Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients

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40-word summary: Zinc sulfate added to hydroxychloroquine and azithromycin may improve outcomes among hospitalized patients.

ABSTRACT

Background: COVID-19 has rapidly emerged as a pandemic infection that has caused significant mortality and economic losses. Potential therapies and means of prophylaxis against COVID-19 are urgently needed to combat this novel infection. As a result of *in vitro* evidence suggesting zinc sulfate may be efficacious against COVID-19, our hospitals began using zinc sulfate as add-on therapy to hydroxychloroquine and azithromycin. We performed a retrospective observational study to compare hospital outcomes among patients who received hydroxychloroquine and azithromycin plus zinc versus hydroxychloroquine and azithromycin alone.

Methods: Data was collected from electronic medical records for all patients being treated with admission dates ranging from March 2, 2020 through April 5, 2020. Initial clinical characteristics on presentation, medications given during the hospitalization, and hospital outcomes were recorded. Patients in the study were excluded if they were treated with other investigational medications.

Results: The addition of zinc sulfate did not impact the length of hospitalization, duration of ventilation, or ICU duration. In univariate analyses, zinc sulfate increased the frequency of patients being discharged home, and decreased the need for ventilation, admission to the ICU, and mortality or transfer to hospice for patients who were never admitted to the ICU. After adjusting for the time at which zinc sulfate was added to our protocol, an increased frequency of being discharged home (OR 1.53, 95% CI 1.12-2.09) reduction in mortality or transfer to hospice remained significant (OR 0.449, 95% CI 0.271-0.744).

Conclusion: This study provides the first *in vivo* evidence that zinc sulfate in combination with hydroxychloroquine may play a role in therapeutic management for COVID-19.

INTRODUCTION

The World Health Organization has declared a pandemic due to spread of the coronavirus disease of 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)[1, 2]. SARS-CoV2 is a single-strand RNA coronavirus, which enters human cells mainly by binding the angiotensin converting enzyme 2 (ACE2)[3]. SARS-CoV2 is primarily transmitted after viral particles are inhaled and enter the respiratory tract and has the potential to cause a severe systemic inflammatory response, acute respiratory disease syndrome (ARDS), multi organ failure, and shock[2, 4]. Laboratory abnormalities found in patients with COVID-19 include lymphopenia, elevation in lactate dehydrogenase, C reactive protein, D-dimer, ferritin and interleukin-6 (IL-6)[5, 6].

Several medications are under investigation for the treatment of COVID-19. Despite limited and conflicting data, the U.S. Food and Drug Administration authorized the emergency use of hydroxychloroquine for the treatment of COVID-19 with or without azithromycin. Chloroquine analogues are weak bases that concentrate within acidic endosomes and lysosomes. Once intracellular, chloroquine analogues become protonated and increase pH resulting in prevention of endosomal trafficking, dysfunctional cellular enzymes, and impaired protein synthesis[7]. This inhibits viral replication through interference with endosome-mediated viral entry or late transport of the enveloped virus. Further, this results in interference with the terminal glycosylation of ACE2 receptor expression which prevents SARS-CoV-2 receptor binding and spread

of infection [8]. Hydroxychloroquine, a hydroxy-derivative of chloroquine, has also been proposed based on *in vitro* activity against SARS-CoV-2 with a three-fold higher cytotoxic potential compared to chloroquine [9]. However, clinical data in humans has yielded mixed results[10-12]. The anti-viral and anti-inflammatory effects of chloroquine have been suggested to account for its potential utility in preventing COVID-19-related pneumonia. Soon current studies will answer whether hydroxychloroquine is effective as monotherapy or in combination with azithromycin. In the case that hydroxychloroquine is found to be ineffective, it may still have a role to play when combined with zinc sulfate. Zinc inhibits RNA dependent RNA polymerase, and has been shown to do this *in vitro* against SARS-CoV[13]. However, it is difficult to generate substantial intracellular concentrations of zinc, therefore prophylactic administration of zinc alone may not play a role against SarCoV-2[14]. When combined with a zinc ionophore, such as chloroquine (hydroxychloroquine), cellular uptake is increased making it more likely to achieve suitably elevated intracellular concentrations[15]. This combination is already being tested as a prophylactic regimen in a randomized clinical trial.

