Review Article

Effect of Hydroxychloroquine and Azithromycin Combination Use in COVID-19 Patients – An Umbrella Review

Kaushik Nag, Kaushik Tripura, Anjan Datta, Nabarun Karmakar[1], Manvi Singh[2], Meenu Singh[3], Kusum Singal[4], Pranita Pradhan[5]

Department of Community Medicine, Tripura Medical College and Dr. BRAM Teaching Hospital, Hapania, Agartala, Tripura, [1]Department of Community Medicine, Dr. B.C. Roy Multi-Speciality Medical Research Centre, IIT Kharagpur, Kharagpur, West Bengal, [2]Department of Pediatrics, Dr. B.R. Ambedkar State Institute of Medical Sciences, Mohali, Punjab, [3]Executive Director, AIIMS Rishikesh, Uttarakhand, [4]Department of Pediatrics, Advanced Pediatric Center, Post Graduate Institute of Medical Education and Research, Chandigarh, [5]Librarian, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Abstract

Background: Hydroxychloroquine and Azithromycin combination was used rampantly in management of COVID-19 patients in different countries. Present review was conducted to evaluate the efficacy of Hydroxychloroquine and Azithromycin combination compared to the control (standard care) and any adverse effect following this combination use in COVID-19 patients if any. **Material and Methods:** We included all the systematic review with or without meta-analysis reporting the effect of Hydroxychloroquine (HCQ) and Azithromycin (AZM) combination use in COVID-19 patient using three databases namely PubMed, medline, CINHAL, Web of Science from July 2020 till Jan 2022. **Results:** The systematic search strategy has identified 104 studies in total, after removal of duplicates only 4 systematic reviews were included in the qualitative synthesis. The various tools for assessing and reporting the data in the reviews were PRISMA, ROBINS-I, Robs2, AMSTAR, MASTER checklists. Mortality among the hydroxychloroquine with azithromycin combination group was significantly higher than among the Standard Care group. The duration of hospital stay in days was shorter in the Standard Care group in comparison with the hydroxychloroquine group or the hydroxychloroquine and azithromycin combination group. Of the 4 systematic reviews included, 3 had low risk of bias and one had unclear risk of bias using the ROBIS tool. Chloroquine or Hydroxychloroquine combination did not shorten the duration of hospital stay. **Conclusion:** Rampant use of Chloroquine or Hydroxychloroquine alone or with Azithromycin combination caused adverse effects like QT prolongation. Finally, there is no evidence to support use of either Hydroxychloroquine with or without Azithromycin, for the treatment of COVID-19.

Keywords: Azithromycin, COVID-19, hydroxychloroquine, patients, PRISMA, umbrella review

Introduction

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to be susceptible to *in vitro* exposure to hydroxychloroquine (HCQ). HCQ and azithromycin (AZM) combination has been found to be effective in early recovery of COVID-19 patients of different countries. We postulate that early administration of HCQ and AZM combination use can slow down progression of respiratory deterioration in COVID-19 patients admitted to intensive care units (ICUs). We will include systematic reviews which investigated the combination of these two drugs together to treat patients with severe COVID-19 with consideration of the risk benefit ratio in this umbrella review.[1] The *in vitro* and observational trial suggests their potential to limit viral replication and the damage to lungs as the most common reasons for ICU admission. Therefore, patients most likely to benefit from the treatment are those with severe, but early disease.[1] We want to evaluate the effect of HCQ and AZM combination on viral clearance as well as any adverse effects of this combination like QT prolongation on electrocardiogram.

P. Gautret in their study on use of hydroxychloroquine and azithromycin as a treatment of COVID-19 included

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Address for correspondence: Dr. Nabarun Karmakar, Assistant Professor Grade- I, Department of Community Medicine, Dr. B.C. Roy Multi-Speciality Medical Research Centre, IIT Kharagpur, Kharagpur-721302, India.
E-mail: drnabarunkarmakar@gmail.com

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hospitalized patients with an age more than 12 years and PCR-documented SARS-CoV-2 in nasopharyngeal samples at admission regardless of their clinical status.[2]

Hydroxychloroquine or chloroquine tends to increase the pH within intra-cellular vacuoles and also alter processes such as protein degradation by acidic hydrolases in the lysosome, assembly of macromolecules in the endosomes, and post-translation modification of proteins in the Golgi apparatus.[3]

