EJMO

DOI: 10.14744/ejmo.2021.16263
EJMO 2021;5(1):63–70

Research Article

A Comparative Study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID-19 Patients

Abu Taiub Mohammed Mohiuddin Chowdhury,[1] Mohammad Shahbaz,[2] Md Rezaul Karim,[3] Jahirul Islam, Guo Dan,[1] Shuixiang He[1]

[1]Department of Gastroenterology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China
[2]Chakoria Upazilla Health Complex, Cox's Bazar, Bangladesh
[3]Biomedical Research Institute of Hubei University of Medicine, Shiyan, China
[4]Department of Epidemiology and Health Statistics, Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China

Abstract

Objectives: We investigated the outcomes of Ivermectin-Doxycycline vs. Hydroxychloroquine-Azithromycin combination therapy in mild to moderate COVID19 patients.

Methods: Patients were divided randomly into two groups: Ivermectin 200µgm/kg single dose + Doxycycline 100mg BID for ten days in group A, and Hydroxychloroquine 400mg for the first day, then 200mg BID for nine days + Azithromycin 500mg daily for five days in group B (Control group). RT-PCR for SARS-CoV-2 infection was repeated in all symptomatic patients on the second day onward without symptoms. Repeat PCR was done every two days onward if the result found positive. Time to the negative PCR and symptomatic recovery was measured for each group.

Results: All subjects in Group A reached a negative PCR, at a mean of 8.93 days, and reached symptomatic recovery, at a mean of 5.93 days, with 55.10% symptom-free by the fifth day. In group B, 96.36% reached a negative PCR at a mean of 9.33 days and were symptoms-free at 6.99 days. In group A 31.67% of patients expressed symptoms caused by medication, this was 46.43% in group B.

Conclusion: The combination therapy of Ivermectin-Doxycycline showed a trend towards superiority to the combination of Hydroxychloroquine-Azithromycin for mild to moderate COVID19 disease.

Keywords: Azithromycin, Bangladesh, COVID-19, Doxycycline, Hydroxychloroquine, Ivermectin, randomized controlled trial (RCT)

Cite This Article: *Mohiuddin Chowdhury ATM, Shahbaz M, Karim MR, Islam J, Dan G, He S. A Comparative Study on Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin Therapy on COVID-19 Patients. EJMO 2021;5(1):63–70.*

Coronavirus disease 2019 (COVID-19) is a global pandemic declared by the world health organization (WHO). Over ninety million people have already been infected by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and billions have been affected by the socioeconomic squeal. As SARS-CoV-2 is a novel virus, there are no proven treatment options yet. Early treatment before the disease becomes severe would be optimal. The

Address for correspondence: Shuixiang He, MD; PhD. Department of Gastroenterology, First affiliated hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China
Phone: 008613991380928 **Email:** dyyyjxk@xjtu.edu.cn
Abu Taiub Mohammed Mohiuddin Chowdhury, MD. Department of Gastroenterology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China
Phone: 008801817711079; 008615529366232 **E-mail:** dr_mohiuddinchy@yahoo.com
Submitted Date: January 21, 2021 **Accepted Date:** February 15, 2021 **Available Online Date:** February 25, 2021

treatment's current considerations include lopinavir/ritonavir, favipiravir, and remdesivir. These are currently in use in moderate to severe COVID-19 patients. Treatments for patients in the early stage of the disease with mild to moderate symptoms have not been well established. Studies have shown that Chloroquine and Hydroxychloroquine (HCQ) are not beneficial in moderate to severe COVID19 disease. However, they have become the current standard for mild to moderate and early disease states. Chloroquine has been shown as a potential suppressor of SARS-CoV-2 in an in vitro study.[1] Though many trials have established a good outcome in mild to moderate cases, unfortunately, chloroquine toxicity is a paramount concern.[2] HCQ, a less toxic derivative, has also been found to be effective.[3] Recently, an anti-parasitic drug Ivermectin has been described as highly effective in an in vitro study against SARS-CoV-2.[4] HCQ-Azithromycin combination therapy has also been shown to be a possibly effective combination therapy in the treatment of SARS-CoV-2.[5, 6] These two studies reported 100% and 83% recovery in the sixth and seventh day with a reduced hospital stay. Alam MT et al.[31] recently described an encouraging result in a case series of COVID19 patients with a combination of Ivermectin and Doxycycline. Till now, there has not been a randomized study of Ivermectin in patients with mild to moderate COVID19. Ivermectin is well-tolerated, less toxic, and has fewer adverse effects than HCQ. HCQ-Azithromycin combination therapy has also been mentioned in the "National guideline for COVID management 4.0" of Bangladesh as an initial therapy against COVID19. Due to drug complications and discouraging statements about HCQ treatment made by WHO, it is crucial to find an effective, economical alternative to HCQ. Therefore, we decided to investigate the efficacy of Ivermectin-Doxycycline combination therapy and compare it to the standard HCQ-Azithromycin treatment according to the "National guideline for COVID management 4.0" among the mild to moderate cases of COVID19 patients.

