

A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients.

Abu Taiub Mohammed Mohiuddin Chowdhury

Xi'an Jiaotong University Medical College First Affiliated Hospital

Mohammad Shahbaz

Chakoria Upazilla Health Complex

Md Rezaul Karim

Hubei University of Medicine

Johirul Islam

Xi'an Jiaotong University Department of Epidemiology And Health Statistics

Dan Guo

Xi'an Jiaotong University Medical Collage First Affiliated Hospital

Shuixiang He (✉ dyyyjxk@xjtu.edu.cn)

Xi'an Jiaotong University Medical College First Affiliated Hospital

Research article

Keywords: Ivermectin, Doxycycline, Hydroxychloroquine, Azithromycin, Randomized Controlled Trial (RCT), COVID-19, Bangladesh

DOI: <https://doi.org/10.21203/rs.3.rs-38896/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background The worldwide COVID-19 pandemic was caused by a newly discovered Coronavirus. The treatment methods for COVID-19 are emerging and rapidly evolving. Existing drugs, including Ivermectin and Hydroxychloroquine, offer the hope of effective treatment in early disease. In this study, we investigated and compared outcomes of Ivermectin-Doxycycline vs. Hydroxychloroquine-Azithromycin combination therapy COVID19 patients with mild to moderate disease.

Methods Patients with mild to moderate COVID-19 disease, tested positive by RT PCR for SARS-CoV-2 infection at Chakoria Upazilla Health Complex, Cox's Bazar, Bangladesh, were included in this study. Patients were divided randomly into two groups: Ivermectin 200µgm/kg single dose + Doxycycline 100 mg BID for 10days in group A, and Hydroxychloroquine 400 mg 1st day, then 200mg BID for 9days + Azithromycin 500 mg daily for 5 days in group B. PCR for SARS-CoV-2 was repeated in all symptomatic patients on the second day onward without symptoms, or, for those who were asymptomatic (throughout the process), on the 5th day after taking medication and repeated every two days onward if the result is positive. Time to negative PCR and time to full symptomatic recovery was measured for each group.

Results All subjects in the Ivermectin-Doxycycline group (group A) reached a negative PCR for SARS-CoV-2, at a mean of 8.93days, and all reached symptomatic recovery, at a mean of 5.93days, with 55.10% symptom-free by the 5th day. In the Hydroxychloroquine-Azithromycin group (group B), 96.36% reached a negative PCR at a mean of 6.99days and were symptoms-free at 9.33days. Group A patients had symptoms that could have been caused by the medication in 31.67% of patients, including lethargy in 14(23.3%), nausea in 11(18.3%), and occasional vertigo in 7(11.66%) of patients. In Group B, 46.43% had symptoms that could have been caused by the medication, including 13(23.21%) mild blurring of vision and headache; 22(39.2%) increased lethargy and dizziness, 10(17.85%) occasional palpitation, and 9(16.07%) nausea and vomiting.

Conclusion The Ivermectin-Doxycycline combination showed a trend toward superiority to the Hydroxychloroquine-Azithromycin combination therapy in the case of patients with mild to moderate COVID19 disease, though the difference in time to becoming symptom-free and the difference in time to negative PCR was not statistically significant.

Background:

Coronavirus disease 2019 (COVID19) is a WHO declared a global pandemic. Over eight million people have already been infected by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and billions have been affected by the socioeconomic sequel. As SARS-CoV-2 is a novel virus, there are not yet proven treatment options. Early treatment, before the disease becomes severe, would be optimal. Current considerations for treatment include Lopinavir/ritonavir, favipiravir, and remdesivir, which are all currently in wide use in the case of moderate to severe COVID19 patients. Treatments for patients earlier in disease with mild to moderate symptoms have not been as well established. Chloroquine and

Hydroxychloroquine (HCQ) are not helpful in moderate to severe disease but have become the current standard for mild to moderate and early disease. Chloroquine has been shown as a potential suppressor of SARS-CoV-2 in a vitro study. [1] Though many trials have shown a good outcome in mild to moderate cases, unfortunately, chloroquine's toxicity is an important concern. [2] The less toxic derivative, Hydroxychloroquine (HCQ), has also been found to be effective. [3] Very recently, Ivermectin, an anti-parasitic drug, 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 6th and 7th day with a reduced hospital stay. Very recently, there have been several observational studies in Bangladesh showing encouraging results in a case series of Covid19 patients given a combination of Ivermectin and Doxycycline. There has not yet been a randomized study of Ivermectin in patients with mild to moderate Covid19. Ivermectin is well-tolerated, with less toxicity and fewer adverse effects compared to HCQ. Due to drug complications, and recent discouraging statements by WHO about HCQ treatment, it is important 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 therapy among the mild to moderate cases of COVID19 patients.