As New York became the epicenter of the pandemic, hospitals in the area quickly adopted investigational therapies, including the use of hydroxychloroquine and azithromycin. Given this proposed synergistic effect of zinc with hydroxychloroquine, practices at NYULH changed and the addition of zinc sulfate 220 mg PO BID along with hydroxcychloroquine 400 mg once followed by 200 mg PO BID with azithromycin 500 mg once daily became part of the treatment approach for patients admitted to the hospital with COVID-19. This study sought to investigate outcomes among patients who

received hydroxychloroquine and azithromycin alone compared to those who received triple therapy with zinc sulfate.

METHODS

We performed a retrospective analysis of data from patients hospitalized with confirmed SARS-CoV-2 infection at NYU Langone Health. Data was collected from electronic medical records (Epic Systems, Verona, WI) for all patients being treated with admission dates ranging from March 2, 2020 through April 5, 2020. Patients were admitted to any of four acute care NYU Langone Health hospitals across New York City. COVID-19 positivity was determined by real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) of nasopharyngeal or oropharyngeal swabs. Prior to March 16, tests were completed by the New York City Department of Health and Mental Hygiene. After that date, NYU Langone clinical laboratory conducted tests using the Roche SARS-CoV2 assay in the Cobas 6800 instruments. On March 31, testing was also conducted using the SARS-CoV2 Xpert Xpress assay in the Cepheid GeneXpert instruments. After March 16, only pharyngeal samples were tested.

Patients were included in the study if they were admitted to the hospital, had at least one positive test for COVID-19, received hydroxychloroquine and azithromycin, and had either been discharged from the hospital, transitioned to hospice, or expired. Patients were excluded from the study if they were never admitted to the hospital or if there was an order for other investigational therapies for COVID-19, including tocilizumab, nitazoxanide, rituximab, anakinra, remdesivir, or lopinavir/ritonavir during the course of

their hospitalization to avoid potential confounding effects of these medications. We collected demographics as reported by the patient and any past medical history of hypertension, hyperlipidemia, coronary artery disease, heart failure, chronic obstructive pulmonary disease, asthma, malignancy other than non-melanoma skin malignancy, and diabetes. We also recorded vital signs on admission, the first set of laboratory results as continuous variables, and relevant medications as categorical variables, including NSAIDs, anticoagulants, antihypertensive medications and corticosteroids ordered at any point during the course of the hospitalization.

Statistics

Patients were categorized based on their exposure to hydroxychloroquine (400 mg load followed by 200 mg twice daily for five days) and azithromycin (500 mg once daily) alone or with zinc sulfate (220 mg capsule containing 50 mg elemental zinc twice daily for five days) as treatment in addition to standard supportive care. Descriptive statistics are presented as mean and standard deviation or mean and interquartile range for continuous variables and frequencies for categorical variables. Normality of distribution for continuous variables was assessed by measures of skewness and kurtosis, deeming the dataset appropriate for parametric or nonparametric analysis. A 2-tailed Student's t test was used for parametric analysis, and a Mann Whitney U test was used for nonparametric data analysis. Pearson's chi-squared test was used to compare categorical characteristics between the two groups of patients. Linear regression for continuous variables or logistic regression for categorical variables was performed with the presence of zinc as the predictor variable and outcome measures (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), as dependent variables. Data was log transformed where appropriate to render the distribution normal for linear regression analysis. Multivariate logistic regression was used to adjust for the timing that our protocol changed to include zinc therapy using admission before or after March 25th as a categorical variable. P-values less than 0.05 were considered to be significant. All analyses were performed using STATA/SE 16.0 software (STATA Corp.).

Study approval

The study was approved by the NYU Grossman School of Medicine Institutional Review Board. A waiver of informed consent and a waiver of the Health Information Portability Privacy act were granted. The protocol was conducted in accordance to Declaration of Helsinki.

RESULTS

Patients taking zinc sulfate in addition to hydroxychloroquine and azithromycin (n=411) and patients taking hydroxychloroquine and azithromycin alone (n=521) did not differ in age, race, sex, tobacco use or past medical history (Table 1). On hospital admission, vital signs differed by respiratory rate and baseline systolic blood pressure. The first laboratory measurements of inflammatory markers including white blood cell count, absolute neutrophil count, ferritin, D-dimer, creatine phosphokinase, creatinine, and C-

reactive protein did not differ between groups. Patients treated with zinc sulfate had higher baseline absolute lymphocyte counts [median (IQR), zinc: 1 (0.7-1.3) vs. no zinc: 0.9 (0.6-1.3), p-value: 0.0180] while patients who did not receive zinc had higher baseline troponin [0.01 (0.01-0.02) vs. 0.015 (0.01-0.02), p-value: 0.0111] and procalcitonin [0.12 (0.05-0.25) vs 0.12 (0.06-0.43), p-value: 0.0493) (Table 1).