Methods

Ethical Consideration and Approval, Informed Consent

This study was approved by the Ethical committee of Chakoria Upazilla Health Complex, Chittagong, Bangladesh. UHC/Chakoria/Ethical Approval/2020/01 (15-04-20). The purpose of the research was explained to participants. Once verbal consent was understood and agreed upon, a written form was given. This was done to get informed consent and legal identification. The individuals who gave consent were enrolled in this study.

Study Population and Data Collection

Patients (16 years to 80 years of age) tested positive for SARS-CoV-2 infection by Real-time polymerase chain reaction (RT-PCR) at Chakoria Upazilla Health Complex, Cox's Bazar, Bangladesh, from second may to the fifth June 2020, were initially included in this study, including those with and without the symptoms. The PCR analysis of the collected samples was performed in Cox's Bazar Medical College. All patients received a full evaluation, including a history of current illness, comorbid condition, and associated complaints. Patients with unstable comorbid conditions like bronchial asthma, chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD), uncontrolled diabetes mellitus (DM), advanced renal and hepatic disease, carcinoma, hospitalized, and immuno-compromised patients were excluded. Patients were examined for oxygen saturation and only those with oxygen saturation of 95% or above who fit the outpatient treatment protocol for COVID19 were included. Patients with respiratory symptoms received chest radiographs. Those with normal or near-normal chest radiographs (up to 10% involvement) were included.

Randomization and Treatment Intervention

Randomization was done using an odd-even methodology and applied to registration numbers, consecutively in a 1:1 ratio, by the hospital registration office. Treatment was given, and the final enrolment was done by the attending physician (investigator). All the patients enrolled in this study were treated as outpatient department (OPD) patients.

For the study, patients were divided into two groups, as follows:

- Group A (n=60): Ivermectin 200µgm/kg single dose + Doxycycline 100mg BID for ten days.
- Group B (n=56): Hydroxychloroquine 400mg for the first day, then 200mg BID for nine days + Azithromycin 500mg daily for five days (considered as the control group).

Ivermectin dosing was determined by the case series performed by Alam MT et al., and HCQ dosing was decided as per "National guideline for COVID management 4.0".

All the subjects were provided with symptomatic treatment such as fever, headache, cough, and myalgia. Drug interactions and contraindications for each individual were considered carefully. The schedule of medication intake was adequately explained to each patient. Group A's instructions included that Ivermectin tablet (200µg/kg) single dose to be taken on an empty stomach an hour before a meal on the first day. Doxycycline 100 mg cap-

sule be taken twice daily after meal for ten days starting from day one. Group B's instructions included Hydroxychloroquine 400mg (two tablets of 200mg each) to be taken on the first day, then 200mg (one tablet) twice daily after meal for nine days. Azithromycin 500mg (one tablet of 500mg) to be taken once daily after meal for five days starting from day one. Patients were advised to self-isolate, take proper nutrition, hydration, and maintain a sanitary environment.

Repeat Nasopharyngeal and Throat Swab PCR

All subjects underwent repeat nasopharyngeal and throat swab PCR for SARS-CoV2 every other day until their PCR was negative. These repeat PCR tests began on the fifth day after taking the medication for subjects who began the study and remained symptom-free. The PCR repeat testing began on the second symptom-free day onward for subjects who began the study with symptoms or developed symptoms. The investigators had telephone contact with all the subjects every three days throughout the study to determine any therapy's adverse effects. A re-evaluation PCR was performed after seven days following the first negative PCR.

Endpoints were a negative PCR and resolution of symptoms. The duration from the first day of drug intake to the negative PCR was counted as the recovery period. The duration from the first day of drug intake to the disappearance of symptoms was counted as the period to symptomatic recovery. "Adverse effects" were determined by the existence of the pharmacological side effects of the particular drug during treatment. A detailed history of adverse effects (other than previous disease symptoms) experienced by each participant was collected during the follow-up sample collection. An asymptomatic participant presented with no symptom of COVID-19 and remained the same until the negative PCR.