Methodology:

All patients who tested positive for SARS-CoV-2 infection by RT PCR at Chakoria Upazilla Health Complex, Cox's Bazar; Bangladesh from May 2nd to June 5th, 2020 were initially included in this study, including those with and without symptoms. The PCR analysis of the collected sample was done 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, COPD, ischemic heart disease, uncontrolled diabetes mellitus, advanced renal and hepatic disease, carcinoma, hospitalized, and Immuno-compromised patients were then excluded. Patients were all examined with a pulse oximeter and only those with normal oxygen saturation of 95% or above were included. Patients with respiratory symptoms received chest radiograph and only those with normal or near-normal chest radiograph were included.

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

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

Group A (n = 60): Ivermectin 200µgm/kg single dose + Doxycycline 100 mg BID for 10days

Group B (n = 56): Hydroxychloroquine 400 mg 1st day then 200mg BID for 9days + Azithromycin 500 mg daily for 5Days.

Dosing of Ivermectin was determined by the current standard of care depending on some observational study performed in Bangladesh. HCQ dosing was decided as per "National guideline for COVID19 management 4.0".

All subjects were also provided with symptomatic treatment for fever, headache, cough, myalgia, etc. Drug interactions and contraindications for each individual were considered carefully. The schedule of medication intake was properly explained to each patient. Instructions for Group A included that the Ivermectin tablet (200 µg/kg) single dose was to be taken on an empty stomach one hour before a meal on the first day and that the Doxycycline 100 mg capsule was to be taken twice daily after food for 10 days starting from day one. Instructions for Group B included that the Hydroxychloroquine 400 mg (2tablets of 200 mg each) was to be taken on the first day then 200 mg (one tablet) twice daily after food for 9days, and that the Azithromycin 500 mg (one tablet of 500 mg) was to be taken once daily after food for 5days starting from day one. Patients were advised to self-isolate, and to take proper nutrition, hydration, and to maintain a sanitary environment.

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 5th day after taking the medication for subjects who began the study and remained symptom-free. For subjects who began the study with symptoms or developed symptoms, the PCR repeat testing began on the 2nd symptom-free day onward. The investigators had telephone contact with all subjects every 3 days throughout the study, to determine if there were any adverse effects or side effects of the therapy.

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 to Negative PCR, and 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 the previous disease symptoms) experienced by each participant was collected during the follow-up sample collection. Informed written consent was obtained in every case. An asymptomatic participant was who presented with no symptom of COVID-19 and remain the same until the negative PCR.

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.

Results:

This study was completed in a pre-determined period from May 2nd to June 5th, 2020. There were 181 patients who tested positive for SARS-CoV-2 infection in that period. 42 patients had comorbid conditions (some required hospitalization) that might affect the recovery time; 14 patients were unwilling to

participate in the study, and 9 patients did not show-up (3 from group A and 6 from group B) for follow-up sample collection, so these were excluded. Following exclusion, 116 patients were included in this study.

Table 1: The total number of patients was 116; male 84 and female 26, age 16 to 80years, mean age 33.94 years (\pm 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 31.91years; male 31.35, and female 34.5 years. [Figure 1 A &B]

Table 1
Baseline characteristics of the study group patients.

Parameters	
Number of patients (n)	116
Male	84 (72.41%)
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	91 (78.45%)
Asymptomatic	25 (21.55%)
Age Group 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%)
Age Group 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%)

Out of the total, 91 (78.45%) were symptomatic, and 25 (21.55%) were asymptomatic patients with contact history. This is 49(81.67%) and 11(18.33%) in the case of Group A; 42 (75%) and 14 (25%) in the case of Group B.

In Group A recovery to negative PCR rate was 100% (60/60). The mean recovery duration to negative PCR was 8.93days (8 to 13days). 41 (63.3%) patients had no new complaints other than their presenting

symptoms. New symptoms that may be attributed to drug adverse effect or progression of COVID-19 disease included lethargy in 14(23.3%), nausea in 11(18.3%), and occasional vertigo in 7(11.66%) of patients. [Figure 1D]

In Group B, out of 56 patients, two male patients were referred to a tertiary hospital and did not recover to a negative PCR as part of the study. The recovery rate to negative PCR was therefore 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. New symptoms that may be attributed to drug adverse effect or progression of COVID-19 disease 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. [Figure 1E]

The difference between Group A and Group B recovery to negative PCR duration is not statistically significant in unpaired t-test, $P = 0.2314$. [Figure 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, $P = 0.44$, Group-B male 9.18 ± 1.90 days and female 8.92 ± 1.32 days, $P = 0.407$. The unpaired t-test between the recovery duration of both group male and both group female individually were not significant $P = 0.18$ and 0.69 , respectively.

