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A moral dilemma: The use of zinc in patients hospitalized with COVID pneumonia

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ABSTRACT A clinical decision report using:

Yao JS, Paguio JA, Dee EC, Tan HC, Moulick A, Milazzo C, Jurado J, Della Penna N, Celi LA. The minimal effect of zinc on the survival of hospitalized patients with COVID-19: an observational study. *Chest*. 2021 Jan;159(1):108-111.
<https://doi.org/10.1016/j.chest.2020.06.082>

for a patient hospitalized with COVID pneumonia requiring high flow oxygen.

Keywords: COVID-19, COVID pneumonia, zinc, zinc supplementation

Clinical-Social Context

Mr. Jonathan Kravitz [pseudonym] is a 51-year-old man, previously in good health, who developed B.1.1.7 variant COVID pneumonia. Many of the employees in his small business were infected with the same variant, requiring the business to shut down completely. Mr. Kravitz required hospitalization and high flow oxygen with additional non-invasive mechanical ventilation to maintain oxygen saturation, a reflection of the severity of his illness. Not being able to breathe, Mr. Kravitz was frightened. This was undoubtedly the first time he experienced a life-threatening situation, given his previous good health.

He was admitted to our service and treated with “all the good stuff.”¹ His medical management included remdesivir², dexamethasone³, vitamins C & D, and zinc. It was the continued use of zinc in the treatment of COVID pneumonia that prompted us to re-evaluate what we have learned over the past year. One year ago at the beginning of this pandemic, we told ourselves that based on animal models, it might help improve immunity for viral infections.^{4,5} Subsequently, there have been innumerable clinical trials on COVID pneumonia in humans. We wanted to know if anyone has been able to show benefits to supplemental zinc given its use in COVID positive patients.

When checking the electronic health record, the order was placed by the pharmacist—not a doctor. We presume it was an order set and is routinely given to all patients admitted with COVID. We wondered should we be giving zinc to all patients admitted with COVID? We talked to one of our infectious disease consultants, who told us “we don’t use zinc at our hospital system.” Further, he stated, “there is an administrative team of pharmacists and physicians at the corporate level who determine the current treatment regimen guidelines for COVID.” He was unable to provide any clinical research to support use of zinc in these guidelines.

EBONY MANIGAULT, MPH is a fourth year medical student at the Wayne State University School of Medicine.



Clinical Question

Does administration of oral zinc benefit patients with COVID pneumonia?

Research Article

Yao JS, Paguio JA, Dee EC, Tan HC, Moulick A, Milazzo C, Jurado J, Della Penna N, Celi LA. The minimal effect of zinc on the survival of hospitalized patients with COVID-19: an observational study. *Chest.* 2021 Jan;159(1):108-111.
<https://doi.org/10.1016/j.chest.2020.06.082>⁶

Description of Related Literature

PubMed was accessed and the search term “zinc” auto-populated the suggested search “zinc Covid”. This was filtered by RCT which resulted in three articles. One article was on herbal preparations and the two others were reviewed further.

The article by Patel et al. documented irritation at the infusion site of high dose zinc, but because the trial was ongoing between waves of COVID hospitalizations, there were inadequate numbers of patients to reach a conclusion.⁷ The article by Thomas et al. discussed the impact of high-dose zinc, high-dose ascorbic acid, or a combination of the two in the reduction of symptom severity in patients with COVID pneumonia in the outpatient setting. The trial was discontinued early because of “low conditional power for benefit”.⁸ Incidentally, ascorbic acid alone or in combination with zinc showed no benefit, making our patient’s management even more puzzling.⁸ Although the study by Thomas et al. had a strong study design (RCT), we felt it did not address the clinical question because it evaluated the efficacy of zinc in the outpatient setting, not hospitalized patients like Mr. Kravitz. Additionally, the primary outcome was patient-reported improvement of symptoms introducing the potential for bias.

