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ORIGINAL ARTICLE

EVALUATION OF THE THERAPEUTIC EFFECTS OF COMBINED HYDROXYCHLOROQUINE AND AZITHROMYCINE IN PATIENTS WITH COVID-19

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Summary

Introduction: Coronavirus pandemic is currently a global health concern with no established treatment guidelines. The aim of the present study was to determine the therapeutic effectiveness of hydroxychloroquine combined with azithromycin in patients with positive coronavirus disease 2019 (COVID-19) admitted to the hospital with severe dyspnea, as well as the incidence of occurrence of adverse effects.

Methods: It was intended to utilize a retrospective clinical study of approximately 250 adult patients admitted to the ALSALAM Teaching Hospital in Mosul city with mild to *moderate* COVID-19 in order to evaluate treatment efficacy in combination with clinical and biochemical findings. Two groups were involved in the research. The first patient group consisted of 250 people who got hydroxychloroquine in conjunction with azithromycin, while the second untreated control group consisted of 100 individuals who received no medication as part of the research.

Results: Baseline parameters (clinical and biochemical assays) did not vary substantially among the two groups. Patients in the treatment group were hospitalized at a rate of 30%, compared to 27% in the untreated control group ($P<0.001$). Between groups, there were no statistically significant changes in mortality, non-invasive oxygen demand, or hospitalization duration. Biochemical and Clinical outcomes were comparable between those receiving hydroxychloroquine with azithromycin and those do not receive any medication.

Conclusion: This treatment regimen was shown to be not affective in mild to severe positve COVID-19 hospitalized patients and was associated with a small number of mild to moderate clinical adverse effects.

Key words: Hydroxychloroquine; Azithromycin; Dyspnea; COVID-19

Introduction

Coronavirus disease 2019 (COVID-19) is a widespread viral infection with a significant mortality rate (1). At first, symptoms such as fever, tiredness, coughing, and myalgia manifest. Dyspnea or Acute Respiratory Distress Syndrome (ARDS) may develop as a result of the symptoms (2). While the majority of individuals who get

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COVID-19 recover, a small percentage of individuals develop ARDS and need hospitalization (3). According to the American Medical Association, 75% of involved patients have minor illnesses, 15% have moderate to severe clinical features, and 3-5% have life-threatening illnesses (4).

Large number of drugs from different classes has been proposed as a therapy for COVID-19 (5); including azithromycin and hydroxychloroquine. Beyond its antiviral and immunomodulatory characteristics, hydroxychloroquine has a well-established safety profile as a result of its application in the management of malaria and autoimmune disorders, among other indications (6, 7). In vitro study, it has been demonstrated that hydroxychloroquine suppresses SARS-CoV-2 entry and replication. Additionally, it inhibits pro-inflammatory cytokine production, which may contribute to the development of dyspnea in people infected with COVID-19 (8, 9). Hydroxychloroquine with azithromycin has been shown in non-randomized studies to reduce the viral load of SARS-CoV-2 (10). On the basis of these mechanisms and early clinical experience, the medication was used to treat COVID-19 in certain settings, although its effectiveness remains disputed (11).

Chronic diseases represent a challenging when coexisted with COVID-19. Hyperlipidemia associated with upset of inflammatory and endothelial markers (12), hypertension increase the risk of cardiometabolic abnormalities (13), and glucose dysregulation upset normal metabolic homeostasis(14). Moreover, patient with chronic diseases are polypharmacy individual (15, 16) due to using hypolipidemic, hypoglycemic, and hypotensive therapy. Collectively, these conditions and drugs are challenging the patient therapeutic response to hydroxychloroquine and azithromycine alongside suggestive potentiation of their adverse effects in particular in critically ill patients. The primary objective of this study was to determine the therapeutic efficacy of hydroxychloroquine combined with azithromycin in adult COVID-19 patients who had moderate to severe Dyspnea. A secondary objective was to document any adverse reactions to the treatment regimen used in this clinical study.