The mean duration of symptomatic recovery was 5.93days (5 to 10 days) in Group A and 6.99days (4 to 12 days) in Group B. [Figure 1G] This difference in time to symptomatic recovery between Group A and Group B is not statistically significant in unpaired t-test, $P = 0.071$. [Figure 1G]

In Group A, over half of the subjects had become symptom-free by 5 days, 27 (55.10%), with the remaining subjects becoming symptom-free on day6 (16.32%), day7 (12.24%), day8 (8.16%), day9 (4%), and day10 (2.04%). [Figure 1H] In Group B, recovery was slower with subjects becoming symptoms free on 4th day 3(7.14%), 5th day 10(23.8%), 6th day 9(21.43%), 7th day 8(19.04%), 8th & 9th day 4(9.52% each), 11th day 2(4.76%), and 10th & 12th day (2.38% each). [Figure 1H]

In the secondary analysis of only those 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, which is not statistically significant in 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 is not statistically significant in unpaired t-test, $P = 0.443$. [Figure 2B] Further analysis shows the highest recovery was achieved on the 8th 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.[Figure 2 C & D] This recovery was relatively slower in Group B. On the 6th day 3(7.5%), 7th day 1(2.5%), 8th day 9(22.5%), 9th & 10th day 8(20%) each, 11th & 12th day 4(10%) each, 13th day 1(2.5%), and 14th day 2(5%) in case of Group B patients with symptoms ($n = 40$). Among asymptomatic patients ($n = 14$) this was 1(7.5%) on the 5th day, 2(14.2%) individually 6th, 7th, 8th, 10th day, 4(28.57%) 9th day, and 1(7.1%) on the 11th day.[Figure 2 C & D]

Discussion:

The COVID-19 pandemic in Bangladesh is part of the Coronavirus worldwide pandemic disease caused by a newly discovered Coronavirus. Initially, it was called the novel Coronavirus and later named severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) due to its similar characteristics with severe acute respiratory syndrome Coronavirus 1 (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 the uniqueness of each medical and research facility, the approach to the care of patients with COVID-19 varies from institution to institution; in Bangladesh, many patients with mild to moderate disease were being treated with Hydroxychloroquine (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.

HCQ, a less toxic derivative of chloroquine, is an antimalarial drug and 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 on antigen cross-presentation may occur, in which a dendritic cell presents the antigen to CD8⁺Tcells. Thus, improving their priming followed by the activation of CD8⁺ T-cells through antigen recognition, this results in the induction of selective killing of the infected cells. Therefore, it may accelerate viral clearance in COVID-19.[13] Some studies show that severe deterioration in some patients with COVID-19 has been closely associated with dysregulated and excessive cytokine release termed "cytokine storm" [14, 15] HCQ was found effective in inhibiting SARS-CoV-2 infection in vitro and can significantly decrease the production of cytokines and especially the pro-inflammatory cytokines.[16]

Azithromycin is in the macrolide group of antibiotic drugs used in the treatment of several bacterial infections, including pneumonia. It is known to reversibly bind to the 50S ribosomal subunit of the 70S ribosome to inhibit the translocation step of protein synthesis, but whether it has an antiviral effect or not is not yet known. It has been studied as part of the possible treatment of COVID-19 in combination 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 the combination therapy of HCQ and Azithromycin.

Ivermectin is a relatively safe and well-tolerated anti-parasitic drug for head lice, scabies, onchocerciasis, and strongyloidiasis that acts by inhibiting nuclear transport activity. [20] In-vitro studies have shown its function against human immunodeficiency virus (HIV), dengue, influenza, and most recently, against SARS-CoV-2. This effectiveness against SARS-CoV-2 infection is due to its critical interaction of RNA viruses responsible for integrase protein nuclear import.[21, 22] A recent report suggests that Ivermectin reduces mortality rates in hospitalized patients with COVID-19.[23] However, it is not known 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 the dose regimens of Ivermectin for COVID-19 treatment or to determine if there is appropriate synergism using combination therapy with another drug.