Chang and his colleagues found that hydroxychloroquine activates the host anti-viral innate immunity.[4]

Azithromycin has well-known immunomodulating and antiviral properties. Azithromycin has been found effective in management of acute respiratory distress syndrome and against Middle-East respiratory syndrome (MERS).[5]

Azithromycin acted as an acidotropic lipophilic weak base to change the pH of endosomes and the trans-Golgi network, which further led to *in vitro* effects on intra-cellular organelles, similar to hydroxychloroquine. This drug has a role in the management of COVID-19 patients.[3]

A few studies had been conducted to assess the risk of QT prolongation and fatal arrhythmias on concomitant use of azithromycin and hydroxychloroquine, especially in patients with malaria. Chloroquine alone produced a marked increase in the duration of action potential and in contrast to azithromycin.[6]

In 2012, Pfizer conducted a randomized, placebo-controlled, parallel study on azithromycin and hydroxychloroquine combination use to protect pregnant patients against malaria and sexually transmitted infections. The study revealed simultaneous administration of chloroquine with azithromycin increased the QTc interval by 5 ms, 7 ms, and 9 ms, respectively.[7] A few studies have tested the combination of azithromycin–chloroquine or hydroxychloroquine in patients with malaria, with no reports of cardiovascular death.[8] Presently, this combination of hydroxychloroquine and azithromycin has been tried in management of COVID-19 patients in various countries. In this background, researchers want to evaluate the efficacy of hydroxychloroquine and azithromycin combination compared to the either hydroxychloroquine or azithromycin alone or any other standard of care treatment and any adverse effect following this combination use in COVID-19 patients.

Methodology

The present review was conducted in accordance with the PRISMA guidelines and registered in PROSPERO under reference no CRD42020206451 including all the systematic reviews with or without meta-analysis reporting the effect of hydroxychloroquine and azithromycin combination use in COVID-19 patient.[9] We included systematic reviews containing any of these studies, randomized controlled trials, non-randomized controlled trials, case controls and observational studies, cohorts, and cross-sectional studies. Study participants were confirmed COVID-19-positive patients getting hydroxychloroquine and azithromycin combination treatment irrespective of their age and severity. The comparator group was either hydroxychloroquine or azithromycin alone or any other standard of care treatment. The outcomes assessed were viral clearance measured by reverse transcriptase polymerase chain reaction (RT-PCR), any adverse effect following this combination (safety issue), and death due to cardiac disease, respiratory disease, sepsis, multi-organ dysfunction syndrome (MODS), or any other cause. Only English literature was searched from 2019 to January 2022 using similar inclusion criteria.

Search strategy

Extensive search was done using three databases, PubMed medline, CINHAL, and Web of Science, till January 2022. The search strategy used for Pubmed was as (((((((((covid 19) OR (“COVID-19” [Supplementary Concept] OR “severe acute respiratory syndrome coronavirus 2” [Supplementary Concept])) OR (((((((2019-nCoV) OR Wuhan coronavirus) OR SARS-CoV-2) OR 2019 novel coronavirus) OR COVID-19 virus) OR coronavirus disease 2019 virus) OR Wuhan seafood market pneumonia virus) OR COVID19 virus)))) AND (((((hydroxychloroquine) OR ((“Hydroxychloroquine/administration and dosage”[Mesh] OR “Hydroxychloroquine/adverse effects”[Mesh] OR “Hydroxychloroquine/therapeutic use”[Mesh]))))) OR ((((((((((((((((((Plaquenil) OR Oxychlorochin) OR Oxychloroquine) OR Hydroxychloroquine Sulfate) OR Hydroxychloroquine Sulfate (1:1) Salt) OR Aminoquinolines) OR Chlorochin) OR Chingamin) OR Khingamin) OR Nivaquine) OR Chloroquine Sulfate) OR Sulfate, Chloroquine) OR Chloroquine Sulphate) OR Sulphate, Chloroquine) OR Aralen) OR Arequin) OR Arechine) OR Chloroquine)))))) AND (((Azithromycin) OR (“Azithromycin”[Mesh])) OR (Sumamed OR Toraseptol OR Vinzam OR CP-62993 OR CP 62993 OR CP62993 OR Zithromax OR Azitrocin OR Azadose OR Ultreon OR Zitromax OR Azithromycin Dihydrate OR Dihydrate, Azithromycin OR Azithromycin Monohydrate OR Monohydrate, Azithromycin OR Goxal OR Zentavion))) AND (systematic review). The other two databases CINHAL and WoS were also searched using the same search terms. Two authors independently screened the abstracts and titles to potentially relevant studies for inclusion. Full text of four systematic reviews was retrieved to determine the eligibility of the study. The third author was contacted to resolve the disagreement for inclusion of the studies.