Material and methods

The study team examined electronic medical records of patients admitted to an ALSALAM Teaching Hospital in Mosul, Iraq, for mild to severe COVID-19-associated dyspnea. The study included patients with COVID-19 who were aged eighteen years old or older and had a subsequent positive reverse transcription polymerase chain reaction (RT-PCR) test from a nasopharyngeal sample. Patients who had been hospitalized in the intensive care unit (ICU) prior to the start of the research were excluded from the study, as were those who did not have a positive real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2 infection. Mild to moderate severity was defined as a quick sequential organ failure assessment (qSOFA) score of 0 or 1, while severe severity was defined as individuals requiring invasive ventilator assistance during the first 24 hours of hospital admission (17). As a result of our study findings, hydroxychloroquine was recommended as a first-line treatment in conjunction with azithromycin. For a total of five days, an oral hydroxychloroquine dosage of about 400 mg twice daily at the start and 400 mg once daily afterwards was combined with a 500 mg azithromycin dose administered once daily by oral or intravenous route. Daily QTc intervals were measured in individuals on hydroxychloroquine, and the findings were reported. Men were administered hydroxycholoquine until their QTc interval rose by 60 milliseconds or until it exceeded 510 milliseconds in women. If the QTc interval rose by more than 510 milliseconds, the hydroxycholoquine was discontinued and the QTc interval was monitored again using an ECG. We used descriptive analysis in statistical analysis to find the correlations between the variables. To analyze the ages and B|MI of the two groups, as well as the initial results of the treated and untreated normal control, the unpaired t-test was employed. A paired student t-test was conducted to compare the findings before and after medication therapy. $P<0.001$ was judged significant for statistical results. All of the measurement items were subjected to non-parametric testing in this study. The Wilcoxon Mann–Whitney test was used to compare two distinct meanings of continuum countable data. For continual counting, the Wilcoxon Mann–Whitney test was utilized.

Results

At first, 387 adult patients were screened for potential inclusion. Ninety-seven (25%) of them tested negative for COVID-19 infection by RT-PCR, and they were thus eliminated from the current research. Out of 387 patients, 250 (75%) were first admitted to the intensive care unit (ICU) and later released due to severe COVID-19-related Acute Respiratory Distress Syndrome (ARDS). The remainder of the patients were euthanized. Two hundred and fifty

of individuals took hydroxychloroquine in combination with azithromycin (the treated group), whereas 100 did not, and were therefore designated the untreated control group. Patients who did not take hydroxychloroquine in conjunction with azithromycin did so for a variety of reasons, including: 44 (47.8 %) who had contraindications to the medication and 32 (34.8 %) who refused to take the medication as a result of their religious beliefs. The participants' demographic and clinical data are included in Table 1. There were no statistically significant variations in BMI between the treated and untreated control groups ($p > 0.05$), and the median BMI in both groups was comparable. According to the findings, the most prevalent chronic illness, was hypertension affecting 53 % of the subjects under study. Diabetes mellitus, which impacted 29.5 percent (57) of the population, heart disease, which afflicted 15.0 percent (30), chronic pulmonary illness, which affected 6.7 percent (13), and cancer, which affected 5.2 percent (10) of the population, were the next most common. There have been no notable differences in the level of previous ailments across the groups.

Table 1. Demographic and Clinical characteristics of the Patients.

Demographic And Clinical Characteristic	Total (N = 350)	Treated Group (N = 250)	Untreated Control Group (N = 100)	p-Value
No. Males (%)	120 (61%)	60 (51%)	50 (51%)	**>0.001**
Age(Years)	70 (45–80)	40 (50)	56 (75)	**<0.001**
BMI, Median (IQR) – Kg/M² **[Normal range 18.5 to 24.9]**	30 (32.4–25.9)	32 (36%)	29 (38%)	**>0.001**
Current Smoker – N. (%)	15 (5%)	9 (8.5%)	6 (2.5%)	**>0.001**
Hypertension – N. (%)	95 (52%)	50 (48%)	39 (49%)	**>0.001**
Diabetes Mellitus – N. (%)	49 (30%)	24 (22%)	35 (36%)	**>0.001**
Heart Disease – N. (%)	37 (16%)	12 (13%)	17 (19%)	**>0.001**
Pulmonary Disease – N. (%)	16(8%)	9 (6%)	7 (8%)	**>0.001**
Oncologic Disease – N. (%)	12 (6%)	5 (3-6%)	5 (6%)	**>0.001**
Antihypertensive Use N. (%)	90 (42%)	45 (40-46%)	40 (38%)	**>0.001**
Previous Use Of hypolipidemic statins – N. (%)	40(20%)	16 (12%)	22 (24%)	**>0.001**
Previous Use Of antidiabetics(Metformin0 – N. (%)	35 (17%)	14 (16%)	17 (19%)	**>0.001**
qSOFA = 0	200(83%)	120(80%)	80 (86%)	**>0.001**
qSOFA = 1	40 (17.6%)	25 (22%)	15 (19%)	
qSOFA = 2	0	0	0	

