



Clinical Efficacy of Hydroxychloroquine or Chloroquine in Patients with COVID-19: An Umbrella Review

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Article Info

Article History:

Received: 18 July 2021

Accepted: 28 October 2021

ePublished: 29 October 2021

Keywords:

-Chloroquine

-COVID-19

-Hydroxychloroquine

-Mortality

Abstract

Background: Many of the known coronaviruses cause a wide range of respiratory infections in humans, and the novel coronavirus is no exception to this rule. Although no drug has yet been discovered to prevent or treat this disease, chloroquine (CQ) and hydroxychloroquine (HCQ) have been widely used in studies showing different results.

Methods: The present study is an umbrella study. The search was conducted for the articles published from January 2020 to November 2020 using the keywords (“COVID-19” OR “SARS-CoV-2” AND “Hydroxychloroquine” OR “Chloroquine” AND “Systematic Review” OR “Metanalysis”). This study was limited to human samples and systematic reviews with or without meta-analysis. The quality of the articles was also evaluated independently by two researchers.

Results: To evaluate the clinical efficacy of HCQ and CQ, a total of 176 papers and 643569 cases ranging from patients with mild pneumonia to intubated critically ill patients were evaluated. Finally, 8 studies were included.

Conclusion: There are conflicting results regarding HCQ or CQ efficacy and safety in the systematic reviews. More evidence is needed to confirm whether these drugs are useful in COVID-19 infection, and their usage as the standard care cannot be recommended based on the majority of the studies included in this umbrella review.

Introduction

Coronaviruses are a large family of viruses that can infect animals and humans. Many known coronaviruses cause a wide range of respiratory infections in humans, ranging from the common cold to more severe illnesses such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). In February 2020, the World Health Organization identified COVID-19 as the disease caused by the novel coronavirus. The virus that causes COVID-19 is known as the acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly known as nCoV-2019.^{1,2} Understanding of COVID-19 is progressing.

This emerging virus and the disease caused by it was unknown until its outbreak in December 2019 in Wuhan, China. Fever, fatigue, and dry cough are the most common symptoms of Covid-19. However, there may be other symptoms such as pain, nasal congestion, rhinorrhea, sore

throat, or diarrhea; these symptoms are usually mild at the beginning. While most of the patients improve without any treatment, one out of six patients with COVID-19 becomes seriously ill and develops pulmonary symptoms and complications. On the other hand, some infected people may not experience any symptoms and be just carriers of the disease. The disease is more likely to get worse and severe in the elderly and in patients with hypertension, cardiovascular disease, or diabetes. The disease can be transmitted through respiratory droplets being spread from the mouth and nose of an infected person while coughing, sneezing, talking, or exhaling.^{3,4}

Although some traditional and modern treatments may reduce or alleviate the symptoms of COVID-19 disease, no drug has yet been discovered to prevent or treat this disease. Glucocorticoids, Azithromycin, Remdesivir, Ropinavir/ritonavir combination therapy, Chloroquine

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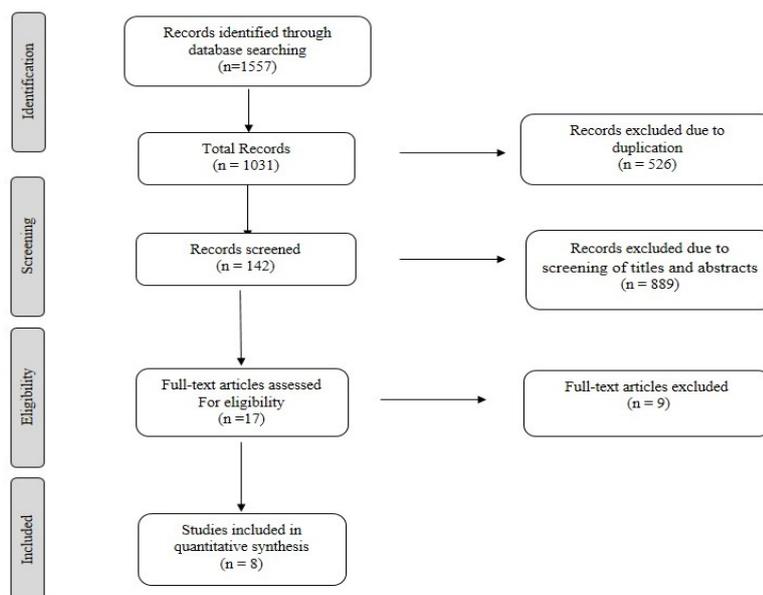


