Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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ZINC

RECOMMENDATION

There is insufficient evidence to recommend the use of zinc as adjunct treatment for patients with COVID-19 infection both in the outpatient and in-patient setting. *(Very low quality of evidence)*

Consensus Issues

There were no issues raised during the consensus panel meeting.

EVIDENCE SUMMARY

Should patients diagnosed with COVID-19 be given zinc as an adjunct treatment?

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Key Findings

Zinc has an anti-viral effect through inhibition of SARS-Cov-1 replication as shown in in vitro studies. It has been suggested that zinc may reduce severity and duration of symptoms of other viral respiratory tract infections when used as an adjunct treatment.

One RCT was found that showed no significant difference on death, mechanical ventilation and recovery after 28 days in patients with COVID-19 when zinc was given as adjunct treatment together with HCQ, based on moderate quality of evidence. Another RCT showed no significant reduction of symptoms in outpatient COVID-19 patients when given zinc gluconate. Three retrospective cohort studies were found which when pooled, showed that adjunct zinc therapy significantly reduced the risk of mortality among COVID-19 patients, however this was from low quality of evidence. Indirect evidence was found, on the use of zinc for upper respiratory tract infections, and this reported no serious adverse effects but an increased risk for non-serious adverse effects such as nasal and throat irritation and GI discomfort.

Introduction

Zinc and zinc ionophores have previously been described to inhibit viral replication in SARS-COV-1 by affecting viral genome transcription, translation, polypeptide processing [1] and direct inhibition of RNA-dependent RNA polymerase [2]. In the 2020 systematic review and meta-analysis of 28 randomized controlled trials done by Hunter et al., there was low to very low quality of evidence on Zinc as an adjunct for the outcomes of reducing severity and duration of symptoms of other viral respiratory tract infections [3].

Review Methods

MEDLINE, Cochrane Library, and gray literature in MedRxIV, and BioRxIV were searched until December 26, 2020. Ongoing trials were searched in Clinicaltrials.gov, Chictr.org, and WHO trial Registry up to December 26, 2020. COVID-19 related studies from COVID-19 Open Living Evidence Synthesis and Living Evidence on COVID-19 were also searched. Existing practice guidelines such as the Australian living CPG, WHO Living CPG and Rapid Evidence Reviews on COVID-19 Management of the Philippine Society of Microbiology and Infectious Diseases (PSMID) were reviewed. The following keywords: MeSH terms for "Zinc" and COVID-19 related terms were used in the search strategy.

P Patients diagnosed with COVID-19

I Zinc PLUS Standard of care

C Placebo or no treatment PLUS Standard of care

O Mortality, clinical deterioration/ development of ARDS, need for mechanical ventilation, hospital length of stay, time to clinical improvement/ recovery, improvement in Chest CT Scan/ X-ray, virologic clearance by PCR test, adverse effects

M RCT, observational studies (cohort, case-control, case series/reports if few included studies)

Subgroup analysis: Severity of disease (mild, moderate, severe); Oxygen requirement (non-O2 requiring, O2 requiring, mechanically ventillated), age, comorbidity, dosage (if this is variable among studies)

Results

Efficacy

The RCT of Abd Elsalam et.al. investigated the effect of zinc as an adjunct to HCQ in RT PCR-confirmed patients with COVID-19 (N=191) from three tertiary care centers in Egypt. It showed no significant effect on death [RR 0.99 (95% CI, 0.30-3.31), p= 0.99], need for mechanical ventilation [RR 0.66 (96% CI, 0.19-2.26), p= 0.58] and recovery after 28 days [RR 0.94 (95% CI 0.55-1.62), p= 0.83]. This study had moderate quality of evidence; imprecision was due to a wide 95% confidence interval and few outcome events [6].

Another RCT [7] investigated the effect of zinc gluconate and ascorbic acid given independently and together, compared to receiving standard of care among outpatient COVID-19 patients at multiple hospitals in Ohia and Florida (N= 214). The outcome investigated was days needed to reach 50% reduction in symptom observed (via self-reported questionnaire) which found no difference between zinc gluconate and standard of care alone (mean difference of -0.80, 95% CI, -2.55-0.95, p=0.37), and showed low quality of evidence. Reasons for downgrading evidence was the moderate to high risk of bias due to absence of blinding, self-reporting of symptoms (patients were not seen physically by healthcare workers), and the inconsistent counts of the data (e.g. lost to follow-up for the zinc group was 11 but the number of those who achieved the primary outcome was 51/58). Other issues are the low dose of zinc used (elemental zinc of only 7mg), and the fact that the study did not reach the target sample size (because of its early termination for futility since there was no effect seen among any of the treatment groups).

