Original Article

A Pilot Study to Assess the Impact of Zinc Hyper-supplementation on Hospital Stay of COVID-19 Patients — Results of a Prospective Controlled Study

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Introduction: Zinc has been hypothesized to have antiviral benefits and a proposed preventive and therapeutic modality for COVID-19. There are no trials reporting the impact of Zinc supplementation on outcomes of hospitalized COVID-19 patients in India.

Aims : To evaluate the therapeutic benefit of Zinc hyper-supplementation on hospital stay and mortality of hospitalized COVID-19 patients.

Methods : A prospective controlled pilot study was performed in a tertiary care hospital on COVID-19 positive patients. On admission, patients were allocated in two groups- Control group receiving standard of care treatment only and intervention group receiving standard of care + tablet Zinc sulphate 100 mg daily. Primary outcomes studied included duration of stay and mortality between the two groups. All patients were followed up till discharge or death.

Results : One hundred and five patients completed the study, out of which 47 were in Zinc (intervention) group and 58 were in Non-zinc (control) group. Both groups were comparable in terms of age distribution, gender, Body Mass Index (BMI) and prevalence of diabetes and hypertension. 27.6% of cases from control group required Intensive care (ICU) admission which was comparable with 31.9% among intervention group (p=0.629). The NEWS-2 severity score was similar in both groups. Mean duration of stay was 8.9 ± 5.1 days in control group which was comparable with 8.6 ± 5.6 days in intervention group (p=0.771). Mortality rate was 3.4% in control group and 2.1% in intervention group and the difference was not significant (p=0.686).

Conclusion : Though Zinc has been hypothesized to demonstrate therapeutic effect on COVID-19 infections, our pilot study shows no impact of hyper-supplementation of Zinc on duration of stay or mortality. However, larger multi-centric studies are required to understand the role of Zinc in reduction of hospital stay and overall SARS-Cov-2 outcomes in hospitalized patients.

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Key words **: Zinc, COVID-19, Hospital stay, Mortality, Prospective study.**

As the world continues to be gripped by the Corona virus disease (COVID-19) pandemic, treatment of the disease is still under evolution. The pathogenesis of COVID-19 is not fully understood, but is probably multifactorial, including a systemic exaggerated inflammatory response and associated thromboembolic complications in some cases[1,2]. Effective vaccination and antivirals are important to dampen the disease burden of the current pandemic. At the same time, it is essential to identify suitable therapeutic agents or supplements to reduce associated morbidity and mortality.

Editor's Comment :

- The benefits of Zinc in reducing hospital stay or mortality in COVID-19 patients is questionable.
- Larger trials are desirable to study the impact of Zinc supplementation in these patients.

One of the hypothesized micronutrient with antiviral effect is Zinc. Zinc is an essential trace element which plays an important role in growth and the maintenance of immune function[3,4]. Zinc deficiency has been associated with an increased risk of certain infections, including viral infections. Studies have shown that the normal Zinc status of an individual is protective of viral infections and Zinc-deficient individuals are at increased risk of acquiring HIV or Hepatitis C[4]. Few Randomized Trials (RCTs) have evaluated the effect of zinc supplementation on the immunological response. Acevedo-Murillo *et al*[5] in their study with 103 children (1 month to 5 years of age) with Pneumonia showed a statistically significant clinical improvement (duration of illness, respiratory rate and oxygen saturation) in the Zinc supplemented group compared to placebo.

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They also demonstrated an increase in the cytokine response in Th1 pattern (IL-2 and INF-gamma) only in the Zinc group with Th2 cytokines (IL-4 and IL-10) being elevated or remaining high in both groups. Another randomized trial on oral supplementation of high-dose zinc (150 mg/day) after stem cell transplantation demonstrated an enhanced thymic function and the output of new CD4 T cells[6]. Currently, to the best of our knowledge, there are no prospective trials reporting impact of Zinc supplementation on outcomes of hospitalized COVID-19 patients in India.

In this study, we wish to evaluate our hypothesis that zinc hyper-supplementation in hospitalized COVID-19 patients is likely to reduce hospital stay and mortality.