Figure 1. Search strategy and study selection process.

(CQ), Hydroxychloroquine (HCQ), Interferon beta, IL-6 inhibitor (Tocilizumab), and Favipiravir are some of the drugs being recently used for patients with COVID-19. CQ and HCQ are drugs that bind to DNA and interfere with protein synthesis to prevent and treat malaria in areas where malaria has been shown to be sensitive to their effects. They are also effective in the treatment of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) by acting on the immune system and reducing inflammation.^{5,6} In addition to anti-malarial and anti-inflammatory effects, these two drugs also have antiviral effects. Studies conducted especially in France show its impacts on COVID-19, but there are contradictory results of the effects of these two drugs in the treatment of COVID-19-induced pneumonia.^{1,7}

So, we decided to review the systematic review studies conducted in this field in order to reach a unity regarding its use in the treatment of COVID-19.

Methods

Search strategy and selection criteria

The present study is an umbrella study conducted at Tabriz University of Medical Sciences based on published articles that complied with the criteria of Preferred Reporting Items for Systematic Reviews (PRISMA) (Figure 1).

The search was conducted for the articles published from January 2020 to November 2020 using the keywords (“COVID-19” OR “SARS-CoV-2” AND “Hydroxychloroquine” OR “Chloroquine” AND “Systematic Review” OR “Meta- analysis”). PICO criteria included:

- Population: patients with COVID-19.
- Intervention: consumption of Hydroxychloroquine or Chloroquine.
- Comparison: no comparison.
- Outcome: drug effects.

Inclusion and exclusion criteria

This study was limited to only human samples and systematic reviews with or without meta-analysis were included (while laboratory studies were excluded). Other studies, including case reports, case series, cohorts, and letter, were excluded. Then, the titles and abstracts of the selected articles were reviewed independently by two researchers. In case of disagreement between the two researchers, it was assigned to an expert third person.

Extraction and evaluation quality of articles

Articles were entered into the study after reviewing the full-text in accordance with the inclusion criteria. The quality of the articles was also evaluated independently by two researchers.

The extracted variables included: name of the first author, country of study, study objectives, type of study, sample size, drug characteristics and doses, mechanism of action of the drug, drug side effects, primary outcome, total outcome, and recommendations.

Statistical analysis

Mean \pm SD was used to describe quantitative data, while frequency and percentage were used to describe qualitative data.

Results

To evaluate the clinical efficacy of CQ and HCQ on the treatment of COVID-19-induced pneumonia and their effect on mortality and disease progression in this group of patients, eight studies (including five systematic reviews and three systematic reviews with meta-analysis) were included. In these studies, most of the articles were clinical trials covering different countries, from the Far East to Australia. PubMed, EMBASE, Scopus, Web of Science, Cochrane, Proquest, and a number of local databases were

used to collect articles.

In this study, a total of 176 papers and 643569 cases ranging from patients with mild pneumonia to intubated critically ill patients were evaluated. The minimum and maximum duration of treatment were 3 to 90 days, respectively. The most common drugs used in combination with CQ and HCQ were azithromycin, corticosteroids, immunoglobulins, antiviral agents, antibacterial agents, vitamin C, vitamin D, and zinc. In the first two studies, the use of CQ or HCQ in the treatment of COVID-19 was recommended. In the 4th, 5th, 6th and 7th studies, using these two drugs has not been recommended at all. The 3rd and 8th studies need high quality and standard clinical trials and more samples. In this way, it can be judged either to use these two drugs in the treatment of patients with COVID-19 or not. And it has not been recommended to use these two drugs yet (Table 1).