Three retrospective cohort studies (Appendix 1: Characteristics of Included Studies) were found. Carlucci et al., investigated the effect of Zinc (50mg elemental zinc twice a day for five days) as adjunct to dual therapy using hydroxychloroquine (HCQ) (400mg loading dose followed by 200mg twice a days for five days) and azithromycin (500mg once a day), compared to the dual therapy without zinc. A total of 932 patients were confirmed to have COVID-19 via RT-PCR and admitted in a hospital in Wisconsin, USA. Outcomes compared were duration of hospital stay, duration of mechanical ventilation, oxygen support, admission and duration of stay to the ICU, death and discharge. This study highlighted the possible benefit of zinc as an adjunct among non-critically ill COVID-19 patients.

Yao et al. compared the effect of zinc (100mg OD) when combined with other COVID-19 regimens (such as lopinavir/ritonavir, IL-6 receptor inhibitors and anticoagulation) with those not receiving zinc, on in-hospital mortality among RT-PCR confirmed COVID-19 patients (N= 242) admitted at a university medical center. Despite receiving different COVID regimens, the group of Yao corrected for this using Inverse Probability weighting with multivariate Logistic Regression Model. Their findings showed a lack of causal relationship between the use of zinc and decrease in mortality.

The cohort study of Frontera (N=3473) observed the effect of Zinc sulfate (50mg once or twice a day) when combined with HCQ (400mg BID as loading then 200mg BID for four days) to in-hospital death among hospitalized RT-PCR confirmed COVID-19 patients in the USA. This study demonstrated that zinc administration with an ionophore leads to a significant reduction in mortality rates.

The overall risk of bias of the three included studies was low to moderate [9]. In contrast to the result of the RCT, the three observational studies showed that adding zinc to COVID-19 management significantly reduced the risk for mortality (pooled RR 0.68 (95% CI 0.58-0.80, I2=13%, p<0.01, N= 4647: Figure 1); however, it was based on very low quality of evidence). In the study of Carlucci et al., there was a significant decrease in mortality or transition to hospice care (OR 0.56, 95% CI 0.38- 0.81, p=0.002 among the participants; however, a subgroup analysis showed that for the subgroup of critically-ill patients, those given zinc did not differ significantly in mortality or transition to hospice from those not given zinc (adjusted OR 0.96 p=0.93) while the significant association was maintained in the subgroup of non-critically ill patients (OR 0.49, p =0.004)

Safety

There was no direct evidence on adverse effects of zinc when used for treating patients with COVID-19. Indirect evidence, from the meta-analysis done by Hunter et al. [3], showed that the use of zinc in other viral respiratory tract infections had no noted serious adverse effects - either with prophylactic (three RCTs, 45mg zinc oral capsule) or therapeutic (16 RCTS 300mg sublingual zinc lozenges) doses (moderate quality of evidence). However, there was increased risk for non-serious adverse effects such as nasal and throat irritation and GI discomfort when zinc was compared against placebo (RR 1.56 (95% CI, 0.73-3.34) from three RCTs, low evidence) or against active controls (RR 1.14 (95% CI, 0.86-1.50 from two RCTs, low evidence).

Recommendations from other groups

The US-NIH COVID-19 Treatment Guidelines Panel neither recommends for or against the use of zinc for treatment of COVID-19 [10]. They recommend however against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (Last updated February 2021). There are no recommendations from CDC, WHO, and the Infectious Diseases Society of America in using zinc as an adjunct treatment for COVID-19.

Ongoing Studies

There are eight ongoing trials on the use of zinc as adjunct treatment for COVID-19 (Appendix 4).