The study by Thomas et al. was cited by a Systematic Review which reported eight articles that measured the outcome variable as “decreased CRP”, a disease-oriented outcome of doubtful clinical significance.⁹

Using Google Scholar, we searched for the highest quality clinical trial. This search re-located a review article addressing the need for carefully designed clinical trials to determine the potential benefits of zinc against progression of COVID-19. Related research papers in Google Scholar were scanned. Again, the same answer as a year ago—there is an animal model and theoretical “hunches” but no clinical evidence of benefit.⁵

While randomized controlled trials typically represent the best level of evidence for an intervention, due to a paucity of articles of this study design we decided to examine cohort studies on this topic. PubMed was accessed using the terms (zinc covid) AND (cohort) yielded 21 articles. Of these, five evaluated treatment of COVID patients with zinc. Two used exclusively zinc with ionophore (hydroxychloroquine) which was not used in our patient and may impact the absorption of zinc, a confounding factor that led us to not choose these papers for further review.^{10,11} Another evaluated zinc lozenges,¹² again a different mode of delivery than what was used in our patient and of dubious applicability to our clinical question. Another appeared to evaluate zinc with and without ionophore, but there was only one line in the paper addressing this topic, and there was no data provided for patients treated with zinc alone, making the paper unusable for our purposes.¹³ The remaining study investigated oral zinc sulfate, using the formulation we saw prescribed at our institution, with and without hydroxychloroquine, thus it was reviewed further.⁶

Yao et. al conducted a retrospective study that assessed survival of hospitalized COVID-19 patients treated with and without zinc sulfate. Analysis was separated based on additional therapies patients received, including hydroxychloroquine and steroids (which our patient also received). The study did not find a significant change in risk of in-hospital mortality between the two groups. This paper fit our patient population of interest and used a less subjective end point compared to the Thomas study (survival vs. patient-reported symptom reduction), thus it was selected for appraisal.

The Grade of Recommendation for the use of zinc in COVID pneumonia using the SORT criteria is B—based on few, poor quality studies indicating lack of benefit.



Critical Appraisal

The selected study meets the criteria for level 2 quality of evidence based on the SORT criteria.¹⁴ Data from 242 COVID-19 patients over a 10-day period at a single institution was collected retrospectively. Patients were stratified by clinical severity using clinical, laboratory, and radiographic data collected in the first 24 hours of admission. While there may be some information bias in relying on documentation to make this determination the use of quantitative values such as oxygen saturation helps to mitigate this.

Several baseline characteristics differed between the zinc sulfate group and control group including size (n = 196 vs n = 46) and ICU admission (29.6% vs 15.2%). Baseline characteristics such as demographic characteristics, underlying conditions, and vital signs in first 24 hours admission demonstrated similar percentages across the two groups.

Patients who did not meet the primary outcome (days from admission to mortality) at the end of the ten-day period were dropped from the study. In the zinc group, 73 (37.2%) patients met the primary outcome versus 21 (45.7%) in the control group. The brevity of this study and the use of a censorship model certainly led to a smaller population for analysis. Mr. Kravitz would have met the inclusion criteria for entry into this study but would've been dropped as he was still alive after 10 days.

The authors used multivariable logistic regression to model the tendency for patients to receive zinc therapy based on factors that might influence a physician to prescribe zinc. These included age, sex, race, heart disease, COPD and clinical severity. None of these factors significantly influenced the propensity to receive zinc thus there is low suspicion for indication bias. If the experience at our institution is any indication, what may account most for what we have seen as the biggest factor in the administration of zinc is a physician's personal belief in the therapy. Subgroup analyses were performed among patients receiving hydroxychloroquine, lopinavir/ritonavir, steroids, and IL-6 receptor inhibitors to assess for differences in mortality.

Results showed an overall average treatment effect on treated (ATET) to be 0.84 days, however this value was not statistically significant. Subgroup analyses were performed among patient receiving hydroxychloroquine, lopinavir/ritonavir, steroids, and IL-6 receptor inhibitors to assess for differences in mortality, with none of these additive therapies resulting in a statistically significant ATET. In fact, the remaining therapies showed worse mortality with zinc sulfate than the therapy alone. In subgroup analysis of the effects of zinc with the above therapies, only zinc sulfate with steroids, had a positive ATET (2.03). With what we now about the efficacy of corticosteroids in the treatment of COVID-19, this is probably more of a reflection of the steroids than the zinc.¹⁵

The greatest weakness of this study is its design. There was no randomization in treatment, but characteristics were similar amongst treatment and control groups. Administration of zinc was based on the clinician's decision, leaving room for selection bias. The study was conducted over a period of 10 days and examined a relatively small population of patients. It is possible that the study did not have enough power to detect a small treatment effect. Recruitment was based on chart review and analysis could be skewed by accuracy of documentation. All of this must be considered when applying this data to our clinical question. Nevertheless, the multivariate analyses may help mitigate some of the confounding and selecting effects.