In univariate analysis, the addition of zinc sulfate to hydroxychloroquine and azithromycin was not associated with a decrease in length of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, average fraction of inspired oxygen, or maximum fraction of inspired oxygen during hospitalization (Table 2). In bivariate logistic regression analysis, the addition of zinc sulfate was associated with decreased mortality or transition to hospice (OR 0.511, 95% CI 0.359-0.726), need for ICU (OR 0.545, 95% CI 0.362-0.821) and need for invasive ventilation (OR 0.562, 95% CI 0.354-0.891) (Table 3). However, after excluding all non-critically ill patients admitted to the intensive care unit, zinc sulfate no longer was found to be associated with a decrease in mortality (Table 3). Thus, this association was driven by patients who did not receive ICU care (OR 0.492, 95% CI 0.303-0.799). We also found that the addition of zinc sulfate was associated with likelihood of discharge to home in univariate analysis (OR 1.56, 95% CI 1.16-2.10) (Table 3). We performed a logistic regression model to account for the time-period when the addition of zinc sulfate to hydroxychloroquine plus azithromycin became utilized at NYULH. After adjusting for this date (March 25th), we still found an association for likelihood of discharge to home (OR 1.53, 95% CI 1.12-2.09) and decreased mortality or transition to hospice however

the other associations were no longer significant (Table 4). The decrease in mortality or transition to hospice was most striking when considering only patients who were not admitted to the ICU (OR: 0.449, p-value: 0.002) (Table 4).

DISCUSSION

While practicing at the epicenter of the pandemic in the United States, we were faced with unprecedented challenges of adopting investigational therapies quickly into clinical practice. Initially, antiviral options at our institution consisted of clinician preference for either ritonavir/lopinavir or hydroxychloroquine plus azithromycin. After the findings of ritonavir/lopinavir in NEJM, we noticed an increase in the use of hydroxychloroquine plus azithromycin[16]. Our providers within the infectious diseases division, clinical pharmacy, and hospitalists discussed the use of zinc sulfate as an addition to hydroxychloroquine, based on the potential synergistic mechanism, and low risk of harm associated with this therapy.

To our knowledge, we provide the first *in vivo* evidence on the efficacy of zinc in COVID-19 patients. After adjusting for the timing of zinc sulfate treatment, the associations between zinc and the need for ICU and invasive ventilation were no longer significant but we did still observe a trend. This observation may be because patients with COVID-19 were initially sent to the ICU quicker, but as time went on and resources became more limited, clinicians began treating COVID-19 patients on general medicine floors for longer periods of time before escalating to the ICU. Future studies are needed to confirm or refute the hypothesis that the addition of zinc sulfate to a zinc ionophore

such as hydroxychloroquine may reduce the need for ICU care in patients with COVID-19.

The main finding of this study is that after adjusting for the timing of zinc therapy, we found that the addition of zinc sulfate to hydroxychloroquine and azithromycin was found to associate with a decrease in mortality or transition to hospice among patients who did not require ICU level of care, but this association was not significant in patients who were treated in the ICU. This result may be reflective of the proposed mechanism of action of zinc sulfate in COVID-19. Zinc has been shown to reduce SARS-CoV RNA dependent RNA polymerase activity *in vitro* [13]. As such, zinc may have a role in preventing the virus from progressing to severe disease, but once the aberrant production of systemic immune mediators is initiated, known as the cytokine storm, the addition of zinc may no longer be effective [17]. Our findings suggest a potential therapeutic synergistic mechanism of zinc sulfate with hydroxychloroquine, if used early on in presentation with COVID-19. However, our findings do not suggest a prophylactic benefit of zinc sulfate in the absence of a zinc ionophore, despite interest in this therapy for prevention. A prophylactic strategy of zinc sulfate should be evaluated to help answer this question.