Data Analysis and Statistics

Data were presented as mean±standard deviation, and statistical analysis was done by Graph pad Prism software. Column analysis was done to find the mean with the standard deviation in each group. T-test was done to see the significance between the values where needed. $P<0.05$ was considered statistically significant.

Results

This study was completed in a pre-determined period from May second to June fifth, 2020, and 181 patients tested positive for SARS-CoV-2 infection in that period. 42 patients had comorbid conditions (some required hospitalization) that might have affected the recovery time, and 14 patients were unwilling to participate in the study. Nonetheless, 9 patients did not show-up (3 from group A and 6 from group B) for the follow-up sample collection, so these were excluded, and 116 patients were finally included in the analysis (Fig. 3).

Demographic Characteristics of the Study Subjects

As shown in Table 1, the total number of patients was 116; male 84 and female 26, age 16 to 80 years, and mean age (33.94±14.12 years). Group A (Ivermectin + Doxycycline): male 43 (71.67%), female 17 (28.33%), age 35.72±15.1 years; males 37 years and female 32.88 years. Group B (Hydroxychloroquine + Azithromycin): male 47 (83.93%), female 9 (16.07%), age 31.91 years; male 31.35, and female 34.5 years. (Fig. 1 a, b) Among the total, 91 (78.45%) were symptomatic, and 25 (21.55%) were asymptomatic patients with contact history. These were 49 (81.67%) and 11 (18.33%) in group A, 42 (75%) and 14 (25%) in group B.

Recovery Rate and Mean Recovery Duration Between Groups

In group A, recovery to negative PCR rate was 100% (60/60). The mean recovery duration to negative PCR was 8.93 days (8 to 13 days). 41 (63.3%) of patients had no new complaints other than their presenting symptoms. New symptoms that may have been attributed to adverse drug effects included

Table 1. Baseline characteristics of the study group patients.

Parameters	
Number of patients (n)	116
Male	90 (77.58)
Female	26 (22.41)
Group A (n, %)	60
Group A Male (n, %)	43 (71.67)
Group A Female (n, %)	17 (28.33)
Group B (n)	56
Group B Male (n, %)	47 (83.93)
Group A Female (n, %)	9 (16.07)
Age (in years)	33.94±14.12 (8 to 80 Years)
Symptomatic (n, %)	91 (78.45)
Asymptomatic (n, %)	25 (21.55)
Agegroup A (in years)	35.72±15.1
Male	37.14±14.72
Female	32.88±16.2
Symptomatic (n, %)	49 (81.67)
Asymptomatic (n, %)	11 (18.33)
Agegroup B (in years)	31.91±12.72
Male	31.35±12.95
Female	34.5±11.74
Symptomatic (n, %)	42 (75)
Asymptomatic (n, %)	14 (25)