Doxycycline is in the tetracycline class of antibiotics that acts via the inhibition of bacterial ribosomes. It is a well-tolerated bacteriostatic drug that has a long history of clinical use.[26] The efficacy and tolerability of Ivermectin and Doxycycline were established in combination with an earlier study for the treatment of onchocerciasis.[27] Several recent studies have suggested a therapeutic role of Doxycycline against COVID-19.[28, 29]

In this randomized treatment study, we used two different drug combinations, Ivermectin-Doxycycline (Group A) and Hydroxychloroquine-Azithromycin (Group B), for the outpatient therapy of patients with mild to moderate COVID-19 in Bangladesh. The presenting symptoms of the COVID19 patients were fever, cough, sore throat, weakness, chest discomfort, breathing difficulty, diarrhoea, myalgia, and abdominal pain. To avoid the influence in the recovery duration, we solely selected the cases devoid of any severe comorbidities. Only patients with mild to moderate disease that could be treated as outpatients were included. HCQ dosing was decided as per "National guideline for COVID19 management 4.0".

The difference in recovery to negative PCR duration was not significant ($P = 0.231$) among the two groups. Still, the mean duration of recovery is shorter 8.933days in the case of Ivermectin-Doxycycline (Group A) than that of Hydroxychloroquine-Azithromycin (Group B) 9.33 days. [Figure 1C] Also, the Ivermectin-Doxycycline group had a better outcome ratio of 100% (60/60) recovery to negative PCR compared to that of HCQ 96.36% (54/56).

The difference in recovery to becoming symptom-free was 5.93days (5 to 10 days) in Group A and 6.99days (4 to 12 days) in Group B. This difference was not statistically significant. The Ivermectin group showed a better symptomatic recovery (5.93days) in comparison to the HCQ group (6.99days). [Figure 1G] In the case of Group-A most of the patients gained symptomatic recovery on the 5th (55.50%), 6th (16.32% and 7th (12.24%) day, this is 23.8%, 21.43% and 19.04% in the Group-B.[Figure 1H] In the case of symptomatic and asymptomatic patients the Ivermectin-Doxycycline combination expressed an earlier and faster relief of COVID features and viral clearance than that of HCQ-Azithromycin combination. [Figure: 2 A, C & D] Though the mean recovery duration is not statistically significant in an unpaired t-test. [Figure 2: B] This suggests Ivermectin-Doxycycline may have better efficacy in reducing the COVID-19 symptoms than that of HCQ-Azithromycin therapy.

Additional considerations are tolerability and compliance. In our study, the Ivermectin-Doxycycline group had better patient compliance and fewer adverse effects as compared to the HCQ-Azithromycin group, 31.67%, and 46.42% respectively. [Figure 1D & E] The adverse effects of HCQ in our study are similar to others,[30] with 39.2% of patients complaining of lethargy-dizziness, and with blurred vision and occasional palpitations noted by 23.21% and 17.85% of patients in the HCQ group. In comparison, the adverse effects seen in Group A were also lethargy, nausea, and occasional vertigo but at a lower rate than in Group B, with 23.3% complaining of these adverse effects in Group A.

The sex difference was examined but there were no significant differences in outcome between the males and females in this study. In case of Group A, both male and female had almost the same duration of recovery to negative PCR (8.9 and 9 days) but in Group B (9.45 and 8.78 days), male patients had a longer duration of recovery to negative PCR than the females (9.18 days and 8.92 days).[Figure 1F]

According to this study, both the Ivermectin-Doxycycline and HCQ-Azithromycin treatment regimens were tolerated and may have been an effective treatment for mild to moderate SARS-CoV-2 infection. With regard to time to becoming symptom-free, Ivermectin-Doxycycline combination is superior to HCQ-Azithromycin therapy for mild to moderate degrees of COVID-19 patients. In addition, the Ivermectin-Doxycycline combination is superior to HCQ-Azithromycin in terms of safety, side-effect profile, and compliance. We strongly believe that increasing the duration of Ivermectin treatment to 3days will offer further benefit in reducing the recovery period of COVID beyond that which was seen in our study. This will also prevent disease progression and morbidity to COVID-19 patients.

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

Conclusion:

Researchers have suggested different drug combination therapies for COVID-19. According to our study, the Ivermectin-Doxycycline combination therapy has a better success of symptomatic relief; shortened recovery duration, reduced adverse effects, and superior patient compliance compared to the Hydroxychloroquine-Azithromycin combination. Based on our outcomes, Ivermectin is a better choice for the treatment of patients with mild to moderate COVID-19 disease. This study has limitations; despite this, 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 the duration of Ivermectin treatment.

