Hydroxychloroquine and Chloroquine in Prophylaxis and Treatment of COVID-19: What Is Known?

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The corona virus disease-19 (COVID-19) pandemic has affected the entire world causing huge economic losses and considerable morbidity and mortality. Considering the explosive growth of the pandemic repurposing existing medicines may be cost-effective and may be approved for use in COVID-19 faster. Researchers and medical practitioners worldwide have explored the use of chloroquine and hydroxychloroquine, in few occasions combined with the macrolide antibiotic azithromycin, for COVID-19 treatment. These two drugs are economic and easily available, and hence gained attention as a potential option for COVID-19 management. As per the available evidence, the outcomes of treatments with these medications are conflicting from both the efficacy and safety (predominantly cardiac related) perspectives. Currently, multiple studies are underway to test the safety and efficacy of these medications and more results are expected in the near future. The retina, the endocrine system (with risk of hypoglycemia), the musculoskeletal system, the hematological system, and the neurological system may also be affected. The use of these drugs is contraindiated in patients with arrhythmias, known hypersensitivity, and in patients on amiodarone. In addition to the published literature, personal communication with doctors treating COVID-19 patients seems to suggest the drugs may be effective in reducing symptoms and hastening clinical recovery. The literature evidence is still equivocal and further results are awaited. There has been recent controversy including retraction of articles published in prestigious journals about these medicines. Their low cost, long history of use, and easy availability are positive factors with regard to use of these drugs in COVID-19.

Keywords: Chloroquine, coronavirus, COVID-19, efficacy, hydroxychloroquine, safety

BACKGROUND

The Coronavirus Disease-2019 (COVID-19) outbreak due to novel coronavirus (2019-nCoV) started in the Chinese province of Hubei in December 2019 and soon progressed across the borders of provinces, countries, and continents,[1] The causative agent shows similarity to the virus causing severe acute respiratory syndrome (SARS) and was named as SARS Corona Virus-2 (SARS CoV-2). Just over 2 months from the reports of the first case in Wuhan, China, the widespread and increasing number of individuals infected forced the World Health Organization (WHO) to declare COVID-19 a pandemic on March 11, 2020. As of August 15, 2020, the total number of individuals infected by COVID-19 is over 21 million with a mortality of over 0.75 million in 216 countries.[2] Beyond these

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direct effects, COVID-19 has led to multiple problems such as unemployment, travel restrictions, and economic losses. Early intervention has been suggested to improve mortality in patients with COVID-19 infection.\(^9\) Considering the urgency of the situation and the lack of definitive treatment, attention has been focused on repurposing existing medicines against the pandemic. Two widely available and used medicines, chloroquine phosphate (CQ) and hydroxychloroquine (HCQ) have received a lot of attention.

There has also been controversy about the evidence and publications dealing with the possible role of CQ and HCQ in COVID-19. Two recent articles dealing with the efficacy and toxicity of these medicines have been retracted.\(^6,5\) A recent article mentions that there is a strong rationale in using CQ to treat infections caused by intracellular organisms.\(^6\) However, an article published in the BMJ mentions that the evidence for these drugs is lacking and the use of these drugs is premature and may be potentially harmful.\(^7\) The authors call for better, properly powered clinical trials of these drugs. A systematic search and narrative review mention that these drugs have shown initial promise in clinical studies and should be fast tracked for further research.\(^8\) The authors mention minimal risk on use, easy availability, cost-effectiveness, and long experience of use in other diseases as important reasons to prefer these drugs especially in developing countries.

A recent letter to the editor suggests that while awaiting data from large, adequately powered clinical trials to evaluate these drugs, they can be used cautiously with initial clinical evaluation and ECG monitoring in hospitalized patients.\(^9\) A recent rapid systematic review of clinical trials mentions that there is not enough data at the time the study was published to support the routine use of CQ and HCQ in COVID-19.\(^10\) The situation is rapidly changing and many large-scale clinical trials are underway. Most patients with COVID-19 have a mild or asymptomatic infection and considering the risk of these medicines they cannot be recommended for treatment or prophylaxis at the present time according to a recent editorial.\(^11\) Similar recommendations were provided by a recent article considering both the potential efficacy and the adverse effect profile of these drugs.\(^12\) Thus the data from the literature is conflicting and there have been reports from treating physicians on the beneficial effects of these drugs in COVID-19.