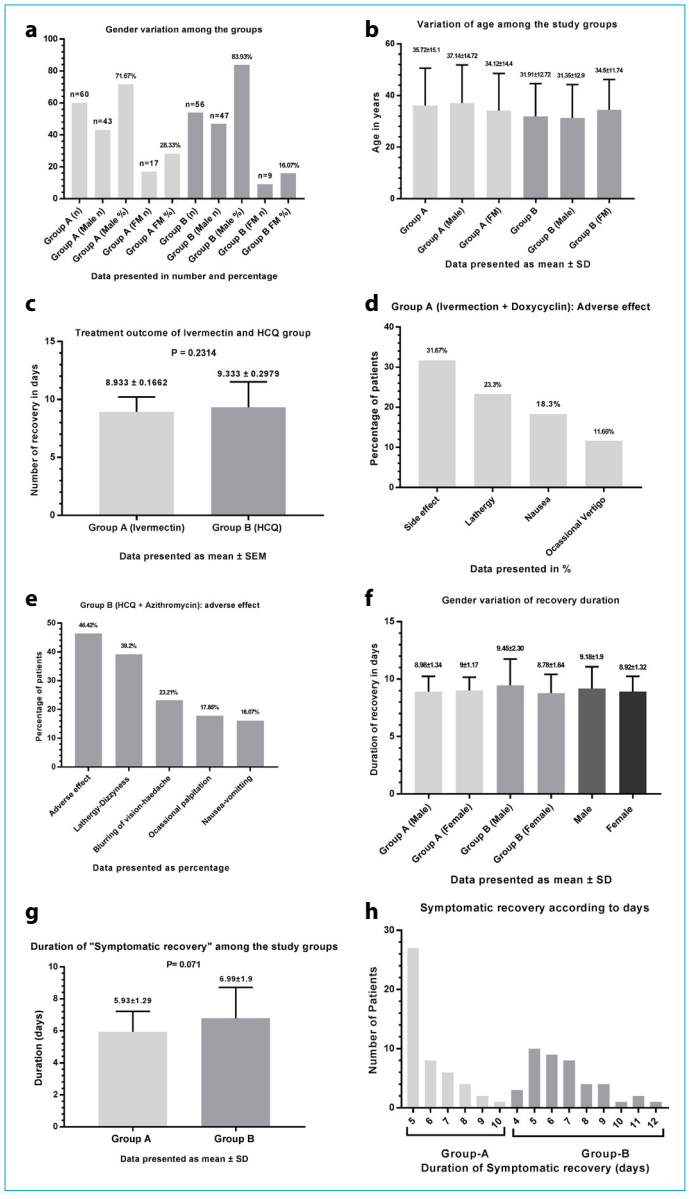

Figure 1. (a) Number of patients according to gender among the groups. **(b)** Gender variation of age among the study groups (data presented as mean±SD). **(c)** Recover duration of Ivermectin-Doxycycline and HCQ-Azithromycin group; note: the difference between the groups' recovery duration is not statistically significant P=0.231. **(d)** Adverse effect expressed by the patients of group A. **(e)** Adverse effect experienced by the patients of group B. **(f)** Variation of the recovery duration according to the gender; note: males in group B and males as gender, in general, have a longer recovery period than the females. **(g)** Duration of the symptomatic recovery (in days) among the groups. The difference between the duration among groups is not significant P=0.071. **(h)** Subgroup analysis of the recovery duration among the groups. Note: group A has a higher number of symptomatic recoveries in the early days; this indicates a better efficacy of Ivermectin-Doxycycline therapy.

lethargy in 14 (23.3%), nausea in 11 (18.3%), and occasional vertigo in 7 (11.66%) of patients (Fig. 1c).

In group B, out of 56 patients, two male patients were referred to a tertiary hospital. They did not recover to a negative PCR as part of the study. Therefore, the recovery rate to negative PCR was 96.36% (54/56). The mean duration of recovery to negative PCR was 9.33 days (5 to 15 days). 30 (53.57%) of the patients had no new complaints other than their presenting symptoms. Fresh symptoms that were recognized as an adverse effect of HCQ included 13(23.21%) with mild blurred vision and headache; 22 (39.2%) with increased lethargy and dizziness, 10 (17.85%) with occasional, mild palpitation, and 9 (16.07%) with nausea and vomiting (Fig. 1e).

Difference in Recovery to Negative PCR between Groups

The difference between group A and group B recovery to negative PCR duration was not statistically significant in unpaired t-test, p=0.2314 (Fig. 1c). Subgroup analysis of the recovery duration: male 9.18±1.90 days and female 8.92±1.32 days, p=0.515; in group A male 8.907±1.342 days and female 9±1.173 days, p=0.44; and in group B male 9.18±1.90 days and female 8.92±1.32 days, p=0.407. The recovery duration of both group males and females were not significant, p=0.18 and 0.69, respectively (Fig. 1f).

The mean duration of symptomatic recovery was 5.93 days (5 to 10 days) in group A and 6.99 days (4 to 12 days) in group B (Fig. 1g). This difference in time to symptomatic recovery between group A and group B is not statistically significant, p=0.071 (Fig. 1g). In group A, over half of the subjects had become symptom-free by five days 27 (55.10%), with the remaining subjects becoming symptom-free on day six (16.32%), day seven (12.24%), day eight (8.16%), day nine (4%), and day ten (2.04%) (Fig. 1h). In group B, recovery was slower with subjects becoming symptoms free on fourth day 3 (7.14%), the fifth day 10 (23.8%), sixth day 9 (21.43%), seventh day 8(19.04%), eighth & ninth day 4 (9.52% each), eleventh day 2 (4.76%), and tenth and twelfth day (2.38% each) (Fig. 1h).