Abbreviations

COVID-19

Coronavirus disease 2019

COPD

Chronic Obstructive Pulmonary Airway Disease.

HCQ

Hydroxychloroquine

RT PCR

Real-time Polymerase Chain Reaction

RNA

Ribonucleic acid

SARS-Cov-2

Severe acute respiratory syndrome Coronavirus 2

WHO

World Health Organization

RCT

Randomized Controlled Trial

Declarations

Clinical trial registration: ClinicalTrials.gov NCT04434144; “A Comparative Study on Ivermectin and Hydroxychloroquine on the COVID19 Patients in Bangladesh”.

Detail study protocol: <https://clinicaltrials.gov/ct2/show/NCT04434144>

Ethics: The study was approved by the hospital ethics committee of ChakoriaUpazilla Health Complex.

Consent to participate: The purpose of this research was explained to the participant. Once the verbal consent was understood and agreed upon, written consent was then obtained from the participants. There was no participant in bellow 16 years.

Consent to publish: The authors have read the manuscript and gave consent to publish.

Competing Interests: None to declare.

Availability of data and materials: The datasets used and/or analyzed during the current study are uploaded as supporting documents after anonymization.

Funding: Not applicable.

This study adheres to CONSORT guidelines and the completed CONSORT checklist is included as an additional file.

Authors' contributions:

ATMMC gave the basic research concept, analyzed & collected the data of COVID19 patients, and wrote the manuscript.

MS was responsible for patient selection, treatment, patient management, follow-ups, patient counseling, and data collection.

MRK partially wrote the discussion part of the article.

GD and JI interpreted the data for analysis.

HS gave the concept of research maintained supervision.

Acknowledgment:

The authors are thankful for the cooperation of the Chokoria Upazilla Health Complex, and Department of Gastroenterology-First Affiliated Hospital of Xi'an Jiaotong University.

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.

Sedzro Divine Mensah; University of Science and Technology China.

Authors' Information:

1. Abu Taiub Mohammed Mohiuddin Chowdhury;

Email: dr_mohiuddinchy@yahoo.com

Department of Gastroenterology, First Affiliated Hospital of Xi'an Jiaotong University, Shaanxi, P.R. China

2. Mohammad Shahbaz

Email: shahbaz27ssmc@yahoo.com

Upazila Health & Family Planning Officer, ChokoriaUpazella health Complex, Cox's Bazar, Bangladesh

3. Rezaul Karim

Email: dr_mdrezaulkarim@hotmail.com

Biomedical Research Institute of Hubei University of Medicine, Shiyan, China.

4. Johirul Islam

Email: pekfusan@gmail.com

Department of Epidemiology and Health Statistics; Xi'an Jiaotong University. China

5. Dan Guo

Email: 1184795810@qq.com

Department of Gastroenterology. The first affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China.

6. He Shuixiang

Email: dyyyjxk@mail.xjtu.edu.cn.

References

1. 10.1038/s41422-020-0282-0
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. 10.1038/s41422-020-0282-0[PMC free article] [PubMed].
2. Weniger H, Organization WH Review of side effects and toxicity of chloroquine. 1979. <https://apps.who.int/iris/handle/10665/65773>. Accessed March 31st, 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;ciaa237 10.1093/cid/ciaa237 [PMC free article] [PubMed].
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. <https://doi.org/10.1016/j.antiviral.2020.104787>.
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.* 2020:105949 10.1016/j.ijantimicag.2020.105949 [PMC free article] [PubMed] [CrossRef] [Google Scholar]].
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> [Google Scholar].
7. Chan JF, 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.* 2020;395(10223):514–23.
8. Li J, et al. "Clinical features of familial clustering in patients infected with 2019 novel coronavirus in Wuhan, China" *Virus Research.* 2020;286:198043.
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.
10. Meyerowitz EA, et al. "Rethinking the role of hydroxychloroquine in the treatment of COVID-19." *FASEB J.* 2020;34(5):6027–37.
11. Savarino A, Tarek M. "Pharmacokinetic bases of the hydroxychloroquine response in COVID-19: implications for therapy and prevention." 2020.
12. Juurlink DN. Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. *Can Med Assoc J.* 2020;192(17):E450–3.
13. Accapezzato D, et al. Chloroquine enhances human CD8 + T cell responses against soluble antigens in vivo. *J Exp Med.* 2005;202(6):817–28.

