0                    |
| 2           | 24  | 1                  | 2                   | 0                    |
| 3           | 24  | 4                  | 10                  | 2                    |
| 4           | 72  | 2                  | 5                   | 1                    |
| 5           | 60  | 3                  | 15                  | 2                    |
| 6           | 58  | 3                  | 14                  | 2                    |
| 7           | 23  | 1                  | 3                   | 0                    |
| 8           | 63  | 2                  | 8                   | 1                    |
| 9           | 27  | 2                  | 7                   | 1                    |
| 10          | 42  | 1                  | 14                  | 1                    |
| 11          | 57  | 1                  | 12                  | 2                    |
| 12          | 19  | 1                  | 3                   | 0                    |
| 13          | 58  | 2                  | 4                   | 1                    |
| 14          | 56  | 2                  | 3                   | 0                    |
| 15          | 24  | 1                  | 3                   | 0                    |
| 16          | 69  | 4                  | 11                  | 3                    |
| 17          | 89  | 3                  | 4                   | 1                    |
| 18          | 33  | 2                  | 10                  | 3                    |
| 19          | 59  | 1                  | 16                  | 4                    |
| 20          | 26  | 1                  | 6                   | 0                    |
| 21          | 32  | 2                  | 13                  | 4                    |
| 22          | 21  | 1                  | 5                   | 2                    |
| 23          | 27  | 1                  | 12                  | 3                    |
| 24          | 28  | 2                  | 6                   | 2                    |
| 25          | 30  | 1                  | 6                   | 2                    |
| 26          | 23  | 1                  | 19                  | 1                    |
| 27          | 40  | 1                  | 18                  | 1                    |
| 28          | 19  | 1                  | 5                   | 0                    |
The clinical course of Case 18 is seen in Figure 1. After 2 days of zinc symptoms began to improve.

Four patients complained of nausea after taking zinc (three with acetate, one with gluconate). Zinc acetate was associated with vomiting in two patients when ingested on an empty stomach; thereafter only zinc gluconate was used, after food.

In this retrospective review, initiation of zinc lozenges was followed by symptomatic and objective improvement in 28 consecutive COVID-19 patients. Zinc gluconate or acetate were initially chosen because they have the most theoretical and experimental effectiveness in the treatment of the common cold, and zinc gluconate was found to be better tolerated than zinc acetate in our patients. The frequent and high dose regimen was chosen for three reasons. First, zinc may directly inhibit SARS-CoV-2 replication; this may require frequent dosing. Second, 2 weeks of 200 mg zinc daily has negligible toxicity. Third, trials of zinc for the common cold that failed were underdosed. Our use of zinc differs significantly from the previous retrospective report in frequency (q2–4 h vs. once daily), length of dosage (>10 vs. 5 days), and type of zinc salt (zinc gluconate/acetate vs. sulfate).

The mechanisms by which zinc may help COVID-19 patients are unknown, but include direct inhibition of viral replication, improvement of mucociliary clearance of SARS-CoV-2, reduction of secondary bacterial infection, improvement of lung and kidney tissue healing after ischemia, modulation of T and B lymphocytes, and restoration of interferon-alpha production. Zinc supplementation reduces the incidence of pneumonia, and improves outcomes in diarrhea. In addition, mild zinc deficiency is often present in those groups at highest risk from COVID-19; namely, the elderly, diabetic, obese, and hypertensive.

In mild cases of COVID-19 about 80% of patients begin improving after Day 10; 20% worsen the second week. Zinc treated patients began improvement after 1.6 days on average. Patients older than 40 began recovery slightly later than under 40; however, the clinical outcome at 7 days was the same, and this is not the typical COVID-19 course.

A recent report by the CDC showed that among symptomatic adult COVID-19 outpatients, 35% were still symptomatic 2–3 weeks after testing positive. For those with SOB, one-third experienced these symptoms weeks later. By contrast, all nine of our patients who were SOB began improving after 2 days, and none were SOB after 7 days. Except for fatigue, all 28 patients were symptom free after 3 weeks.

This study has limitations intrinsic to any retrospective review: absence of blinding and a control group. However, given the low toxicity and cost of oral zinc, it would seem prudent to begin testing of zinc in a controlled trial.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

Eric Finzi MD, PhD
Allan Harrington MD

1George Washington School of Medicine, Washington, District of Columbia, USA
2Johns Hopkins School of Medicine, Baltimore, Maryland, USA
Correspondence
Eric Finzi, MD, PhD, George Washington School of Medicine, 2120L St, Washington, DC, 20037, USA.
Email: Finzieric8@gmail.com
Funding: No funding was provided for this study.
Abbreviations: SARS-CoV-2, SARS-coronavirus-2; SARS-CoV-1, SARS-coronavirus-1; SOB, short of breath

ORCID
Eric Finzi http://orcid.org/0000-0002-4685-7785

REFERENCES
1. Lanke K1, Krenn BM, Melchers WJ, Seipelt J, Kuppeveld FJ. PDTC inhibits picornavirus polyprotein processing and RNA replication by transporting zinc ions into cells. J Gen Virol. 2007;88(Pt 4):1206-1217.
2. te Velthuis AJW, van den Worm SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2 +) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PloS Pathog. 2010;6:e1001176.
3. Hemilä H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. JRSM Open. 2017;8(5):2054270417694291. https://doi.org/10.1177/2054270417694291
4. Carlucci P, Tania T, Petrilli, et al. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients Medrxiv. https://doi.org/10.1101/2020.05.02.20080036
5. Jothimani D, Kailasam E, Danielraj S, et al. COVID-19: poor outcomes in patients with zinc deficiency. Int J Infect Dis. 2020;100:343-349. https://doi.org/10.1016/j.ijid.2020.09.014. Epub ahead of print. PMID: 32920234; PMCID: PMC7482607.
6. Finzi E. Treatment of SARS-CoV-2 with high dose oral zinc salts: a report on four patients. Int J Infect Dis. 2020;99:307-309. https://doi.org/10.1016/j.ijid.2020.06.006. Epub 2020 Jun 6. PMID: 32522597.
7. Eby GA 3rd Zinc lozenges as cure for the common cold—a review and hypothesis. Med Hypotheses. 2010;74(3):482-492. https://doi.org/10.1016/j.mehy.2009.10.017. Epub 2009 Nov 10. PMID: 19906491; PMCID: PMC7173295.
8. Wessels I, Rolles B, Rink, L. The potential impact of zinc supplementation on Covid-19 pathogenesis. Front Immunol. 2020;11:1712.
9. Prasad AS, Beck FW, Bao B, et al. Zinc supplementation decreases incidence of infections in the elderly: effect of zinc on generation of cytokines and oxidative stress. Am J Clin Nutr. 2007;85:837-844. https://doi.org/10.1093/ajcn/85.3.837
10. Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. Pediatrics. 1998;102:1-5. https://doi.org/10.1542/peds.102.1
11. Dhingra U, Kisenge R, Sudfeld CR, et al. Lower-dose zinc for childhood diarrhea—a randomized, multicenter trial. N Engl J Med. 2020;383(13):1231-1241. https://doi.org/10.1056/NEJMoa1915905. PMID: 32966722; PMCID: PMC7466932.
12. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multisite health care systems network—United States, March-June 2020. MMWR Morb Mortal Wkly Rep. 2020;69:993-998.