Mean Duration of Time to Negative PCR between Groups

In the secondary analysis of subjects who began the study with symptoms, the mean duration of time to negative PCR was 9.061 days in group A and 9.738 days in group B. This was not statistically significant in the unpaired t-test, p=0.0714. The mean duration of time to becoming negative PCR of patients without symptoms was 8.364 days in group A and 7.917 days in group B, which was not statistically significant in unpaired t-test, p=0.443 (Fig. 2b). Further analysis showed the highest recovery was achieved on the eighth day among group A patients in case of both asymptomatic (n=11) and symptomatic (n=49) patients,

8 (72.72%) and 22 (44.89%), respectively (Fig. 2 c, d). This recovery was relatively slower in group B. On the sixth day 3 (7.5%), seventh day 1 (2.5%), eighth day 9 (22.5%), ninth and tenth day 8 (20%) each, eleventh and twelfth day 4 (10%) each, thirteenth day 1 (2.5%), and fourteenth day 2 (5%) in group B patients with symptoms (n=40). Among asymptomatic patients (n=14), this was 1 (7.5%) on the fifth day, 2 (14.2%) individually on the sixth, seventh, eighth, tenth day, 4 (28.57%) on the ninth day, and 1 (7.1%) on the eleventh day (Fig. 2 c, d). No significant difference in the recovery duration was found in the subgroup analysis of the recovery duration according to the study groups' age. 61 to 70 years in group A had the longest recovery duration, 9.5±2.12, and 71 to 80 years was the shortest 8days. In group B, this was 11.71±2.48 days in the 41 to 50 years and 8.37±2.44 days in the 10 to 20 years age group (Fig. 2 e).

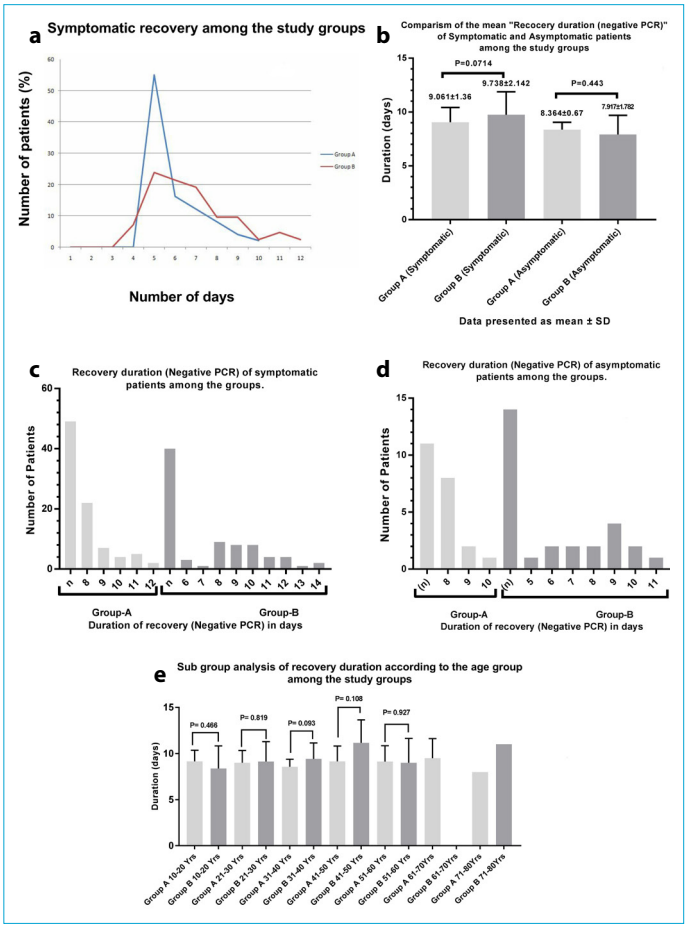

Figure 2. (a) Comparison between the symptomatic recoveries among the study groups. Note: group A (Ivermectin-Doxycycline) showed a pick recovery on the 5th day. In group B (HCQ-Azithromycin), the symptomatic recovery started relatively earlier on the 4th day but had a slow trend. **(b)** The mean duration of recovery (beginning of the treatment to the negative PCR) of the patients with and without symptoms among groups A& B was not statistically significant in the subgroup analysis. **(c)** Subgroup analysis of recovery duration of the symptomatic patients among the study groups. Maximum numbers of negative PCR were achieved on the 8th day in both groups. Group A 22 (44.89%) and group B 9 (22.5%). The recovery rates are faster in group A, though relatively earlier but slow in group B. **(d)** Subgroup analysis of the asymptomatic patients' recovery duration. Most group A patients gained viral clearance on 8th day 8 (72.72%). Not: first PCR was done on the 5th day. In group B, 1(7.1%) was recovered on the 5th day and 2 (14.2%) on the 6th day. The highest recovery was observed on the 9th day 4 (28.57%). **(e)** Subgroup comparison of the recovery duration according to age.