Discussion

CQ and HCQ are 70-year-old drugs used to prevent and treat malaria in areas where malaria has been shown to be sensitive to its effects. These drugs are used orally, have a hepatic metabolism, their excretion is renal, and have several side effects, including gastrointestinal and cardiac side effects, headache, seizures, and visual disturbances (retinal damage). These drugs bind to DNA and interfere with protein synthesis, inhibit DNA and RNA polymerases, and reduce inflammation by affecting the immune system, and are thought to be involved in the treatment of SLE and RA by this mechanism. In addition to their anti-malarial effect, they also have antiviral effects, and recent studies have shown their impact on COVID-19. However, there is less evidence, and many clinical trials are required.⁸⁻¹⁴

The evaluation of these eight systematic reviews is as follows:

1-Cortegiani *et al.*¹ reported the results of 23 studies, including 2820 cases of COVID-19 pneumonia, as follows: Treatment period was seven to fourteen days which was accompanied by lopinavir/ritonavir. It reduces fever and improves respiratory symptoms including, a decrease in respiratory rate and an increase in SPO₂, which eventually accelerates the recovery time and reduces the time required to achieve negative Real-PCR results. It decreases the length of hospital stay, mortality rate, and other associated infections. It lowers serum levels of inflammatory factors, improves blood cell count (CBC), corrects coagulation factors, and accelerates the improvement of pulmonary imaging changes. This drug in standard doses can be very effective. It has high safety, low cost and is effective in treating severe infections in patients who need to be admitted to the ward or ICU or need oxygen therapy. To justify the clinical research on CQ in patients with COVID-19, there is rational, preclinical, and efficacy evidence as well as evidence of safety from long-term clinical use for other cases. However, its clinical use must either adhere to the Monitored Emergency Use of Unregistered and Investigational Interventions (MEURI)

framework or be ethically approved by the World Health Organization as a validated test.

2- Patil *et al.*² announced the results of 100 studies, including 590368 cases, as follows:

HCQ and CQ are effective in several studies (in vitro and clinical studies) in the treatment of mild to severe pneumonia caused by COVID-19. The use of this drug has also been suggested in China. Control Dutch Center of Disease recommends this drug in severe forms. The Italian society of infections & Tropical Disease recommends its use. Detailed information about safety, adverse effects, and dose of HCQ and CQ should be available to medical staff. Careful monitoring of adverse reactions, drug effects, toxicity, and toxicological mechanisms is required to assist clinical practice worldwide. In order to design a safe and effective protocol with the prevention of side effects, it is necessary to monitor the clinical results.

3- Rawaf *et al.*³ reported the results of 6 studies involving 16,818 patients with COVID-19 pneumonia as follows:

HCQ is more available than CQ, and its interaction with lopinavir/ritonavir is less. They reduce fever and cough, shorten the course of the disease, reduce the rate of intubation and mortality. They reduce the time required to achieve negative Real-PCR results, accelerate the improvement of lung imaging findings and shorten the course of the disease. They are effective in treating and controlling the exacerbation of pneumonia. HCQ and CQ, in combination with azithromycin, are more effective in curing the disease. HCQ has better results than patients treated with Lopinavir/Ritonavir. HCQ in combination with azithromycin has a better effect. The presence of broad-spectrum antibiotics in combination with HCQ acts better in the treatment of pneumonia. The combination of HCQ with darunavir/cobicistat is better than triple antibiotic therapy (levofloxacin, piperacillin, plus tazobactam). China uses CQ to prevent and treat COVID-19 pneumonia. Clinical outcomes were poor, and mortality rates were high. Understanding the effects of other diseases such as hypertension, diabetes, and obesity is effective in finding a cure for COVID-19. Future research should strictly adhere to standard and accurate guidelines for RCTs and cohort studies to provide unbiased information about these drugs.