In this article, the authors provide an overview on the safety and efficacy of CQ and HCQ, two-time tested medications in COVID-19 management mainly based on the published literature. Research is ongoing and new data about the efficacy and safety of these two medicines is likely to emerge.

**Search Strategy**

The authors searched the PubMed and the Google Scholar database using the terms “Chloroquine," “Hydroxychloroquine,” “Antiviral," “Coronavirus," and “COVID-19.” A total of 474 preliminary results were obtained with many of them being *in-vitro* studies, opinions, reviews, and editorials. The Norwegian live map of COVID-19 evidence was also searched. Newspaper and magazine articles were also examined as was the Clinicaltrials.gov database. The same search terms were used for searching the Clinical Trials database as mentioned before. A total of 46 studies were obtained on searching the Clinicaltrials.gov database. The abstracts were carefully screened by the authors. Those which were decided to be relevant to the study on the basis of consensus were included and the full texts obtained. The full texts were read through carefully and relevant ones were included in the study. The Micromedex database was used to obtain information especially about the adverse effects of the medicines. Articles till August 15, 2020 were included.

**Chloroquine and Hydroxychloroquine**

Chloroquine phosphate, developed in 1934, was used for malaria treatment during and following World War II though resistance is now becoming a problem.\(^13\) HCQ introduced in 1955 differs from CQ by a hydroxyl group and is known to have less toxicity while preserving the efficacy.\(^14\) The United States Food and Drug Administration (US FDA) approved indications for CQ include malaria prophylaxis, malaria treatment, and non-intestinal amoebic infection, and that for HCQ include systemic lupus erythematosus (SLE), malaria prophylaxis, malaria treatment, and treatment of rheumatoid arthritis.\(^15\) However, these drugs are also used in many other conditions related to the immune system and dermatology. Recently, there has been widespread debate regarding use of these two drugs in COVID-19 management.\(^16-18\)

The major benefit of these two drugs is their low cost. The cost of 250 mg CQ tablet is less than 2 US cents in India while HCQ tablet 200 mg costs about 8 US cents. While cost may vary across countries, these two medicines are likely to be much cheaper than other potential therapeutic options. The cost will be much lower on bulk procurement and supply. This opens up more avenues for these medicines to be used for chemoprophylaxis and treatment if they are shown to be effective.
Proposed mechanism of action in COVID-19

Chloroquine appears to be a versatile antiviral agent with activity against a number of viruses.\(^{[19]}\) CQ and HCQ have a similar mechanism of action inhibiting the binding of the viral particles to the cell surface receptors. CQ interferes with sialic acid biosynthesis and the synthesis of host cell surface receptors to which corona viruses bind.\(^{[20]}\) CQ and HCQ can interfere with pH-dependent endosome-mediated entry of enveloped viruses like SARS CoV-2. The viral and endosomal membranes fuse together leading to the release of the viral genome into the cytosol which can be inhibited.\(^{[21]}\) The intracellular site of coronavirus budding is determined by the localization of M-proteins in the Golgi complex and CQ and HCQ may affect this budding.\(^{[22]}\)

Unique advantages of these two medicines

In the absence of any specific treatment and the long road ahead for the development of vaccination, several official guidelines have already incorporated HCQ and CQ into the recommended treatment of patients with COVID-19. These drugs have been widely used for over six decades in many patient populations like those infected with malaria and autoimmune diseases like rheumatoid arthritis around the globe, and the safety profile of the drug is well characterized.\(^{[23,24]}\)

The other advantage is that they are already in the essential drug list of many countries and pre-existing in hospital formularies. Hence the drugs are readily available for the treatment of COVID-19 patients without any delays in procurement. The third advantage of these drugs is that there are many manufacturers worldwide with US FDA approved manufacturing facilities.\(^{[25,26]}\)

Efficacy of these medicines in COVID-19

The Norwegian Institute of Public Health (NIPH) has created a live map of COVID-19 evidence as a collaborative project between the Institute, McMaster University, Health Sciences, Cochrane Belgium, and the Belgian Red Cross.\(^{[27]}\) The authors have used the evidence presented in this map to examine proof of efficacy of CQ and HCQ in COVID-19. There were a total of seven systematic reviews on this topic. Shah et al.\(^{[28]}\) in their systematic review examined five studies and concluded that though the preclinical studies are promising there is a dearth of clinical evidence to support use of HCQ and CQ in the condition. Observational studies or high-quality randomized studies are urgently required.