References

[1] Pal A, Squitti R, Picozza M, Pawar A, Rongioletti M, Dutta AK, et al. Zinc and COVID-19: Basis of Current Clinical Trials [Internet]. Biological Trace Element Research. Humana Press Inc.; 2020 [cited 2021 Jan 18]. p. 1–11. Available from: https://doi.org/10.1007/s12011-020-02437-9

[2] Frontera JA, Rahimian JO, Yaghi S, Liu M, Lewis A, de Havenon A, et al. Treatment with Zinc is Associated with Reduced In-Hospital Mortality Among COVID-19 Patients: A Multi-Center Cohort Study. Res Sq [Internet]. 2020 Oct 26 [cited 2020 Dec 28]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/33140042

[3] Hunter J, Arentz S, Goldenberg J, Yang G, Beardsley J, Myers SP, et al. Benefits and risks of zinc for adults during covid-19: rapid systematic review and meta-analysis of randomised controlled trials. medRxiv [Internet]. 2020 Jan 1;2020.11.02.20220038. Available from: http://medrxiv.org/content/early/2020/11/04/2020.11.02.20220038.abstract

[4] Arentz S, Hunter J, Yang G, Goldenberg J, Beardsley J, Myers SP, et al. Zinc for the prevention and treatment of SARS-CoV-2 and other acute viral respiratory infections: a rapid review. Adv Integr Med [Internet]. 2020 Dec 1 [cited 2020 Dec 26];7(4):252–60. Available from: https://pubmed.ncbi.nlm.nih.gov/32837895/

[5] Eubanas G. Should zinc supplements be used in the prevention of COVID-19? - [Internet]. 2020 [cited 2021 Jan 3]. Available from: https://www.psmid.org/should-zinc-supplements-be-used-in-the-prevention-of-covid-19/

[6] Abd-Elsalam S, Soliman S, Esmail ES, Khalaf M, Mostafa EF, Medhat MA, et al. Do Zinc Supplements Enhance the Clinical Efficacy of Hydroxychloroquine?: a Randomized, Multicenter Trial. Biol Trace Elem Res [Internet]. 2020 Nov 27 [cited 2020 Dec 26];1–5. Available from: https://pubmed.ncbi.nlm.nih.gov/33247380/

[7] Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, et al. Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection. JAMA Netw Open [Internet]. 2021 Feb 12 [cited

2021 Feb 13];4(2):e210369. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776305

[8] Yao JS, Paguio JA, Dee EC, Tan HC, Moulick A, Milazzo C, et al. The Minimal Effect of Zinc on the Survival of Hospitalized Patients With COVID-19: An Observational Study. Chest [Internet]. 2020 [cited 2020 Dec 26]; Available from: https://pubmed.ncbi.nlm.nih.gov/32710890/

[9]Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. medRxiv [Internet]. 2020 Jan 1 [cited 2020 Dec 26];2020.05.02.20080036. Available from: https://doi.org/10.1101/2020.05.02.20080036

[10] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed January 29,2021.

Appendix 1: Characteristics of Included Studies

Study author	Population	Intervention	Control	Outcome
Abd-Elsalam	Confirmed RT-PCR positive in three egyptian tertiary care centers from June 23 to August 23,2020 Divided into mild, moderate, severe and critical based on WHO classification	Zinc sulfate 220mg (elemental zinc 50mg) BID HCQ (400mg BID D1, then 200mg BID x 4 days) Standard of care	HCQ (400mg BID D1, then 200mg BID x 5 days) Standard of care	Recovery within 28 days Death Need for mechanical ventilation
Thomas	N=214 Patients > 18 years old who were newly diagnosed by RT-PCR in an outpatient setting From April 27 to October 14, 2020	Zinc gluconate (50mg OD at bedtime) x 10 days n=58 (20 did not complete follow-up: 11 lost, 9 discontinued intervention) *58 zinc + ascorbic acid x 10 days (11 did not complete: 3 lost, 8 discontinued)	Standard of care only (n=50) *ascorbic acid (8000mg over 2-3x/day) N=48 (14 did not complete, 7 lost, 7 discontinued)	Days required to reach 50% reduction in symptoms