4 - Patel *et al.*⁴ reported the results of 6 studies, including 3973 cases, as follows:

Sensitivity analysis is based on participants' characteristics, severity status, and short-term prevention. Summary of the meta-analysis of six observational studies shows that the use of HCQ does not reduce the mortality rate in COVID-19 patients. The use of HCQ has no benefit in reducing mortality rates in patients receiving standard therapies. The risk of mortality was significantly higher in those receiving HCQ, especially when azithromycin was added. It emphasizes the need for active monitoring of mortality data and the risk-benefit ratio of randomized studies regarding the effect of HCQ in COVID-19 patients. Future studies should have more follow-up of mortality data. This systematic review was performed based on

Table 1. Characteristics of studies.

No.	Database	Aim	Type-Total	Type-Individual	Exclude	Studies	Samples	Cases	Doses of HCQ and CQ	Treatment duration	Other accompanying medications
1	PubMed, EMBASE, and three trial Registries, Chinese Clinical Trial Registry, Clinicaltrials.gov and the International Clinical Trials Registry Platform (WHO ICTRP) to identify ongoing trials	Summary of efficacy and safety of chloroquine and hydroxychloroquine in the treatment of COVID-19 pneumonia + In vitro description	Systematic review	RCT (23)+ one narrative letter, one in-vitro study, one editorial, expert consensus paper, two national guideline documents		23	2820	Pneumonia (Mild ,common, Sever)	Chloroquine Phosphate: Respiratory Chloroquine Phosphate: The first dose is 1 gram for 2 days (2 tablets daily - each tablet is 500 mg) then 0.5 grams for 12 days Hydroxychloroquine sulfate tablets: 0.2 g twice daily for 14 days Hydroxychloroquine sulfate tablets: 6 tablets on the first day (each tablet is 200 mg) + 6 tablets in the next 6 hours, 2 tablets daily from day 2 to day 10	7-14 Days	Lopinavir/Ritonavir
2	-	Evaluation of mechanism of action, efficacy and safety of chloroquine and hydroxychloroquine used as a treatment for COVID-19 infection	Systematic review	-	-	103	590368		CQ (loading dose 600 mg as base CQ followed by 300 mg after 12 hours and 300 mg twice daily; total duration of treatment: 5 days). HCQ (loading dose 400 mg twice daily and then 200 mg twice daily; total treatment duration 5 days)	5-90 days	Vit C, Vit D, Zinc, Lopinavir, Losartan, ascorbic acid, azithromycin, UNIKINON, Lopinavir/ritonavir, baricitinib, sarilumab, Remdesivir, interferon b 1A, Oseltamivir, sofosbuvir/ ledipasvir, interferon B 1b, Sofosbuvir/ ledipasvir, lopinavir/ritonavir, Ivermectine, bromhexine, favipiravir, Remdesivir, Nitazoxanide, glucose tablet, rabeprazole, favipiravir, Camostat mesilate, imatinib

Table 1 Continued.