Another systematic review included six papers and 23 ongoing clinical trials. CQ seems to be effective in stopping \textit{in-vitro} replication of the virus. The authors concluded that there are indications to justify use of CQ in patients suffering from COVID-19, however, under monitored conditions of use.\(^{[29]}\)

A systematic review of 19 records and 24 trial registries was conducted and the results reported in Spanish. The authors concluded that only one small, non-randomized clinical trial supports the use of HCQ in COVID-19. They conclude by calling for more clinical trials to determine the efficacy and safety of these two medicines in COVID-19.\(^{[30]}\) A similar conclusion was reached by another systematic review examining the evidence from a rapid review of the literature conducted on March 28, 2020.\(^{[31]}\)

A large clinical trial of HCQ in hospitalized patients with COVID-19 began in early April in the United States. This study named Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease study, or ORCHID study will enroll over 500 adults and is a double-blind, placebo controlled clinical trial.\(^{[32]}\) Another ongoing trial, the proactive prophylaxis with azithromycin and chloroquine in hospitalized patients with COVID-19 (ProPAC-COVID) trial is also ongoing and will be a double-blind placebo-controlled trial with a primary completion date of October 31, 2020.\(^{[33]}\) The Australasian COVID-19 (ASCOT) trial plans to randomize patients to multiple treatments including HCQ and the combination of lopinavir/ritonavir and the trial design is set up to investigate new treatments once they become available.\(^{[34]}\) The revised guidelines of the Ministry of Health and Family Welfare, and the National Task force for COVID-19 infections recommends the use of HCQ in all asymptomatic health workers, asymptomatic frontline workers deployed in containment zones and police/paramilitary personnel involved in COVID-19 activities, and asymptomatic household contacts of laboratory confirmed cases.\(^{[35]}\)

The use of HCQ in the prevention of COVID-19 in cancer patients undergoing treatment is being studied in an ongoing clinical trial.\(^{[36]}\) A randomized controlled trial is underway to study the effect of HCQ on prevention of COVID-19 infection among healthcare professionals.\(^{[37]}\) A multicenter trial in the US is enrolling individuals who are close contacts of patients with either laboratory confirmed or clinically suspected COVID-19 infection. The study is designed to test the efficacy of HCQ as post-exposure prophylaxis in these individuals along with the safety and tolerability of the medicine.\(^{[38]}\)

The COVID-19 pandemic has reduced in intensity in many countries. The situation is fluid with a secondary resurgence in others. In the Netherlands, an open label
clinical trial examining CQ, HCQ, and supportive care in COVID-19 was terminated due to non-availability of the required number of patients.[39] A clinical study evaluating the efficacy of CQ or HCQ in COVID-19 by Tanta University, Egypt is ongoing and is expected to be completed by the end of this year.[40] A multicenteric study by the University of Oxford is ongoing in multiple countries and is currently recruiting healthcare workers and other staff working in facilities where there have been COVID-19 cases.[41] The effect of these drugs in preventing COVID-19 in the healthcare setting is being studied with an estimated completion date of April 2021. Clinical trials are ongoing in a number of countries including Brazil,[42] Pakistan,[43] Germany,[44] Mexico,[45] Greece,[46] France,[47] and Austria[48] among others. A study has been completed in Pakistan and is currently undergoing quality control (QC) review by the National Library of Medicine.[49]

**Safety Profile**

Chloroquine can cause irreversible damage to the retina, hearing loss, tinnitus, elevated liver enzymes, loss of appetite, vomiting, and diarrhea. Similarly, the adverse effects of hydroxychloroquine are irritability, headache, weakness, hair lightening or hair loss, stomach upset, dizziness, muscle pain, and itching.[50] Some of the serious adverse effects encountered during the use of these medications are listed in Table 1.[51]

On April 24, 2020, the US FDA cautioned about the cardiovascular safety of these medications including QT interval prolongation, ventricular tachycardia and ventricular fibrillation, and death in some patients.[51] The US FDA further warned regarding the use of these drugs in COVID-19 outside the hospital settings and even in clinical trials due to the cardiovascular effects. On June 16, 2020, the US FDA withdrew its emergency use authorization to use CQ and HCQ in the treatment of COVID-19 patients.[52]