Study author	Population	Intervention	Control	Outcome
Frontera	Hospitalized COVID-19 confirmed patients aged >/18yrs old by RT-PCR admitted from Mar 10 -May 20	Zinc sulfate (50mg elemental Zn) PO OD or BID HCQ 400mg BID x 1 day then 200mg BID x 4 days	Did not receive Zn + ionophore	In-hospital death
Carlucci	Hospitalized COVID-19 confirmed patients via RT-PCR from March 2- April 11, 2020	Hydroxychloroquine (400mg loading followed by 200mg BID x 5 days Azithromycin (500mg OD) with Zinc sulfate (50mg elemental zinc) BID x 5 days	Hydroxychloroquine (400mg loading followed by 200mg BID x 5 days azithromycin (500mg OD)	Duration of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, average FiO2, maximum FiO2, admission to the intensive care unit (ICU), duration of ICU stay, death/ hospice, need for intubation, and discharge destination
Yao	Patients with COVID-19 confirmed via RT-PCR admitted at the Hoboken University Meical center April 11,2020	100mg elemental Zinc OD (no mention when therapy was started nor for how long it was given)	No zinc given (patients received different COVID-19 meds)	In hospital mortality

Appendix 2: GRADE Evidence Profile

Question: Zinc as adjunct to standard card compared to standard care alone for patients with COVID-19
Setting: COVID-19 confirmed patients in inpatient and outpatient setting

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	zinc as adjunct to standard card	standard care alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	5/96 (5.2%)	5/95 (5.3%)	**RR 0.9896** (0.2961 to 3.3077)	**1 fewer per 1,000** (from 37 fewer to 121 more)	⨁⨁◯◯ LOW	CRITICAL
Mortality												
3	observational studies	not serious	not serious [c]	not serious	not serious	none	248/1613 (15.4%)	16.3%	**RR 0.68** (0.58 to 0.80)	**52 fewer per 1,000** (from 68 fewer to 33 fewer)	⨁⨁◯◯ LOW	CRITICAL
need for mechanical ventilation												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	4/96 (4.2%)	6/95 (6.3%)	**RR 0.66** (0.19 to 2.26)	**21 fewer per 1,000** (from 51 fewer to 80 more)	⨁⨁◯◯ LOW	IMPORTANT
need for mechanical ventilation												
1	observational studies	not serious	not serious	not serious	very serious [b]	none	91 cases 841 controls		**OR 0.804** (0.487 to 1.330)	-	⨁◯◯◯ VERY LOW	IMPORTANT
							-	11.9%		**21 fewer per 1,000** (from 57 fewer to 33 more)		
symptom reduction (assessed with: mean days (SD))												
1	randomised trials	very serious [d]	not serious	not serious	not serious	none	58	50	-	MD **0.8 lower** (2.55 lower to 0.95 higher)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. no blinding
b. few events, confidence interval too wide
c. different results among the three studies
d. no concealment, symptom scale is self-reported

Appendix 3: Forest Plot

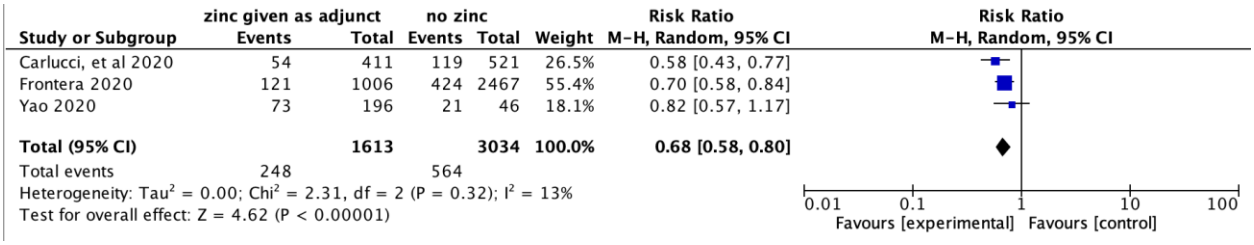

Figure 1. Forest plot showing the effect of zinc as an adjunct to mortality of patients with COVID-19. Used values are data presented from each observational study