Data extraction and data synthesis

The systematic search strategy has identified 104 studies, and a total of 77 records were found after duplicate removal. Out of 77 articles, 73 articles were excluded as they do not meet eligibility criteria. Only four systematic reviews were included fulfilling the inclusion criteria of the present review [Figure 1]. Data were extracted by two reviewers using a pre-standardized data extraction form. Any discrepancies were resolved through

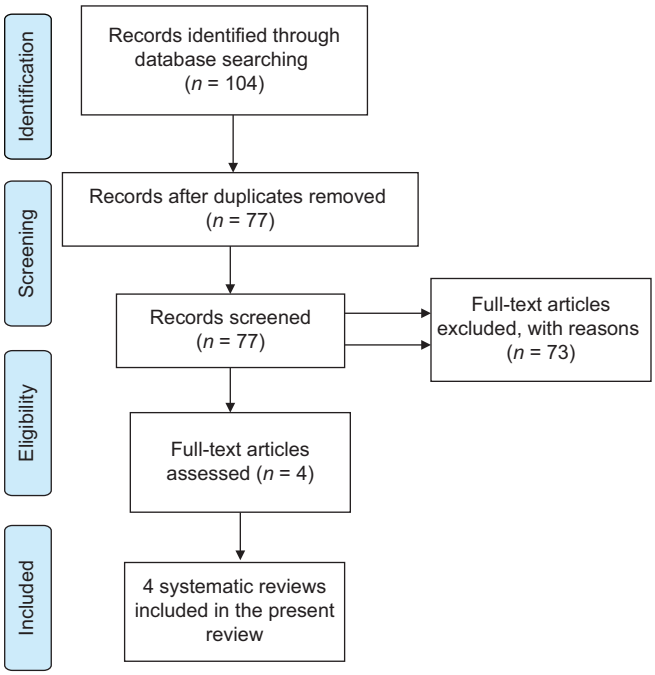

Figure 1: PRISMA flow chart

discussion with the third author. All the four included studies were critically reviewed at every stage of data extraction, study appraisal, and data synthesis. Data extraction was done using the author's details, publication year, region of study, number of study participants, number of studies included in systematic reviews, study designs of the included studies, heterogeneity, guidelines followed in systematic review, and outcome details. Quality assessment of included studies was done by using The Jadad scale, ROBINS-I tool, and Newcastle-Ottawa Scale (NOS) checklists.

Results

Four systematic reviews were included in the qualitative synthesis. The characteristic of the included reviews is given in Table 1. The various tools for assessing and reporting the data in the reviews were PRISMA, ROBINS-I, Robs2, AMSTAR, and MASTER checklists.

Ghazy RM *et al.* identified 14 studies from online databases through June 2020. The studies included in the meta-analysis were three randomized control trials (RCTs), two non-randomized control trials (non-RCT), three case–control studies, and six retro or prospective cohort studies. This systematic review and meta-analysis aimed to assess mortality rate, duration of hospital stay, need for mechanical ventilation (MV), virologic cure rate (VQR), time to a negative viral polymerase chain reaction (PCR), radiological progression, experiencing drug side effects, and clinical worsening. Mortality was not different between the standard care (SC) group and HCQ groups. However, mortality among the hydroxychloroquine and azithromycin combination group was significantly higher compared to the standard care group. The duration of hospital stay in days was shorter in the standard care group in comparison to hydroxychloroquine or the hydroxychloroquine and azithromycin combination group. The overall virologic cure rate at days 4, 10, and 14 among patients exposed to HCQ did not differ significantly from the Standard Care group. Side effects were more reported in the HCQ group than in the standard care group. Radiological improvement and clinical worsening were not statistically different between hydroxychloroquine and standard care groups, respectively. Risk of bias was low in this systematic review using the ROBINS tool [Table 2].[10]