Materials and Methods

A prospective interventional pilot study was performed in a tertiary care hospital. After obtaining Institutional Ethic Committee (IEC) approval, trial was registered with national trial registry. Informed consent was obtained from all patients/relatives to participate in the trial.

Protocol of Trial :

After admission, patients were allocated into either of the two groups as below.

Intervention — Tablet Zinc sulphate 100 mg (Two tablets of Zinconia 50 mg- Zuventus health care)

Duration : 1.5 months (28th July to 17th September, 2020)

Regimen and Dosing :

Group 1 (control group) : Standard of care (Standard of care medications only).

Group 2 (intervention group) : Active Comparator (Zinc sulphate- 100 mg to be taken daily from admission for 1 month) and standard of care treatment.

Study Design : This was a single-centre, prospective study of 105 hospitalised COVID-19 patients, prior to a formal study with proposed sample size of 174 patients in each arm (range from 143-218 depending on assumptions about change in group mean for primary endpoints). We assumed, 80% power ie, beta - 0.02 and α of 0.05; with Standard Deviation (SD)/variance between the group for Mortality rate ie, all-cause mortality (outcome measure) was about 5%; and for the duration of hospital stay was 5 days.

The subjects were assigned either to

(a) Standard treatment only (control group) or

(b) Zinc combined with standard treatment (intervention group).

Method of allocation : All patients on admission were allotted an "in-patient" hospital identification (IP ID) number. Patients with odd numbered IP ID were assigned "group 1" (standard of care) and even numbered IP ID "group 2" (intervention). Due to COVID-19 related limitations of movement in indoor areas and emergency admission of patients in critical condition, alternate allocation based on odd and even IP ID was considered a feasible method.

Eligibility Criteria:

Inclusion criteria :

Subjects were included if they met criteria as outlined below:

- Patients aged 18 years or more
- Patients with diagnosis of COVID-19 on RT-PCR test

Exclusion criteria:

Subjects meeting any of the following criteria were excluded from the study:

- Pregnant or lactating women
- Patients with dementia, learning disability, mental health needs
- Deemed unfit for the study according to the investigator

Follow up: Till discharge from hospital or death

Outcome Measures:

Primary Outcome Measures:

- Duration of hospital stay
- Mortality rate

Secondary Outcome Measures:

- Incidence of ICU admission
- Incidence of pneumonia and respiratory failure
- Incidence of Bilevel positive airway pressure (BIPAP) and mechanical ventilator requirement
- Severity on admission as per National Early Warning Score (NEWS) 2 score
- Blood parameters (CRP)

Statistical analysis: Data was prospectively entered in excel document. Statistician was blinded about the two groups and participants. Categorical data were expressed as percentage (%). Continuous data were presented as mean and Standard Deviation (SD). Statistical analysis was performed using SPSS version 24.0 (IBM Corp NY). Continuous data was analyzed using independent 't' test or Mann-Whitney test depending on normality of distribution. Categorical data was analyzed using Pearson's Chi square test or Fischer's Exact test. A 'p value' of less than 0.05 was considered statistically significant (95% confidence interval). Patients with protocol violation were excluded from analysis.

Results

Out of one hundred and twenty five patients enrolled in the study, 105 (84%) patients were included in analysis. 47 patients were in Zinc (intervention) group and 58 were in Non-Zinc (control) group. Both groups were comparable in terms of age distribution, gender, Body Mass Index (BMI) and prevalence of diabetes and hypertension (Table 1).

Admission Parameters : On admission, 27.6% of cases from control group required Intensive Care Unit (ICU) admission which was comparable with 31.9% among intervention group (p=0.629). 79.3% of the cases had fever in control group which was comparable with 74.5% in intervention group and difference was not significant. 58.6% of the cases had cough in control group which was comparable with 63.8% in intervention group. 36.2% of the cases had shortness of breath in control group which was comparable with 42.6% in intervention group. The NEWS-2 severity score was similar in both groups, 3.5 ± 3.1 in control and 3.4 ± 2.9 in intervention group (p=0.922). 81% of the cases had O2 saturation > 95% in control group which was comparable with 78.7% in intervention group. 92.6% of the cases had elevated CRP (> 5) in control group which was comparable with 87.0% in intervention group (Table 2).