This study has several limitations. First, this was an observational retrospective analysis that could be impacted by confounding variables. This is well demonstrated by the analyses adjusting for the difference in timing between the patients who did not receive zinc and those who did. In addition, we only looked at patients taking

hydroxychloroquine and azithromycin. We do not know whether the observed added benefit of zinc sulfate to hydroxychloroquine and azithromycin on mortality would have been seen in patients who took zinc sulfate alone or in combination with just one of those medications. We also do not have data on the time at which the patients included in the study initiated therapy with hydroxychloroquine, azithromycin, and zinc. Those drugs would have been started at the same time as a combination therapy, but the point in clinical disease at which patients received those medications could have differed between our two groups. Finally, the cohorts were identified based on medications ordered rather than confirmed administration, which may bias findings towards favoring equipoise between the two groups. In light of these limitations, this study should not be used to guide clinical practice. Rather, our observations support the initiation of future randomized clinical trials investigating zinc sulfate against COVID-19.

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	Zinc N=411	**No Zinc** N=521	**P-value**
Demographics			
Age	63.19 ± 15.18	61.83 ± 15.97	0.0942
Female Sex	147 (35.7%)	201 (38.6%)	0.378
Race			0.428
African American	68 (16.5%)	81 (15.5%)	
White	189 (46.0%	244 (46.8%)	
Asian	30 (7.3%)	30 (5.8%)	
Other	97 (23.6%)	142 (27.2%)	
Multiracial/Unknown	27 (6.6%)	24 (4.6%)	
History			
Tobacco use			0.142
Never or Unknown	306 (74.5%)	382 (73.3%)	
Former	76 (18.5%)	115 (22.1%)	
Current	29 (7.1%)	24 (4.6%)	
Any cardiovascular condition	182 (44.3%)	248 (47.6%)	0.313
Hypertension	154 (37.5%)	208 (39.9%)	0.445
Hyperlipidemia	99 (24.1%)	148 (28.4%)	0.138
Coronary Artery Disease	36 (8.8%)	41 (7.9%)	0.624
Heart Failure	26 (6.3%)	22 (4.2%)	0.149

Asthma or COPD	50 (12.2%)	56 (10.7%)	0.499
Diabetes	105 (25.5%)	130 (25.0%)	0.835
Malignancy	23 (5.6%)	33 (6.3%)	0.638
Transplant	3 (0.7%)	2 (0.4%)	0.473
Chronic Kidney Disease	47 (11.4%)	44 (8.4%)	0.127
BMI kg/m^2	29.17 (25.8-33.42)	29.29 (25.77-33.2)	0.8611
Admission Characteristics			
Oxygen saturation at presentation	94 (91-96)*	94 (91-96)**	0.1729
Respiratory Rate, respirations per minute	20 (19-24)	20 (18-24)	**0.0460**
Pulse, beats per minute	97.66 ± 18.61	99.40 ± 19.82	0.0858
Baseline Systolic BP, mmHg	134.83 ± 20.84	132.41 ± 21.87	**0.0435**
Baseline Diastolic BP, mmHg	76.66 ± 12.62	76.59 ± 14.22	0.4670
Temperature, degrees Celsius	37.65 ± 0.82	37.72 ± 0.94	0.1354
White blood cell count 10^3/ul	6.9 (5.1-9.0) N=400	6.9 (5.1-9.3) N=500	0.5994
Absolute neutrophil count, 10^3/ul	5.15 (3.6-7.05) N=388	5.4 (3.8-7.5) N=488	0.0838
Absolute lymphocyte count, 10^3/ul	1 (0.7-1.3) N=388	0.9 (0.6-1.3) N=482	**0.0180**
Ferritin, ng/mL	739 (379-1528) N=397	658 (336.2-1279) N=473	0.1304
D-Dimer, ng/mL	341 (214-565) N=384	334 (215-587) N=435	0.7531
Troponin, ng/mL	0.01 (0.01-0.02) N=389	0.015 (0.01-0.02) N=467	**0.0111**
Creatine Phosphokinase, U/L	140 (68-330) N=343	151.5 (69.5-398.5) N=344	0.4371
Procalcitonin, ng/mL	0.12 (0.05-0.25) N=395	0.12 (0.06-0.43) N=478	**0.0493**