3	MEDLINE, EMBASE, Global Health, and HMIC	Our goal is to provide evidence for clinical decision for the treatment of COVID-19		Case report (1) Systematic review and meta-analysis (1) Cohort (1) Systematic review (1) RCT (2)		6 16818	Any type of study but mostly pneumonia	Oral Hydroxychloroquine sulfate 200 mg to 600 mg daily for 10 days 500 mg Chloroquine twice daily in mild to severe pneumonia Oral hydroxychloroquine sulfate 200 mg, three times a day for 10 days + azithromycin 500 mg on the first day and then 250 mg for 4 days	At least 3 days	Azithromycin Corticosteroids Immunoglobulin Ceftriaxone Oxygen therapy, antiviral agents, Antibacterial agents, darunavir / cobicistat
4	PubMed, Google Scholar, medrxiv.org, biorxiv.org, mediterranean-infection.com/pre-prints-ihu and CNKI	Summary of the effects of hydroxychloroquine on mortality in patients with COVID-19	Systematic review and meta-analysis	1 prospective, 5 retrospective studies	non-comparative, in-vitro and animal studies	6 3973	asymptomatic, Upper respiratory tract infection, lower respiratory tract infection, intubation	Hydroxychloroquine varied from 1 to 3 tablets daily, with a total of 20 to 811 tablets taken during the course. Or hydroxychloroquine + azithromycin tablets	7 days to more than 27 days	Azithromycin
5	PubMed, EMBASE, Scopus, Web of Science, Cochrane Clinical Trial Registry and Chinese Clinical Trials Registry for trials	Evidence from human clinical trials for the antiviral effects of hydroxychloroquine and chloroquine	Systematic review	RCT	Animal or laboratory experiments were excluded from the study	6 250	-	200 to 1200 mg	3 to 21 days	Lopinavir/Ritonavir
6	PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Science, Technology Journal Database (VIP), WANFANG DATA, clinical trial registry platforms, websites MedRxiv and BioRxiv	Identifying the effectiveness and safety of the drug	Systematic review	RCT		4 141	Mild to severe	200 to 2000 mg	2 to 10 days	rbidol (80% patients) + Interferon-α spray Azithromycin
7	PubMed - MEDLINE, EMBASE-OVID, Scopus, Web of Science, the Cochrane Library, medRxiv.org,	Assessed RCTs evaluating HCQ effects vs. controls on clinical and safety outcomes in hospitalized COVID-19 patients.	Systematic Review and Meta-Analysis	RCT		13 18,540	hospitalized COVID-19 patients with pneumonia	Total dose of hydroxychloroquine in the RCTs varied between 2000 and 12,400 mg	5 to 30 days	Standard treatment only (O2 therapy, antiviral agents, antibacterial agents and immunoglobulin, with or without corticosteroids)& placebo

Table 1 Continued.

<p>∞ PubMed, Google Scholar, and medRxiv</p>	<p>is the use of CQ or HCQ effective and safe in reducing mortality and improving the clinical course, fever remission, and virologic clearance as compared with no CQ/HCQ</p>	<p>Systematic Review and Meta-analysis</p>	<p>12 were cohort studies which had a control group and 3 RCTs.</p>	<p>15 10,659</p> <p>patients ranged from asymptomatic to severe and critically ill COVID-19</p>	<p>600 mg twice daily</p>	<p>from day 6 to day 28</p> <p>the use of other supportive care interventions including corticosteroids, antiviral drugs, tocilizumab, and IVIG</p>
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observational studies. This systematic review was performed on trials with small sample sizes. Virology and clinical improvement were not studied. In terms of age, the presence of other underlying diseases and co-morbidities, the severity of the disease, co-interventions, and supportive care were not matched between the groups.

5- Rodrigo *et al.*⁵ reported the results of 6 studies, including 250 cases of COVID-19 associated pneumonia, as follows:

HCQ or CQ reduces fever and cough; it relieves symptoms and viremia by day 28. It reduces the length of hospital stay and mortality rate. There was no statistically significant effect in terms of clearance of viremia by day 7, fever clearance time, and time to discharge. There was a statistically significant effect in terms of viremia clearance by day 6. Significant faster cough relief and fever recovery were observed. The difference in the time to aviremia, the proportion of aviremic patients, and symptom resolution by day 28 were not statistically significant. The difference in clearance of viremia by day 14, faster radiological resolution, and reduced hospital stay were not statistically significant. In the high-dose group, mortality by day 13 was significantly higher. More evidence is needed to confirm whether HCQ or CQ is useful in COVID-19 infection. The sample size should be calculated according to the standards. Double-blind trials should be designed. Clinical trials with larger sample sizes, proper randomization, blindness, and age-matching between the groups should be designed.