ICU patients : Overall, 7(6.7%) patients required ventilator support, 6 (5.7%) required BIPAP support. COVID-19 associated pneumonia was seen in 31 (29.5%) patients and ARDS in 26 (24.8%) patients. No difference was seen in the ventilator requirement, BIPAP support, COVID-19 pneumonia or ARDS in both groups (p=0.992) (Table 3).

Outcomes: 3.4% of the cases died in control while 2.1% in intervention group and difference was not significant (p=0.686). Mean duration of stay was 8 days (Range 4-28 days) in control group which was comparable with 6 days (Range 3-28 days) in intervention group (p=0.966) by Mann Whitney test (Table 4).

Further trial on statistically significant sample was discontinued as no significant alteration in primary end points was noticed on interim analysis in this pilot study. Continuation of study was considered futile by the investigators as approved by the Institutional Ethics Committee.

Discussion

Presently, there is no definitive curative therapy for COVID-19. Therefore, the current treatment protocols involve a multimodal approach with antivirals, steroids and anticoagulation therapy[7]. Supplementation with Zinc is increasingly recommended in the management of COVID-19 patients[8] even though no prospective trial has been undertaken or published on the role of zinc in reducing COVID-19 related morbidity or mortality in hospitalized patients. To our knowledge, this is the first pilot trial comparing outcomes after therapeutic Zinc Hyper supplementation for COVID-19 in hospitalized patients.

In our study, majority of patients were above 50 years of age, belonged to male gender (72.4%) and

Table 1 — *Demography and co-morbidity distribution of patients in Control and Intervention groups*

Parameters	Control	Intervention	P value
No of cases	58	47	
Age (Years) :			
Mean ± SD	56.03 ± 14.52	54.81 ± 12.84	0.649
Range	18 – 90 years	26 – 84 years	
BMI :	N = 34	N = 27	
Mean ± SD	25.83 ± 4.44	24.33 ± 2.97	0.121
Range	19.53-42.37kg/m^2	16.88-28.65 kg/m^2	
Gender n (%) :			
Male	43 (74.1)	33 (70.2)	0.655
Female	15 (25.9)	14 (29.8)	
Diabetes n (%)	21 (36.2)	16 (34)	0.817
Hypertension n (%)	28 (48.3)	22 (46.8)	0.881

Table 2 — *Parameters on admission in control and intervention groups*

Parameters	Control	Intervention	P value
No of cases	58	47	
ICU admission n (%)	16 (27.6%)	15 (31.9%)	0.629
Fever n (%)	46 (79.3%)	35 (74.5%)	0.557
Cough n (%)	34 (58.6%)	30 (63.8%)	0.586
Shortness of breath n (%)	21 (36.2%)	20 (42.6%)	0.507
NEWS-2 score (Mean ± SD)	3.5 ± 3.1	3.4 ± 2.9	0.922
O2 saturation >95%n (%)	47 (81%)	37 (78.7%)	0.123
90 – 95%	4 (6.9%)	8 (17%)	
< 90%	7 (12.1%)	2 (4.3%)	
Elevated CRP (>5 mg%)n (%)	50 (92.6%)	40 (87%)	0.349

Table 3 — *Complications and ventilator support requirement in control and intervention groups*

	Control N (%)	Intervention N (%)
Ventilator	4 (6.9%)	3 (6.4%)
BIPAP	4 (6.9%)	2 (4.2%)
Pneumonia	16 (27.6)	15 (31.9%)
ARDS	14 (24.1)	12 (25.5%)

Table 4 — *Mortality and duration of stay between control and intervention groups*

Parameters	Control	Intervention	P value
No. of cases	58	47	
Mortality	2 (3.4%)	1 (2.1%)	0.686
Duration of stay:			
Median+Interquartile range	8 + 4.75	6 + 4.5	0.966

had a mean BMI of 25 kg/m^2. Hypertension was reported in 47.6% while type 2 diabetes was present in 35.2% patients. A meta-analysis by Sanyaolu *et al*[9] on a total of 1786 patients showed 1044 (58.5%) were males with a mean age of 41 years. The most common comorbidities identified in these patients were Hypertension (15.8%), cardiovascular disorders (11.7%) and Diabetes (9.4%).

