

LETTER TO THE EDITOR

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,¹ and the RNA polymerase of SARS-CoV-1.² 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%).³ Hospitalized COVID-19 patients taking supplemental zinc in addition to standard therapy were reported to have lower death rates,⁴ and patients with lower zinc levels on admission had higher mortality.⁵ We recently reported that four outpatient COVID-19 patients taking high dose oral zinc appear to recover shortly after initiation of zinc.⁶

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, $p \leq .001$,

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.

TABLE 1 Summary of response of clinical symptoms to zinc

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

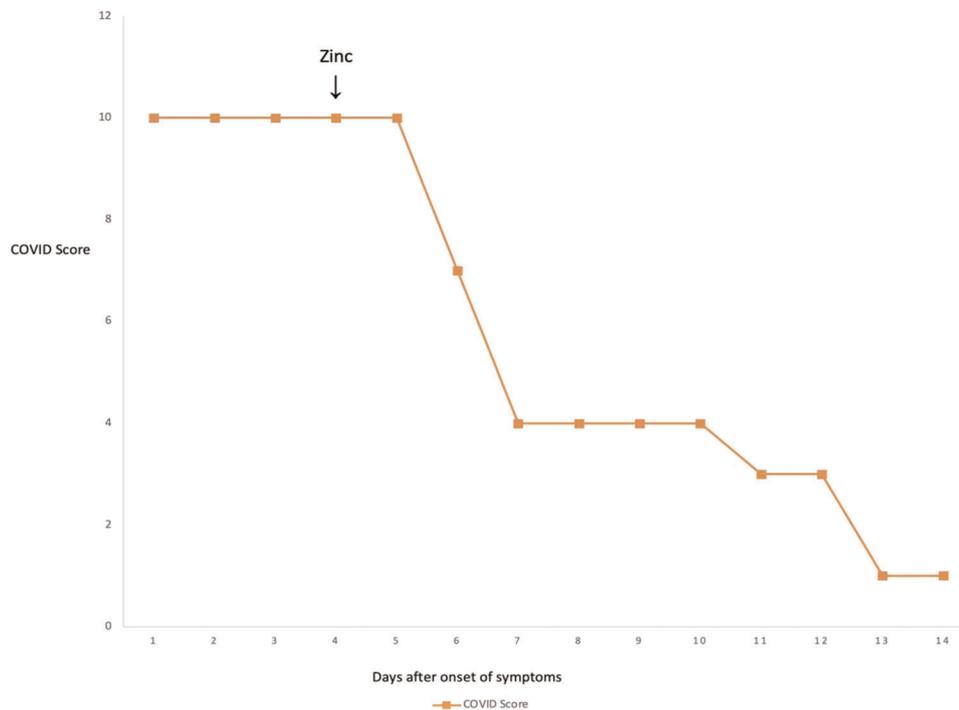


FIGURE 1 COVID symptom score of Case 18 over time. The arrow shows the start of zinc

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,⁷ 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.⁷ Our use of zinc differs significantly from the previous retrospective report⁴ 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.^{8,9} Zinc supplementation reduces the incidence of pneumonia,¹⁰ and improves outcomes in diarrhea.¹¹ In addition, mild zinc deficiency is often present in those groups at highest risk from COVID-19; namely, the elderly, diabetic, obese, and hypertensive.⁸

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 report¹² 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.

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Abbreviations: SARS-CoV-2, SARS-coronavirus-2; SARS-CoV-1,
SARS-coronavirus-1; SOB, short of breath

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