Appendix 4: Characteristics of Ongoing Studies

	Clinical Trial ID / Title	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04641195 Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India	18 Years and older (Adult, Older Adult)	Dietary Supplement: Vitamin D3 (cholecalciferol) •Dietary Supplement: Zinc (zinc gluconate) •Dietary Supplement: Zinc (zinc gluconate) & Vitamin D (cholecalciferol) •Other: Placebo	(1) Vitamin D (180,000 IU bolus at enrollment, followed by 2000 IU daily); (2) Zinc (placebo at enrollment followed by one daily dose of 40 mg); (3) Vitamin D and Zinc; or (4) Placebo	•Time to recovery •All-cause mortality •Necessity for assisted ventilation •Individual symptoms duration •Vitamin D •Zinc •Interleukin 6 (IL-6) •Angiopoietin-2 •sTREM-1 •Immunoglobulin M (IgM) •Immunoglobulin (IgG)
2	NCT04621461 Placebo Controlled Trial to Evaluate Zinc for the Treatment of COVID-19 in the Outpatient Setting	30 Years and older (Adult, Older Adult)	•Dietary Supplement: Zinc Sulfate 220 MG •Drug: Placebo	placebo	•Number of participants hospitalized and/ or requiring repeat emergency room visits •Number of participants admitted to the Intensive care unit (ICU) •Number of participants on a ventilator •All-cause mortality •Time to resolution of COVID-19 symptoms •Severity of symptoms

	Clinical Trial ID / Title	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
3	NCT04472585 Efficacy of Subcutaneous Ivermectin With or Without Zinc and Nigella Sativa in COVID-19 Patients	18 Years and older (Adult, Older Adult)	Drug: Nigella Sativa / Black Cumin •Drug: Ivermectin Injectable Solution •Other: Placebo •Drug: Zinc	placebo	qRT-PCR Severity of symptoms
4	NCT04447534 Zinc With Chloroquine/ Hydroxychloroquine in Treatment of COVID-19	18 Years and older (Adult, Older Adult)	•Drug: Chloroquine •Drug: zinc	Chloroquine alone	Number of patients with improvement or mortality
5	CTRI/2020/07/026340 Prospective study to assess therapeutic role of Zinc in COVID-19 patients	18 years to 80 years old diagnosed with COVID-19	Zinc (100mg OD) plus standard of care	Standard of care	Reduction of symptoms, length of hospital admission, ICU admission, ventilator requirement, complications, rate of discharge
6	ACTRN12620000454976 Randomised controlled trial for high-dose intravenous zinc as adjunctive therapy in SARS-CoV-2	Symptomatic hospitalized COVID-19 adults	IV zinc chloride (0.5mg/kg/day) diluted in 250 mL normal saline x 7 days	placebo	lowest oxygen saturation (or greatest level of supplemental oxygenation) for non-ventilated patients and worst PaO2/FiO2 for ventilated patients, ICU and in-hospital mortality, length of stay in ICU or hospital, duration of supplemental oxygen, severe adverse drug events

	Clinical Trial ID / Title	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
	(COVID-19) positive critically ill patients				
7	NCT04621149 / A Phase 2 Screening Study of Candidate Non-prescription Treatments for COVID-19: A Patient-driven, Randomized, Factorial Study Evaluating Patient-reported Outcomes (PROFACT-01)	COVID-19 patients from ages 20 to 70 with mild symptoms treated on an outpatient basis	(1) chlorine dioxide aqueous solution (2) placebo with zinc acetate (3) chlorine dioxide aqueous solution with zinc acetate (4) placebo with famotidine, lactoferrin and green tea extract (5) chlorine dioxide aqueous solution with famotidine, lactoferrin and green tea extract (6) zinc acetate with famotidine, lactoferrin and green tea extract (7) chlorine dioxide aqueous solution with zinc acetate and famotidine, lactoferrin and green tea extract	Placebo drug	Primary Outcome Measure: Time to clinical improvement Secondary Outcome Measures: (1) Adverse event incidence (2) admission to hospital
8	**IRCT20180425039414N2 / The effect of zinc on the treatment and clinical course of patients with SARS-cov2 (COVID-19)**	18 years of age or older Diagnosis of COVID-19 by RT PCR and CT scan of the lungs Blood oxygen levels are between 90 and 93 percent Breathing rate between 20 and 24 per minute Heart rate between 100 and 130 beats per minute	two 200 mg hydroxychloroquine sulfate tablets every 12 hours on the first day and then 200 mg every 12 hours. In addition to the above, zinc tablets with a dose of 220 mg twice a day orally during the patient's hospitalization will be prescribed.	two 200 mg hydroxychloroquine sulfate tablets every 12 hours on the first day and then 200 mg every 12 hours.	(1) Clinical response (2) Mortality (3) Hospital stay