Chi G *et al.* included a total of 10 randomized controlled trials in their network meta-analysis of randomized controlled trials from inception to March 7, 2021. They included published RCTs that investigated the efficacy of azithromycin (AZ) or hydroxychloroquine (HCQ) or the combination of azithromycin and hydroxychloroquine among hospitalized patients with COVID-19 infection. The outcomes of interest were all-cause mortality and the use of mechanical ventilation. There was no significant effect on mortality associated with hydroxychloroquine and azithromycin combination groups, azithromycin alone, or hydroxychloroquine alone. Evidence from RCTs suggests that azithromycin with or without hydroxychloroquine has no significant effect on the mortality or mechanical ventilation rates in hospitalized patients with COVID-19. Risk of bias was unclear in this systematic review using the ROBINS tool [Table 2].[11]

Mittal N *et al.* aimed to evaluate efficacy and safety of hydroxychloroquine (HCQ) and chloroquine (CQ) for the role in COVID-19 management in their systematic review and meta-analysis till November 2020. They included both observational and interventional clinical studies comparing efficacy of chloroquine or hydroxychloroquine combination to standard management with other drugs like azithromycin for COVID-19 patients. Out of total 903 studies, 19 studies were included in synthesis of meta-analysis. There was no difference in unadjusted mortality rate with HCQ/CQ alone versus control although higher probability of death was observed when combined with azithromycin. Chloroquine or hydroxychloroquine treatment was associated with significantly increased rates of virological cure and radiological cure compared to the control group. Judicious and monitored use of chloroquine or hydroxychloroquine for treatment of COVID-19 patients was recommended in low- to middle-income countries with emphasis on no mortality benefit. Risk of bias was low in this systematic review using the ROBINS tool [Table 2].[12]

Fiolet T *et al.* compared the mortality rate between patients treated with chloroquine or hydroxychloroquine with or without azithromycin and patients on standard-of-care treatment among patients 18 years old confirmed COVID-19 patients. Out of 839 articles, 29 articles were included, three were randomized controlled trials, one was a non-randomized trial, and 25 were observational studies. Hydroxychloroquine was not significantly associated with mortality: the pooled relative risk (RR) was 0.83 for all studies and RR = 1.09 for randomized

Table 1: Characteristics and Results of included Reviews

Year	Authors	Type of population	Number of studies included	Study design	Number of subjects	Results	Heterogeneity	Reporting guidelines followed
2020	Ghazy RM *et al.*[10]	Recruited patients with confirmed SARS-COV-2 virus, No restriction regarding country, race, gender, or age.	14	Fourteen studies were included in the meta-analysis: 3 RCTs, 2 non-RCTs, 3 case–control studies, and 6 retro or prospective cohort studies.	11,394	Mortality was not different between the standard care (SC) and HCQ groups (RR=0.99, 95% CI 0.61–1.59). Mortality among the HCQ+AZM was significantly higher than among the SC (RR=1.8, 95% CI 1.19–2.27).	I^2=82% I^2=70% I^2=92% I^2=81%	PRISMA, Cochran risk assessment tool, Jadad, ROBINS-I, and NOS checklists.
2021	Chi G *et al.*[11]	Hospitalized patients with COVID-19 infection	10	A total of 10 RCTs were included in the final analysis.		No significant effect on mortality associated with AZ plus HCQ OR=0.562 [0.168–1.887], AZ alone (OR=0.965 [0.865–1.077]), or HCQ alone (OR=1.122 [0.995–1.266]; P=0.06).	No heterogeneity was identified (Cochran's Q=1.68; P=0.95; τ^2=0; I^2=0% [95% CI: 0%–0%]).	Revised Cochrane risk of bias tool for randomized trials (RoB 2).
2021	Mittal N[11]	SARS-CoV-2-infected patients	19	Observational (prospective/ retrospective, case-control/ cohort) and interventional clinical studies (RCTs)	12810	For HCQ/CQ + AZ combination, there was a statistically significant rise in unadjusted mortality rate compared to control, [unadjusted OR=1.84 (1.47–2.31), P<0.00001]. HCQ/CQ + AZ resulted in statistically significant increased odds of disease progression compared to control [OR=1.74 (1.36– 2.22), P<0.0001]	I^2=73%; I^2=81%	PRISMA statement and "Cochrane guidelines for Systematic Reviews of Interventions".
2021	Fiolet T[13]	Patients with confirmed COVID-19	29	Among the 29 articles, three were RCTs, one was a non-randomized trial, and 25 were observational studies, including 11 with a critical risk of bias and 14 with a serious or moderate risk of bias.	32943	Hydroxychloroquine was not significantly associated with mortality: pooled relative risk (RR) 0.83 (95% CI 0.65-1.06, n=17 studies) for all studies and RR 1.09 (95% CI 0.97-1.24, n=3 studies) for RCTs. Hydroxychloroquine with azithromycin were associated with an increased mortality (RR 1.27; 95% CI 1.04-1.54, n=7 studies).	I^2=38%	ROBIN-I and Rob2 Tool