Creatinine, mg/dL	0.97 (0.8-1.34) N=400	0.99 (0.8-1.27) N=499	0.4140
C-Reactive Protein, mg/L	104.95 (51.1-158.69) N=398	108.13 (53-157.11) N=480	0.9586
Medications recorded during hospitalization			
NSAID	53 (12.9%)	74 (14.2%)	0.563
Anticoagulant	402 (97.8%)	511 (98.1%)	0.772
ACE inhibitor or ARB	138 (33.6%	175 (33.7%)	0.997
Beta Blocker	91 (22.1%)	132 (25.3%)	0.256
Calcium Channel Blocker	89 (21.7%)	104 (20.0%)	0.527
Corticosteroid	40 (9.7%)	47 (9.0%)	0.711

Table 1: Comparisons of baseline characteristics and hospital medications. Data are represented as median (IQR) or mean $\pm$ SD. Sample size is reported where it differed due to lab results not tested. P-values were calculated using 2-sided t-test for parametric variables and Mann Whitney U test for nonparametric continuous variables. Pearson χ^2 test was used for categorical comparisons. $P < .05$ was deemed significant. Laboratory results represent the first measured value while hospitalized.

*measured on supplemental oxygen for 86.4%

**measured on supplemental oxygen for 83.1%

	Zinc	No Zinc	β Coefficient	P-value
Length of Hospital stay (in days)*	6 (4-9) N=411	6 (3-9) N=521	0.015	0.646
Duration of mechanical* ventilation (in days)	5 (3-8) N=33	5 (3-9) N=86	0.040	0.667
ICU Duration (in days)*	4.85 (1.97-7.94) N=38	5.54 (2.65-9.32) N=82	-0.062	0.504
O2 Flow rate max*	6 (3-15) N=353	6 (3-15) N=426	-0.015	0.679
O2 Flow rate avg*	3.05 (2.1-6.3) N=353	3.5 (2.5-7.5) N=426	-0.062	0.082
FiO2 AVG	61.52 ± 32.03 N=107	65.26 ± 34.48 N=117	-.056	0.402
FIO2 MAX	74.94 ± 35.75 N=107	71.98 ± 35.85 N=117	0.041	0.538

Table 2: Comparisons of continuous hospital outcomes. Data are represented median (IQR) and as mean ± SD. Sample size is reported for each variable tested. β Coefficients and P-values were calculated using linear regression. N was specified for each comparison. *P* < .05 was deemed significant. *variables were log transformed for regression analysis

	Zinc N=411	**No Zinc** N=521	**Odds Ratio**	**95% Confidence Interval**	**P-value**
Discharged home	317 (77.1%)	356 (68.3%)	1.56	1.16-2.10	**0.003**
Needed ICU	38 (9.2%)	82 (15.7%)	0.545	0.362-0.821	**0.004**
Needed Invasive Ventilation	33 (8.0%)	86 (16.5%)	0.562	0.354-0.891	**0.014**
Expired/Hospice	54 (13.1%)	119 (22.8%)	0.511	0.359-0.726	**<0.0001**
Expired/Hospice**	28 (73.6%) N=38	61 (74.4%) N=82	0.964	0.401-2.31	0.934
Expired/Hospice***	26 (6.9%) N=373	58 (13.2%) N=439	0.492	0.303-0.799	**0.004**

Table 3: Comparison of categorical hospital outcomes. Data are represented as N(%). P-values were calculated using logistic regression. $P < .05$ was deemed significant. N was specified for subgroup analyses.

**After excluding all non ICU patients

***After excluding all ICU patients

	Zinc N=411	No Zinc N=521	Adjusted Odds Ratio	Adjusted 95% Confidence Interval	Adjusted P-value
Discharged home	317 (77.1%)	356 (68.3%)	1.53	1.12-2.09	**0.008**
Needed ICU	38 (9.2%)	82 (15.7%)	0.733	0.471-1.14	0.168
Needed Invasive Ventilation	33 (8.0%)	86 (16.5%)	0.804	0.487-1.33	0.396
Expired/Hospice	54 (13.1%)	119 (22.8%)	0.559	0.385-0.811	**0.002**
Expired/Hospice**	28 (73.6%) N=38	61 (74.4%) N=82	1.03	0.404-2.64	0.947
Expired/Hospice***	26 (6.9%) N=373	58 (13.2%) N=439	0.449	0.271-0.744	**0.002**

Table 4: Adjusted comparison of categorical hospital outcomes. Data are represented as N(%). P-values were calculated using multivariate logistic regression adjusting for patient admission after March 25th as a categorical variable. $P < .05$ was deemed significant. N was specified for subgroup analyses.

**After excluding all non ICU patients

***After excluding all ICU patients