14. Ye Q, et al. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect.* 2020;80(6):607–13.
15. Mahmudpour M, et al. "COVID-19 cytokine storm: The anger of inflammation." *Cytokine*, 2020, p. 155151.
16. Liu J, 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.
17. Schaper C. "A Mechanism of Action for Hydroxychloroquine and Azithromycin to Inhibit Coronavirus Disease COVID-19." 2020.
18. Chen J, et al. "COVID-19 infection: the China and Italy perspectives." *Cell Death & Disease*, vol. 11, no. 6, 2020.
19. Molina JM, 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*. 2020;50(4):384.
20. Laing R, et al. Ivermectin – Old Drug, New Tricks? *Trends in Parasitology*. 2017;33(6):463–72.
21. Caly L, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020;178:104787.
22. Serap ŞİMŞEKYAVUZ, Serhat ÜNAL. "Antiviral treatment of COVID-19." *TURKISH JOURNAL OF MEDICAL SCIENCES*, vol. 50, no. SI-1, 2020, pp. 611–619.
23. Rajter JC, et al. "ICON (Ivermectin in COvid Nineteen) study: Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19." 2020.
24. Momekov G. 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.
25. Schmith VD, et al. "The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19." 2020.
26. Holmes NE. and Patrick G. Charles. "Safety and Efficacy Review of Doxycycline. *Clinical Medicine Insights: Therapeutics*. 2009;1:471–82.
27. Abegunde AT, et al. "Doxycycline plus ivermectin versus ivermectin alone for treatment of patients with onchocerciasis." *Cochrane Database of Systematic Reviews*, no. 1, 2016, p. CD011146.
28. Sodhi M. and MahyarEtminan. "Therapeutic Potential for Tetracyclines in the Treatment of COVID-19." *Pharmacotherapy: The Journal of Human Pharmacology Drug Therapy*. 2020;40(5):487–8.
29. Conforti C, 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.
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> [Google Scholar].