Discussion

The COVID-19 pandemic in Bangladesh is part of the coronavirus worldwide pandemic disease caused by a newly discovered coronavirus. It was initially called novel coronavirus and later named SARS-CoV-2 due to its similar characteristics with SARS-CoV-1.[7-9] The treatment methods for COVID-19 are emerging and rapidly evolving because of ongoing research being done worldwide by a record number of investigators. Due to each medical and research facility's uniqueness, the approach to patient care with COVID-19 varies from institution to institution in Bangladesh. Many patients with mild to moderate disease were treated with HCQ and Azithromycin. New concerns about HCQ has led us to seek alternatives with shorter recovery time and better tolerability. Thus, we have undertaken a comparative therapeutic analysis, comparing these standard drugs with Ivermectin and Doxycycline.

In this randomized treatment study of groups A and B, the presenting symptoms of the COVID19 patients were fever, cough, sore throat, weakness, chest discomfort, breath-

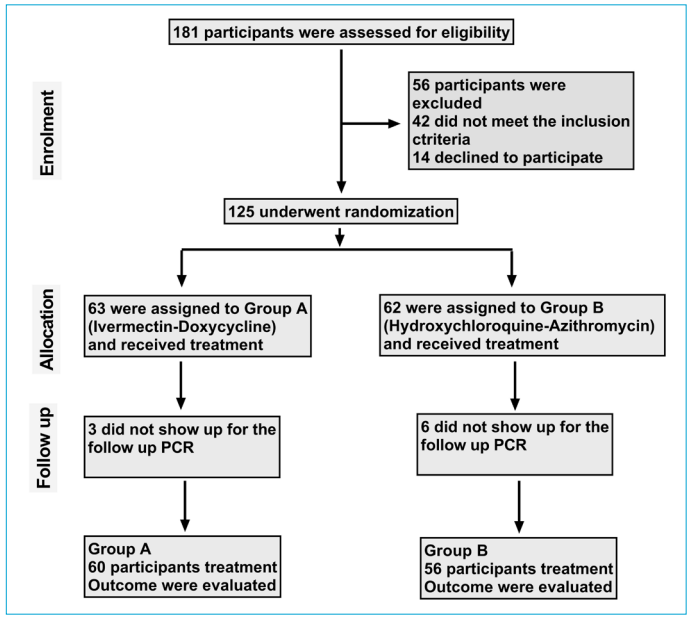

Figure 3. Flow diagram of randomization and treatment assignment of the participants.

ing difficulty, diarrhea, myalgia, and abdominal pain. To avoid the recovery duration's influence, we solely selected the cases devoid of severe comorbidities. The difference in recovery to negative PCR duration was not significant (p=0.231) among the two groups. The mean recovery duration is shorter, 8.933 days in group A than in group B, 9.33 days (Fig. 1 c). Also, group A had a better outcome ratio of 100% (60/60) recovery to negative PCR compared to that of group B 96.36% (54/56).

HCQ has decades of treatment use as an immunomodulator.[10] At present, it has been the topic of discussion concerning its potential use to treat patients with COVID-19.[11] It is thought that the effect of HCQ results in the selective killing of the infected cells. Therefore, it may accelerate viral clearance in COVID-19.[13] Some studies showed that severe deterioration in some patients with COVID-19 had been closely associated with dysregulated and excessive cytokine release termed "cytokine storm."[14, 15] HCQ was found to inhibit SARS-CoV-2 infection in vitro and significantly decrease cytokine production, especially the pro-inflammatory cytokines.[16] Correspondingly, Azithromycin is a macrolide group of antibiotics. It has been studied as part of possible treatment of COVID-19 combined with HCQ and has been reported to add benefit.[17, 18] However, a recent report failed to establish whether it has any antiviral activity or any synergistic activity with HCQ in the treatment of COVID-19.[19] Therefore, a further comparative study can enhance the significance of HCQ- Azithromycincombination therapy.