Patients who had previously used medications reported using angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at a rate of 50% (750/189), statins at a rate of 40 (20%), and metformin at a rate of 17 %, with no statistically significant difference between the groups.

According to the findings, a statistically significant difference ($p = 0.03$) was discovered between the two groups. Despite the fact that all patients had an average of 12 damaged lung segments (IQR 1-20, a non-significant difference in the number of damaged lung segments were existed between the groups.

Following biochemical investigation, it was determined that both groups of patients had comparable baseline and peak values for leukocytosis and lymphocyte counts, fibrinogen and D-dimer levels, as well as hepatic enzymes and troponin levels, with no statistically significant difference between them (Table 2 and Figure 1). There were no significant variations in leukocytosis and lymphocyte counts, fibrinogen, or D-dimer levels between the two groups at baseline or during the disease's peak.

Table 2. Biochemical Assays of the treated and untreated groups.

Parameters	Treated Group (N = 250)	Untreated Control Group (N = 100)	p-Value	Reference Range
Leukocytes (µm³)				**4.500 to 11.000**
Baseline	5000	6000	>0.001	
Peak	6700	6700	>0.001	
Lymphocytes (µm³)				**1.000 to 4.800**
Baseline	1650	1240	>0.001	
Nadir	1000	900	>0.001	
Fibrinogen (mg/dl)				**200 to 400**
Baseline	500	400	>0.001	
Peak	560	353	>0.001	
D-Dimer (ng/ml)				**≤500**
Baseline	800	1120	>0.001	
Peak	1250	1500	<0.001	
LDH (U/L)				**140 to 280**
Baseline	500	350	>0.001	
Peak	450	340	<0.001	
Baseline Troponin (ng/L)	6	8	>0.001	**0 to 0.04**
Ast (U/L)				**10 to 40**
Baseline	50	55	>0.001	
Peak	60	60	>0.001	
Alt (U/L)				**7 to 55**
Baseline	35	50	>0.001	
Peak	60	40	>0.001	
hsCRP (mg/dl)				**1.0 to 3.0**
Baseline	7	13		
Peak	**15**	**17**	**<0.001**	