Figures

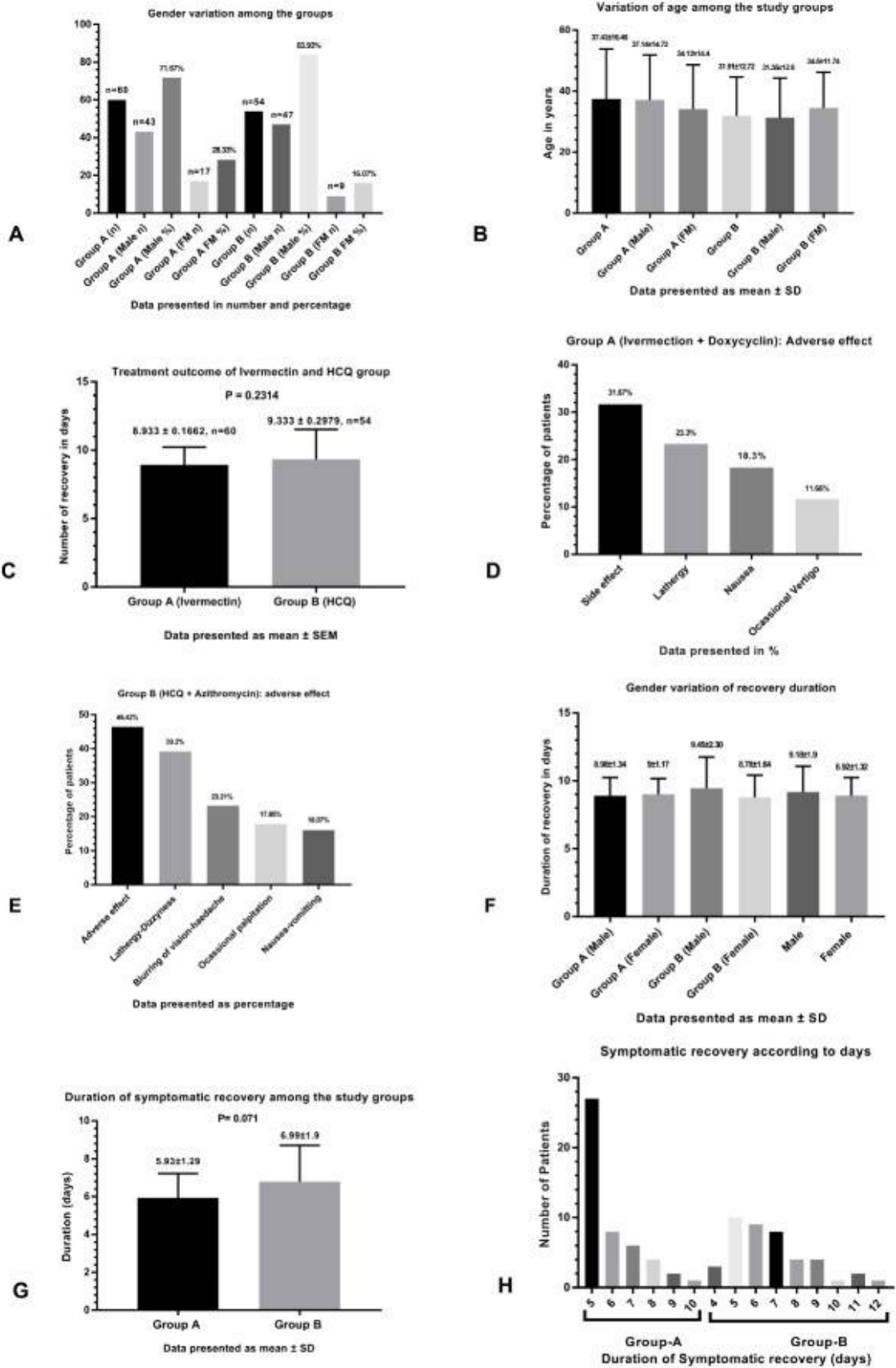


Figure 1

(A) Number of patients according to gender among the groups. (B) Gender variation of age among the study groups (data presented as mean \pm SD). (C) Recover duration of Ivermectin-Doxycycline and HCQ-Azithromycin group; note: the difference between the recovery duration among the groups 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.