Fever was the most common reported symptom in 77.1% patients, followed by cough (61%) and shortness of breath (39%). In a Meta-analysis by Yang *et al*[10], the most prevalent clinical was fever (91.3%, 95% CI: 86-97%), followed by cough (67.7%, 95% CI: 59-76%), fatigue (51.0%, 95% CI: 34-68%) and dyspnea (30.4%, 95% CI: 21-40%). In current study, ICU admission was required in 29.5%, while in a meta-analysis by Abate *et al*[11] in 25,000 patients it was 32%. A study by Lagier *et al*[12] showed 91.5% patients had a NEWS-2 score of 0-4 and elevated CRP was significantly associated with poor outcomes. In current study, mean NEWS-2 score was 3.5 and an elevated C-reactive protein (CRP > 5 m/dl) was seen in 90% patients.

In the meta-analysis by Abate[11], the prevalence of mortality among COVID-19 patients admitted in ICU was 31% (95% CI: 26 to 36). In current study, subgroup analysis showed mortality in ICU patients was 9.7%. In a study by Lagier[12], the duration of stay ranged from 7.3 to 9.2 days while overall mortality was 0.9%. Mean duration of stay in our study was 8.7 days, similar in both groups while overall mortality was seen in 2.9% patients in our study.

Ours is the only prospective study comparing outcomes of supplemental Zinc in COVID-19 hospitalized patients. A similar study by Jothimani *et al*[7] compared outcomes in patients with Zinc deficiency and normal Serum Zinc Levels. In our study, there was no difference in duration of stay and mortality across the two groups. Similar incidence of ICU admission, COVID-19 pneumonia and ARDS was seen in both groups. In their study[7], COVID-19 patients (n=47) showed significantly lower Zinc levels when compared to healthy controls (n=45). Further, amongst the COVID-19 patients, 27 (57.4%) were found to be Zinc deficient. These patients were found to have higher rates of overall complications (p=0.009), acute Respiratory Distress Syndrome (18.5% *versus* 0%, p = 0.06), corticosteroid requirement (p = 0.02), prolonged hospital stay (p = 0.05), and increased mortality (18.5% *versus* 0%, p = 0.06). The Odds Ratio (OR) of developing complications was 5.54 for zinc deficient COVID-19 patients. A retrospective analysis by Yao *et al*[13] showed Zinc Sulfate was not significantly associated with a change in risk of in-hospital mortality (adjusted hazard ratio, 0.66; 95% CI, 0.41 to 1.07; P ¼ .09). A trial by Thomas *et al*[14] in ambulatory (non-hospitalized) patients showed patients who received standard care (without Zinc or Ascorbic Acid supplementation) achieved a 50% reduction in symptoms at a mean (SD) of 6.7 (4.4) days compared with 5.5 (3.7) days for the Ascorbic Acid group, 5.9 (4.9) days for the zinc Gluconate Group, and 5.5 (3.4) days for the group receiving both (overall P=0.45). There was no significant difference in outcomes among the treatment groups. A non-randomized trial by Elalfy[15] showed that the combined use of Nitazoxanide, Ribavirin and Ivermectin plus Zinc Supplement effectively cleared the SARS COV2 from the Nasopharynx in a shorter time than symptomatic therapy.

Limitations : Limitations of our study include lack of prior serum Zinc levels, single center with limited sample size as this is a pilot study with short duration of follow up. Also, it was not possible to match the patients on other treatments received due to variability of disease severity.

Conclusion :

Though Zinc has been hypothesized to demonstrate beneficial effect on COVID-19 infections, our pilot study shows no difference of hyper-supplementation of Zinc on duration of stay or mortality. However, larger multi-centric trials are required to understand the role of Zinc in reduction of hospital stay and overall SARS-Cov-2 outcomes in hospitalized patients.

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Conflict of Interest : None

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