6- Zhong *et al.*⁶ reported the results of 4 studies involving 141 patients with mild to severe COVID-19 pneumonia as follows:

It causes rapid viral clearance and negative PCR results, lowers CRP levels and duration of lymphopenia, and reduces side effects. It accelerates the improvement in chest radiographic results. It reduces fever, duration of fever, cough, and recovery time of symptoms. It reduces the incidence of ARDS, intubation, and mechanical ventilation. HCQ improves chest radiographic results. It shortens recovery time, body temperature, and cough. HCQ decreases CRP and lymphopenia more rapidly. It causes faster clearance of virus

and azithromycin facilitates its viral elimination effect. It improves the symptoms. HCQ significantly reduced recovery time compared to the control group. The results of HCQ in eradicating SARS-CoV-2 in COVID-19 patients are unfortunately inconsistent, so it cannot be recommended as standard care. We have to wait for large-scale randomized clinical trials with specific endpoints and target populations to confirm the HCQ effects in COVID-19. Larger scale RCTs are seriously needed. Patients with severe COVID-19 should be evaluated instead of patients with mild or moderate symptoms. Confounding effects such as antiviral or other agents used in the control group should be considered and adjusted. The initial dose and timing of the treatment should be standardized; for example anti-coronavirus drugs should be used in the early stages. Specific endpoints such as virus eradication or viral loading shedding, mortality, and clinical outcomes (including improvement in symptoms, radiographic outcomes, intubation rate, and ICU admission) should be estimated. **7- Hernandez *et al.*⁷** reported the results of 13 studies, including 18540 cases of COVID-19 pneumonia, as follows:

Treatment period only was 5 to 30 days with Standard treatment. HCQ non-significantly increased all-cause mortality by 7% at day 14 in seven RCTs and by 8% at day 30 in seven RCTs. HCQ did not reduce the need for mechanical ventilation at 14 or 30 days, high-flow nasal cannula, or non-invasive ventilation at 14 days. HCQ do not use in hospitalized patients with COVID-19 because the RCTs completed to date did not demonstrate a favorable balance of benefits to harm. Hydroxychloroquine should not be recommended as a treatment for hospitalized COVID-19 patients.

8- Elavarasi *et al.*⁸ reported the results of 15 studies involving 10659 cases of COVID-19 pneumonia as follows:

Treatment period was 6 to 28 days with the use of other supportive care (corticosteroids, tocilizumab, IVIG). The evidence is shown to be of very low quality for the outcome mortality, clinical deterioration/ ARDS/ need for mechanical ventilation, virologic

clearance (cohort studies), time to fever resolution (cohort studies), and ECG abnormalities. There is very low-quality evidence to suggest that neither CQ nor HCQ improves mortality or clinical course, nor does it hasten virologic clearance in the treatment of COVID-19. RCT studies of adequate sample size with high-quality methodology are needed to provide definite answers to the efficacy and safety of CQ and HCQ in COVID-19.

Conclusion

Although HCQ or CQ in standard doses has been shown to be safe and effective in treating severe COVID-19 infection in some studies, others have not shown its efficacy for treating hospitalized COVID-19 patients and even serious adverse events have been reported. More evidence is needed to confirm whether these drugs are useful in COVID-19 infection, and their usage as the standard care cannot be recommended based on the majority of the studies included in this umbrella review.

Ethical Issues

This manuscript was approved in the ethics committee of Tabriz University of Medical Sciences. (IR.TBZMED.REC.1399.919).

Author Contributions

Study Concept: HS. Study design: MA and LV. Systematic search: KS. Critical reviews: SS, AM, and HS. Data extraction: MG and SS. Data analysis: MG. Writing the manuscript: KS. All authors have read and approved the final version of manuscript.

Acknowledgements

This research was extracted from the thesis for a MD by Mahta Ahmadpour entitled, "Hydroxychloroquine or chloroquine in covid-19: Systematic review of systematic reviews". We would like to appreciate of the cooperation of Clinical Research Development Unit, Imam Reza General Hospital, Tabriz, Iran in conducting of this research.

Conflict of Interest

The authors report no conflicts of interest.

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