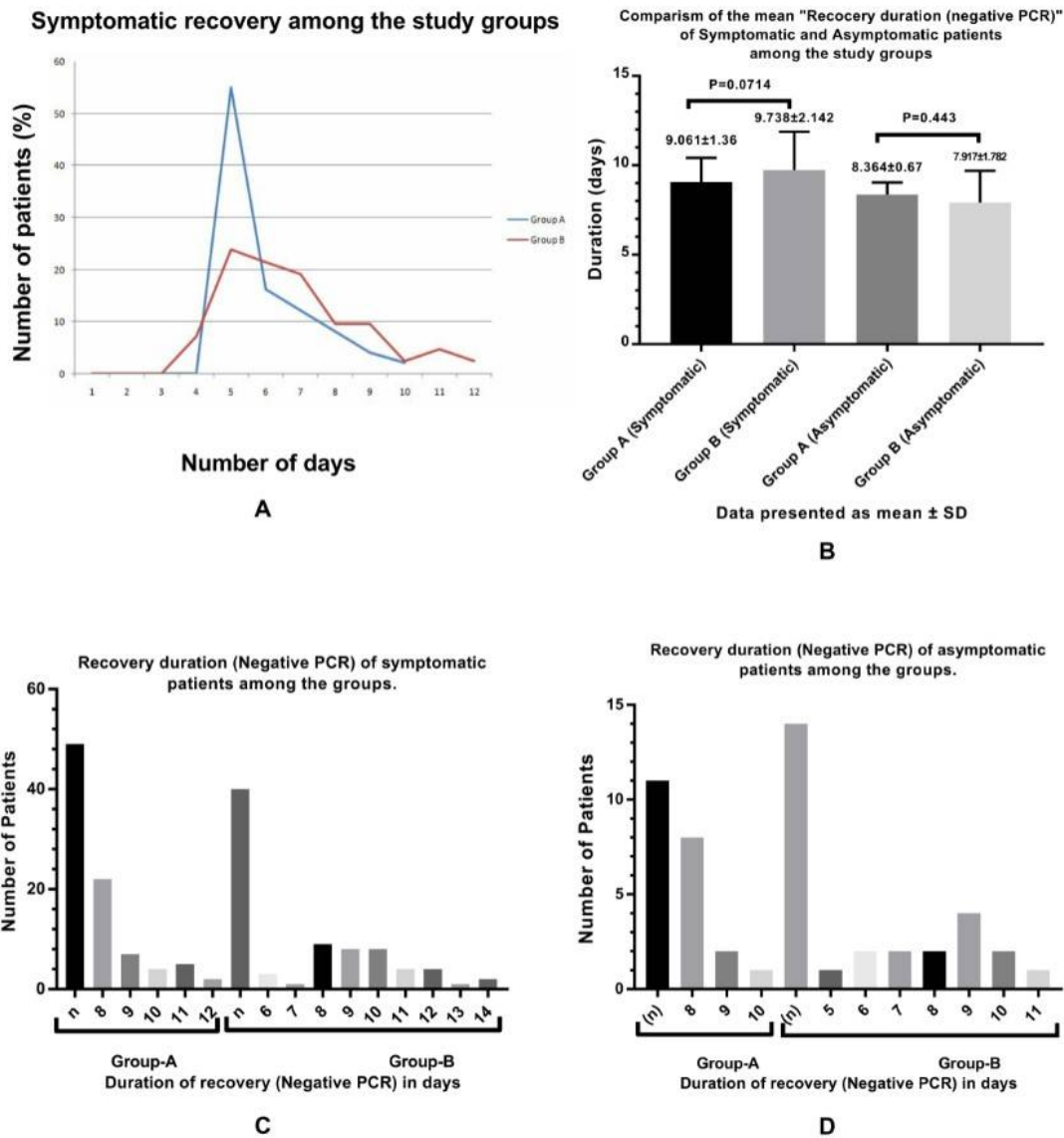


Figure 2

(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) Mean duration of recovery (beginning of the treatment to the negative PCR) of the patients with and without symptoms among Group 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 recovery duration of the asymptomatic patients. Most patients in Group A 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%)

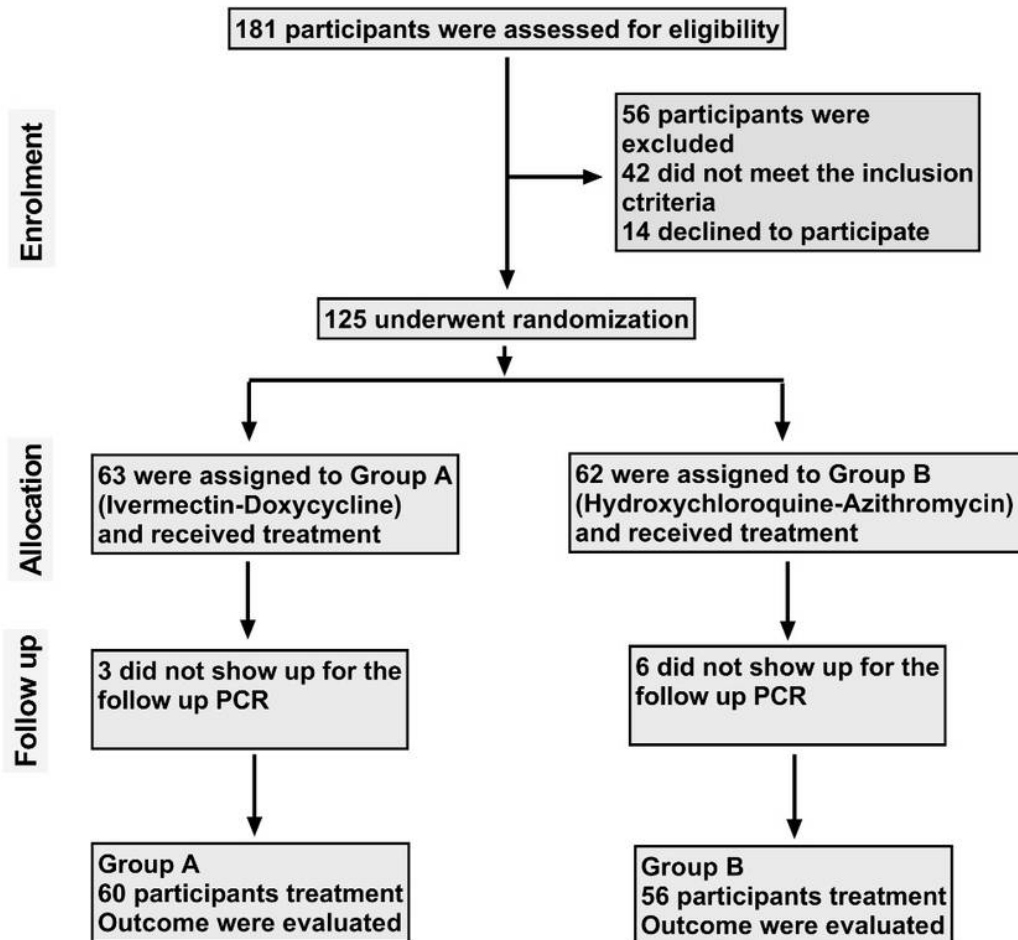


Figure 3

Flow diagram of randomization and treatment assignment of the participants.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supportingdata2.docx](#)
- [CONSORT2010checklist.docx](#)