On March 22, 2020, the Indian Council for Medical Research (ICMR) issued an advisory for offering chemoprophylaxis with hydroxychloroquine for asymptomatic frontline healthcare workers involved in providing care to COVID-19 patients (both suspected and confirmed), and asymptomatic household contacts of confirmed patients. The ICMR recommended dose is 400mg twice a day on day 1, followed by 400mg once weekly for the next 7 weeks; to be taken with meals for the asymptomatic health workers while for asymptomatic household contacts, the same dose is to be taken for 3 weeks duration.[53]

**Precautions, contraindications, and use in special populations**

The undesirable consequences of these medicines can be minimized by identifying and monitoring the individuals at greatest risk. Both are 4-aminoquinoline compounds which are derivatives of quinine, having similar contraindications and precautions.[54] Both CQ and HCQ are contraindicated in patients with known hypersensitivity to 4-aminoquinoline compounds (for example: Amodiaquine) or with retinal or visual field changes due to any causes. Similarly, they should be avoided in patients at increased risk for arrhythmia or with a prolonged QT interval while initiating therapy. Additionally, HCQ is contraindicated for use in children <6 years or weighing <35 kg[55] and CQ is contraindicated for use in patients using amiodarone.

**Use in pregnancy**

Although there are no conclusive reports on the use of chloroquine containing compound in pregnancy for COVID-19, a recent study has justified the use of HCQ in pregnant women who have contracted the SARS-CoV-2 coronavirus.[56] Adverse perinatal outcomes were

| System          | Chloroquine                          | Hydroxychloroquine                  |
|-----------------|--------------------------------------|-------------------------------------|
| Cardiovascular  | Atrioventricular block, cardiomyopathy, ventricular tachycardia, heart failure, torsades de pointes, prolonged QT interval | Prolonged QT interval, torsades de pointes, ventricular tachycardia |
| Endocrine       | Hypoglycaemia                        | Hypoglycaemia (severe)              |
| Blood related   | Aplastic anaemia, haemolytic anaemia  | Agranulocytosis, anaemia, aplastic anaemia, haemolysis, pancytopenia, thrombocytopenia |
| Hepatic         | Hepatitis, increased liver enzymes    | —                                   |
| Immunologic     | Anaphylaxis                          | —                                   |
| Neurologic      | Extrapyramidal effects, seizure      | Extrapyramidal effects              |
| Ophthalmic      | Disorder of macula of retina, retinal disorder | Retinal disorder (7.5%) |
| Otic            | —                                    | Hearing loss                        |
| Musculoskeletal | —                                    | Disorder of muscle                  |
not found to be associated with a total daily dose of less than or equal to 400 mg maternal dose of HCQ.\textsuperscript{[57]}

**Use in the elderly**

Although there is no special dosage adjustment recommended for the elderly patients, it is advisable to monitor them closely for efficacy and safety. A simulation study virtually added these medications to the regimen of elderly persons on polypharmacy.\textsuperscript{[58]}

The authors concluded that the addition increased the risk of drug interactions and of the long QT syndrome.

**Use in patients with renal impairment**

It is recommended to observe caution in patients with renal impairment and also in individuals taking concomitant drugs known to be nephrotoxic. As these drugs have long half-lives, it is warranted that their adverse reactions be monitored closely during treatment and after discontinuation of treatment. The dose adjustment pattern in renal failure is mentioned in Table 2.

**Recommendations**

Based on the available evidence as on August 15, 2020, there is insufficient evidence to recommend use of these drugs and more concrete evidence on their efficacy and safety in COVID-19 is required. Results from clinical trials underway may provide more definite guidance. Recently there have been reports in the media that pharmaceutical companies had pressured the editors of both The Lancet and the New England Journal of Medicine to publish a series of negative studies about HCQ in their journals.\textsuperscript{[59]} The low cost of these drugs may not make it worthwhile for the pharmaceutical industry to recommend their widespread use. A recent review mentions that the published clinical trial results are contradictory while \textit{in-vitro} studies suggest antiviral activity.\textsuperscript{[60]}

Many clinicians have reported positive outcomes in treating COVID-19 patients using these drugs. Hopefully recent studies underway will provide more definite answers.

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### Conflicts of interest

There are no conflicts of interest.

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