Table 2: Risk of bias assessment of the included reviews

Review	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk of bias in the review
Ramy Mohamed Ghazy *et al*.[10]	Low	Low	Low	Low	Low
Gerald Chi *et al*.[11]	Low	Low	Unclear	Unclear	Unclear
Niti Mittal *et al*.[12]	Low	Low	Low	Low	Low
Thibault Fiolet *et al*.[13]	Low	Low	Low	Low	Low

controlled trials. Hydroxychloroquine with azithromycin combination use was associated with an increased mortality among COVID-19 patients. Risk of bias was low in this systematic review using the ROBINS tool [Table 2].[13]

Discussion

Summary of the findings

Hydroxychloroquine with azithromycin combination did not show any benefit in terms of virological cure; rather, mortality was increased with addition of azithromycin. The need for mechanical ventilation was not improved by chloroquine or hydroxychloroquine alone or in combination with azithromycin, and there was no role of this combination in prevention of radiological progression.[10] Chloroquine or its derivative, hydroxychloroquine, combined with or without azithromycin did not change the mortality or mechanical ventilation rates in COVID-19-hospitalized patients.[11] Random use of CQ/HCQ alone or with azithromycin combination caused arrhythmias like QT prolongation in high-risk population for SARS-CoV-2.[12] Significant efficacy of hydroxychloroquine alone for the treatment of people with COVID-19 was not found in different studies; rather, the combination of hydroxychloroquine and azithromycin increased the risk of mortality.[13] Judicious and monitored use of chloroquine or hydroxychloroquine in treatment of COVID-19 infection caused by COVID-19 patients was recommended in low- to middle-income countries with emphasis on lack of mortality benefits.[12]

Chivese T *et al.* in their meta-review investigated the efficacy and safety of CQ and HCQ with or without azithromycin to treat COVID-19 till June 3, 2020. The main outcomes of the meta-review were mortality, the need for intensive care services, disease exacerbation, viral clearance, and occurrence of adverse events. The meta-review showed that use of hydroxychloroquine with or without azithromycin for treating COVID-19 did not show any benefit in terms of reducing mortality or the severe complications of COVID-19, including transfer to the ICU, intubation, mechanical ventilation, virological cure, or disease exacerbation. The combination of these drugs was associated with a higher risk of adverse effects like diarrhea, nausea, and vomiting. Their findings did not support any future use of either chloroquine or hydroxychloroquine, with or without azithromycin, for the treatment of COVID-19.[14]

Shahsavarinia K in their review also found no benefit for patients with COVID-19 who received hydroxychloroquine or chloroquine alone or in combination with azithromycin during the current pandemic. They also found increased risk of developing life-threatening arrhythmias, such as Torsa de pointes (TdP), ventricular tachycardia (VT), and sudden cardiac arrest, especially in critically ill patients.[15]

This umbrella review had a few limitations like inclusion of different observational studies used in systematic reviews and possibility of selection bias in the included observational studies, non-randomized control trials. Strengths of this review include the inclusion of data of individuals with confirmed COVID-19 only.

Conclusion

Use of hydroxychloroquine with or without azithromycin increased mortality. Chloroquine or hydroxychloroquine combination did not shorten the duration of hospital stay and also no significant benefit in terms of radiological progression, transfer to the ICU, mechanical ventilation, virological cure, or disease exacerbation. Rampant use of chloroquine or hydroxychloroquine alone or with azithromycin combination caused adverse effects like diarrhea, nausea, vomiting, and QT prolongation. Finally, there is no evidence to support any future use of hydroxychloroquine with or without azithromycin for the treatment of COVID-19. Therefore, we recommend against hydroxychloroquine and azithromycin combination use for treatment of COVID-19 patients due to the significant risk of cardiac adverse events with the absence of any significant mortality benefit.

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Conflicts of interest

There are no conflicts of interest.

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