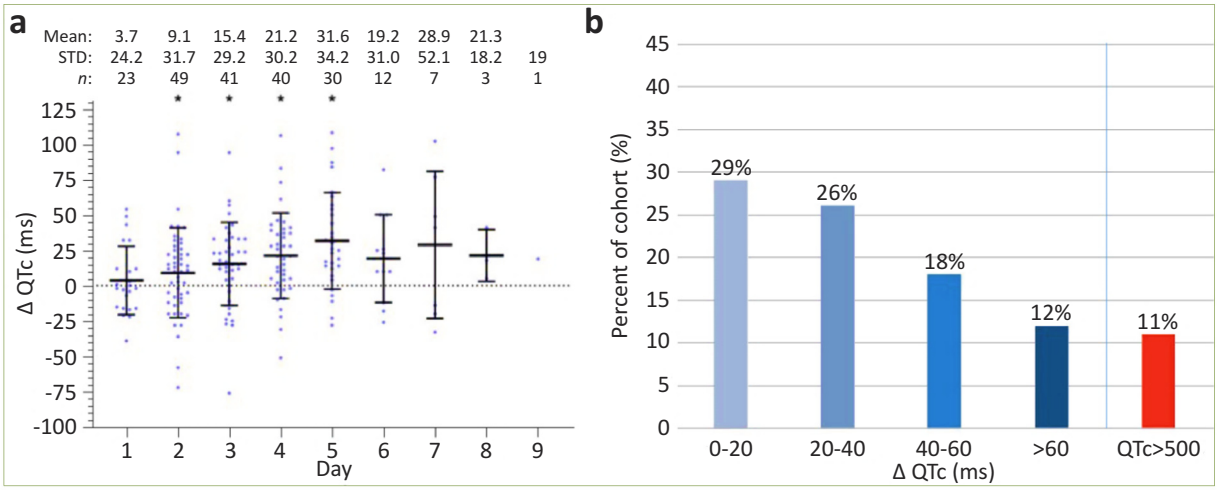

Figure 1. Changes In Qtc Interval On Combined Hydroxychloroquine And Azithromycin (P < 0.001).

When compared to the untreated control group, the treated group had lower high sensitivity C-reactive protein (hsCRP) levels at baseline and higher levels throughout the study. During the follow-up period, the treated group had higher levels of lactate dehydrogenase (LDH) than the control group that had not been treated. As expected, non-statistically significant differences in clinical end outcomes between the two groups were observed when comparing them to the baseline group in the experiment (Table 3). On the basis of the findings, invasive oxygen treatment was determined to be necessary in a total of 45 patients (23 %) who were transferred to the critical care unit: 30 patients (25 %) in the treated group and 18 patients (21%) in the untreated control group. Twenty-two patients died, accounting for 11.5 % of all deaths, with 11 deaths occurring in each of the two patient groups. The remaining patients were relieved of their responsibilities as a result of this decision. Only 9 patients (8%) of the patients who received the treatment complained of gastrointestinal problems, indicating that the therapeutic association was well tolerated by the patients. P = 0.08 indicates that 15 patients (16.0 %) were assigned to the treated group, whereas 15 patients (16.0 %) were assigned to the untreated control group. As a result of QTc prolongation, a total of 8% (8/101) of patients had their hydroxychloroquine discontinued, with subsequent ECG normalization happening after cessation and no arrhythmias being discovered. Because no ECG was performed on the patients in the untreated control group, the QT interval could not be established in that group of participants.

Table 3. Clinical Consequences In The Treated And Untreated groups.

Clinical Consequences	Total (N = 350)	Treated Group (N = 250)	Untreated Control Group (N = 100)	p-Value
Hospitalization(ICU) – N. (%)	55 (23%)	30 (27%)	25 (24%)	>0.001
Death – N. (%)	35 (12%)	16 (21%)	19 (13%)	>0.001
Duration Of Hospitalization – Days – Median (IQR)	8 (6–13)	8 (6–12)	9 (6–14)	>0.001

Discussion

An overall, 250 adult COVID-19 patients were hospitalized to ALSALAM Teaching Hospital in Mosul city in Iraq for mild to moderate dyspnea were compared to 100 apparently healthy controls. No statistical changes in clinical and biochemical findings were espied betwixt the treated and the untreated control groups, which was due to the similarity of their demographic baseline characteristics. The treatment group differed in terms of age and hsCRP levels at the start of the study. It has been observed that succession of hydroxychloroquine and azithromycin was unsuccessful in the management of COVID-19-associated dyspnea in younger individuals with milder pneumonia and lower hsCRP levels. Due to QTc prolongation in nearly all of the patients who received this combination, despite the fact that it was generally well tolerated, it was discontinued in nearly 11 % of the patients who received it. The researchers discovered that the indication of hydroxychloroquine alone, in combination with azithromycin, or with no drugs was conjoined with an increased risk of in-hospital mortality in patients with COVID-19 virus infection. Certain individuals required intensive care, according to the findings, and COVID-19 was found to be associated with that need in some cases. The azithromycin dosage used in the study was significantly lower than the hydroxychloroquine dosage used in the research, despite the fact that the hydroxychloroquine was obtained from our hospital. For the therapeutic remedies of severe COVID-19 infection in individuals who are apparently free from cardiovascular risk factors, the combination of hydroxychloroquine and azithromycin was investigated (5). In laboratory animals, hydroxychloroquine, either alone or combined with azithromycin, was shown to reduce COVID-19 mortality (18). On the other hand, subsequent research has revealed the inverse. Patients with COVID-19 were treated with hydroxychloroquine in the COALITION II trial (800 mg per day for approximately ten days). The combination of hydroxychloroquine and azithromycin had no therapeutic advantages for milder SARS-CoV-2 infections (19, 20). According to our data, patients with mild to moderate COVID-19-related dyspnea gain no advantage from the combination of hydroxychloroquine and azithromycin in terms of mortality, need for invasive oxygen therapy, rate of ICU transfers, or length of hospital stay. According to the researchers, hydroxychloroquine was evaluated for efficacy alone or in combination with azithromycin in patients with mild to moderate disease severity (seven days) (11, 21). They had comparable clinical outcomes. According to the study (22), patients who got hydroxychloroquine alone or in combination with other drugs had higher liver enzyme levels. The hsCRP and LDH peak values were statistically higher in the treated-exposed patients than in the untreated control group, indicating