On the other hand, Ivermectin is a relatively safe and well-tolerated anti-parasitic drug that can inhibit nuclear transport activity.[20] Recently, in-vitro studies have shown its function against SARS-CoV-2.[21, 22] A recent report suggested that Ivermectin reduces mortality rates in hospitalized patients with COVID-19.[23] However, it is unknown if antiviral levels are attainable while using known dosing regimens of Ivermectin therapy in patients with COVID-19.[24, 25] Thus, it is vital to investigate Ivermectin's dose regimens for COVID-19 treatment or to determine if there is appropriate synergism using combination therapy with another drug. Also, Doxycycline is a tetracycline class of antibiotics with a long history of clinical use.[26] The efficacy and tolerability of Ivermectin and Doxycycline were established in combination with an earlier study to treat onchocerciasis.[27] Several recent studies have suggested a therapeutic role of Doxycycline against COVID-19.[28, 29]

In our study, the difference in recovery to become symptom-free was not statistically significant (Fig. 1c). Nevertheless, the Ivermectin group showed better symptomatic recovery than the HCQ group (Fig. 2 a-d). According to the age among study groups, the difference was not statistically significant (Fig. 2 e). Ivermectin-Doxycycline combination expressed an earlier and faster relief of COVID features (Fig. 1 g) and viral clearance than the HCQ-Azithromycin combination. However, the mean recovery duration is not statistically significant (Fig. 1c). In the Ivermectin-Doxycycline group a greater number of patients gained faster symptomatic recovery than that of the HCQ group (Fig. 1h] This suggests Ivermectin-Doxycycline may have better efficacy in reducing the COVID-19 symptoms than HCQ-Azithromycin therapy.

The Ivermectin-Doxycycline group had better patient compliance and fewer adverse effects compared to the HCQ-Azithromycin group (Fig. 1 d, e). The adverse effects of HCQ in our study are similar to others.[30, 31] The sex difference was also examined, but there were no significant differences between males and females in this study (Fig. 1 f). According to this study, the Ivermectin-Doxycycline treatment regimen was well tolerated, and effective treatment for mild to moderate degrees of SARS-CoV-2 infection. Not only concerning the time to become symptom-free and the viral clearance, but also in terms of safety, side-effect profile, and compliance the Ivermectin-Doxycycline combination is superior to HCQ-Azithromycin therapy for mild to moderate degrees of COVID-19 patients. We strongly believe that increasing the dose and the duration of Ivermectin treatment will further benefit in reducing the recovery period of COVID19 infection beyond that which was seen in our study. This will also prevent disease progression and morbidity in COVID-19 patients.

Our study has limitations, and these include relatively small sample size, the dose of Ivermectin, and case selection. The outcome may be biased by factors like disease severity, lack of cooperation of some participants, and unknown comorbidity.

Conclusion

Researchers have suggested different drug combination therapies for COVID19. According to our study, the Ivermectin-Doxycycline combination therapy has better symptomatic relief, shortened recovery duration, fewer adverse effects, and superior patient compliance compared to the Hydroxychloroquine-Azithromycin combination. Based on this study's outcomes, the Ivermectin-Doxycycline combination is a superior choice for treating patients with mild to moderate COVID-19 disease. Despite this study's limitation, we tried to select our study group patients without any major or unstable comorbid condition as far as possible to avoid differences in treatment outcomes among the groups. Further study is required on a larger scale with an increase in Ivermectin treatment duration.

Disclosures

Acknowledgment: Alexis Lieberman, MD; Associate chief for Ambulatory Pediatrics and Director of the Adolescent Program at Albert Einstein Medical Center in Philadelphia, Pennsylvania, for his kind assistance in editing this manuscript.

The authors are tankful to all the doctors and staffs of the Chakoria Upazilla Health Complex, Department of Gastroenterology-First Affiliated Hospital of Xi'an Jiaotong University, and to Ministry of Health and Family welfare Bangladesh.

Other affiliation of Abu Taiub Mohammed Mohiuddin Chowdhury: Ministry of Health and Family welfare Bangladesh.

Ethics Committee Approval: The study was approved by the local ethical committee of Chakoria Upazilla Health Complex, Cox's Bazar, Bangladesh. Approval no: UHC/Chakoria/Ethical Approval/2020/01(15-04-20)ClinicalTrials.gov ID: NCT04434144.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.T.M.M.C.; Design – A.T.M.M.C.; Supervision – S.H.; Materials – M.R.K.; Data collection &/or processing – A.T.M.M.C., J.I., G.D.; Analysis and/or interpreta-tion – A.T.M.M.C. Literature search – M.R.K.; Writing – A.T.M.M.C.; Critical review – S.H.