Clinical Application

Mr. Kravitz experienced the devastation associated with being hospitalized with COVID pneumonia. He was emotionally shaken by the diagnosis and the ensuing hospitalization. He often expressed his fears related to his prognosis and was afraid of being discharged without getting the "good stuff". Our goal for him was to provide him with the most appropriate treatment using evidence-based medicine. The standard treatment at our hospital is dexamethasone and remdesivir. The addition of zinc is left to the discretion of the treating infectious disease physician. The lack of discussion surrounding COVID-19 treatment, the perceived benign nature of using zinc and the pleas from Mr. Kravitz for the "good stuff" are aspects of his admission that may give insight into the use of zinc in his treatment plan. However, the beliefs of the treating infectious disease physician seemed to be an overriding factor.

The article by Yao et al demonstrated a lack of causal association between the use of zinc and the survival of hospitalized patients with COVID-19. Although Mr. Kravitz was started on zinc while admitted, we would advise against prescribing it based on the literature that was reviewed. Regarding internal validity, the study's conclusion does make sense based on the results of the study. Before the decision to use zinc for COVID pneumonia is applied

widely, stronger evidence is necessary. A randomized controlled trial would provide stronger evidence to support this treatment modality.

New Knowledge Related to Clinical Decision Science

It has been a long year. Sanchez, et al wrote about the first week the COVID pandemic disrupted an entire hospital. “There were no clinical trials in humans, merely speculation and theories from laboratory models.” Patients were routinely prescribed a cocktail of Azithromycin, hydroxychloroquine, and zinc. After thousands of clinical trials, we now know that hydroxychloroquine has no benefit and known cardiac harms.¹⁵ But zinc? Well, the thinking back then was, “It might help and it can’t hurt.”

What is the ethical professional basis of using a therapeutic agent that has no proven benefit, but adds to the hospital bill \$400-500 per bag. Do we pretend to use clinical evidence when we make decisions? Are we still acting like lemmings just to humor somebody’s ego?

We work at an Accountable Care Organization, which means doctors are supposed to use professional judgment and use resources wisely, avoiding treatments that have no added-value so the resources can be diverted to high impact treatments. Are we wasting resources by giving zinc? Does prescribing zinc reinforce the cultural belief that healthcare resources are limitless? We wonder if they use zinc in the United Kingdom, where the Public Health Service has a budget of 50% per capita of the USA, but better health outcomes.

Our service consults two Infectious Disease Specialists. One of them routinely prescribes zinc with vitamins and the other does not. The primary care team is supposed to think independently about questions we ask consultants and there is frequently an interaction between providers to reach a consensus about treatment—a social dimension to practicing medicine. It is prudent to have these conversations as it benefits the patient as well as the providers. It became apparent to us that we were simply avoiding these conversations. Maybe we are just too tired. Yet, eventually, we have to ask ourselves what type of professionals do we want to become.

In an anonymous straw poll, eight of nine members of our medicine team thought we shouldn’t prescribe zinc in this clinical setting. The single person who opted to treat with zinc argued that this is an inexpensive medication that likely does no harm. Further, he compared it to the price tag of some of the other COVID therapies with similar therapy investigations. Despite the overwhelming response of the straw poll, zinc is still prescribed. This is an example of passive decision making, the literal antithesis of Clinical Decision Science. By avoiding the obligation to make an informed decision, we are making a decision—one that we apparently disagree with.

Outpatient self-medication chat rooms are rife with “advice” on how to decrease the longevity and symptoms of COVID and prevent hospitalizations, with supplementation. One pharmacy posted a Yahoo.com article as recently as 05/21/2021 positing the benefits of zinc as an “important treatment for Covid-19.”¹⁶ If we are prescribing “snake oil”, what reputational damage are we doing to the profession of medicine? Trust is an intangible but very real asset within the relationship between the public and the medical community. We must earn the trust of the public by maintaining scientific integrity. To maintain integrity, we need to continue to follow the Clinical Decision Science to guide our practice.

Conflict Of Interest Statement

The authors declare no conflicts of interest.

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