greater systemic inflammation. Recent meta-analyses of individuals with COVID-19 who received hydroxychloroquine monotherapy or in combination with azithromycin discovered no evidence of a positive impact (23, 24). As a result of the homogeneous groups, we were able to make fair comparisons and increase the reliability of our findings. Additionally, the same hospital and medical team cared for all of the patients involved. Comparing clinical and biochemical results in adult patients admitted to the hospital for mild to moderate COVID-19-related dyspnea to conventional treatment revealed no significant improvement in either, and there were only a few minor adverse effects. When 1561 COVID-19 patients were brought to the hospital for treatment, researchers from RECOVERY found that large dosages of hydroxychloroquine didn't have any impact on 28-day mortality, but they did have detrimental consequences on their health (Increased length of stay in the hospital, progression to invasive mechanical ventilation, and eventual death) (9). Furthermore, it was shown that hydroxychloroquine was unsuccessful in COVID-19 patients who were admitted to the hospital, independent of the dosage administered (5). Patients with moderate to severe COVID-19 related dyspnea who received hydroxychloroquine and azithromycin did not experience a reduction in mortality, a reduction in the need for invasive oxygen treatment, a reduction in the rate of ICU transfers, or a reduction in the length of hospital stay, according to the findings of our study. The experimental groups might have positive outcome than the control treatment group because, among other things, they had a younger median age, a lower percentage of pulmonary involvement (though the number of affected lung segments remained largely unchanged), and a lower hsCRP than the untreated control group. The researchers wanted to see if hydroxychloroquine, alone or in combination with azithromycin, might help those with mild to moderate disease severity by improving their clinical state. There were no significant changes in clinical outcomes across the groups, as predicted. According to the conclusions of the research (25, 26), individuals who took hydroxychloroquine, either alone or in combination with other medications, had greater QTc prolongation and increased liver enzymes than those who did not receive either drug. Despite the fact that there were no differences in liver enzyme levels between the two groups (27), the treated group had higher hsCRP and LDH peak values than the untreated control group, indicating increased systemic inflammation (27). As a side note, recent meta-analyses of COVID-19 patients treated with hydroxychloroquine alone or in combination with azithromycin revealed that when treatment was discontinued, there was no improvement in moderate to severe disease (28, 29).

The study limitation includes small sample size and localization of the study on unicenter, we recommend to re-conduct the study with expanding the sample size and base on multi-central approach. Different age groups should be included in any further study to better identify the effects according to age groups.

Conclusion

A dualistic mode of use of azithromycin-hydoxychloroquine shown no improvement in symptoms of hospitalized COVID-19 positive patients when this dualistic therapy compared to other standard therapy regardless of degree of severity from mild to severe dyspnea or acute respiratory distress syndrome.

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Conflicts of interest

The authors declare no conflict of interest.

Adherence to Ethical Standards

The study approved by ethical committee in the University of Mosul. The study is registered by the scientific committee in the Department of Pharmacology and Toxicology/College of Pharmacy in the University of Mosul (DPTCP05 on 21/04/2021).

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