References

1. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel Coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269-271. [CrossRef]
2. Weniger H, Organization WH Review of side effects and toxicity of chloroquine. 1979.https://apps.who.int/iris/handle/10665/65773. Accessed March thirty-first, 2020.
3. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of Hydroxychloroquine for the treatment of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020. [CrossRef]
4. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020. [CrossRef]
5. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and Azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020.
6. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Sevestre J. Clinical and microbiological effect of a combination of Hydroxychloroquine and Azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. Mediterr-Infect.2020:101663 https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf [CrossRef]
7. Chan, Jasper F., et al. "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster." The Lancet, vol. 395, no. 10223, 2020, pp. 514-523. [CrossRef]
8. Li, Jinzhong, et al. "Clinical features of familial clustering in patients infected with 2019 novel coronavirus in Wuhan, China." Virus Research, vol. 286, 2020, p. 198043. [CrossRef]
9. "Clinical findings in a group of patients infected with the 2019 novel Coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series." BMJ, 2020, p. m792. [CrossRef]
10. Meyerowitz, Eric A., et al. "Rethinking the role of hydroxychloroquine in the treatment of COVID-19." The FASEB Journal, vol. 34, no. 5, 2020, pp., 6027-6037. [CrossRef]
11. Savarino, Andrea, and Mohammad Tarek. "Pharmacokinetic bases of the hydroxychloroquine response in COVID-19: implications for therapy and prevention." 2020.
12. Juurlink, David N. "Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection." Canadian Medical Association Journal, vol. 192, no. 17, 2020, pp. E450-E453. [CrossRef]
13. Accapezzato, Daniele, et al. "Chloroquine enhances human CD8+ T cell responses against soluble antigens in vivo." Journal of Experimental Medicine 2005;202:6:817-828. [CrossRef]
14. Ye, Qing, et al. "The pathogenesis and treatment of the `Cytokine Storm' in COVID-19." Journal of Infection 2020;80:6:607-613. [CrossRef]
15. Mahmudpour, Mehdi, et al. "COVID-19 cytokine storm: The anger of inflammation." Cytokine 2020;155151. [CrossRef]
16. Liu, Jia, et al. "Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro." Cell Discovery, vol. 6, no. 1, 2020. [CrossRef]
17. Schaper, Charles. "A Mechanism of Action for Hydroxychloroquine and Azithromycin to Inhibit Coronavirus Disease COVID-19." 2020. [CrossRef]
18. Chen, Jun, et al. "COVID-19 infection: the China and Italy perspectives." Cell Death & Disease, vol. 11, no. 6, 2020. [CrossRef]
19. Molina, J.M., et al. "No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection." Médecine et Maladies Infectieuses, vol. 50, no. 4, 2020, p. 384.
20. Laing, Roz, et al. "Ivermectin – Old Drug, New Tricks?" Trends in Parasitology, vol. 33, no. 6, 2017, pp. 463-472. [CrossRef]
21. Caly, Leon, et al. "The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro." Antiviral Research, vol. 178, 2020, p. 104787. [CrossRef]
22. ŞİMŞEK YAVUZ, Serap, and Serhat ÜNAL. "Antiviral treatment of COVID-19." Turkish Journal of Medical Sciences, vol. 50, no. SI-1, 2020, pp. 611-619. [CrossRef]
23. Rajter, Juliana C., et al. "ICON (Ivermectin in COvid Nineteen) study: Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19." 2020. [CrossRef]
24. Momekov, Georgi, and DenitsaMomekova. "Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens." 2020. [CrossRef]

25. Schmith, Virginia D., et al. "The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19." 2020. [CrossRef]
26. Holmes, Natasha E., and Patrick G. Charles. "Safety and Efficacy Review of Doxycycline." Clinical Medicine Insights: Therapeutics 2009;1:471-482. [CrossRef]
27. Abegunde, Ayokunle T., et al. "Doxycycline plus ivermectin versus ivermectin alone for treatment of patients with onchocerciasis." Cochrane Database of Systematic Reviews, no. 1, 2016, p. CD011146. [CrossRef]
28. Sodhi, Mohit, and MahyarEtminan. "Therapeutic Potential for Tetracyclines in the Treatment of COVID-19." Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2020;40:5:487-488. [CrossRef]
29. Conforti, Claudio, et al. "Doxycycline, a widely used antibiotic in dermatology with a possible anti-inflammatory action against IL-6 in COVID-19 outbreak." Dermatologic Therapy, 2020, p. e13437 [CrossRef]
30. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Sevestre J. Clinical and microbiological effect of a combination of Hydroxychloroquine and Azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. Mediterr-Infect.2020:101663 https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf
31. A Case Series of 100 COVID-19 Positive Patients Treated with Combination of Ivermectin and Doxycycline Mtalam, R Murshed, E Bhiuyan, S Saber, RfAlam, Rc Robin; Bangladesh Coll Phys Surg 2020; 38: 10-15) DOI: https://doi.org/10.3329/jbcps.v38i0.47512. [CrossRef]