



(REVIEW ARTICLE)



## Role of hydroxychloroquine and chloroquine in prophylaxis against COVID19 review study

Kumar Surendra \*, Gupta Harsh, Bhandiwad Chandrashekhar, Meena Babu Lal, Mali Manoj, Jangid Ravindra and K R Anil

*Resident, Medicine Department, S P Medical College, Bikaner, Rajasthan, India.*

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### Abstract

The ongoing coronavirus pandemic has pushed that global healthcare system in crises and led to huge losses in terms of life and property. Different drugs for prophylaxis against COVID-19 including Chloroquine (CQ) or Hydroxychloroquine (HCQ) have been tried. This study was performed to systematically review the role of CQ and HCQ in the prophylaxis of COVID-19. Various databases like PubMed, EMBASE, ClinicalTrials.gov, International Clinical Trials Registry Platform and Cochrane Library databases were searched for studies that evaluated the prophylactic role of CQ or HCQ on SARS-CoV-2 (pre-clinical studies) or COVID-19 (clinical studies) until 6th May 2020. The available literature was critically appraised. A total of 36 articles were screened and 4 *in vitro* pre-clinical studies and 2 clinical opines, 4 clinical studies and promising clinical trials registered at clinicaltrials.gov were included in analysis. The pre-clinical studies showed the prophylactic effects of CQ and HCQ against SARS-CoV-2. On the other hand, the clinical opinions advocated the prophylactic use of CQ and HCQ against COVID-19. However, no original clinical studies on the prophylactic role of CQ or HCQ on COVID-19 were available. Although Preclinical trials and *in vitro* studies support the use of CQ and HCQ in prophylaxis against COVID19, there is a dearth of concrete clinical data to support the same. However, in a resource poor country the benefits of chemoprophylaxis will augment the safety of Frontline workers against COVID19. Long term follow up studies and high quality randomised controlled studies are required to establish the fact more prudently.

**Keywords:** COVID-19; Hydroxychloroquine; Prophylaxis; SARS-CoV-2

### 1. Introduction

By the end of December 2019 a number of mysterious new cases of pneumonitis started appearing in Wuhan province which was unlike any other infection known to Health authorities. On subsequent evaluation it was found to be a Corona virus [1].' Corona viruses belong to the Corona viridae family in the Nidovirales order. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named as a corona virus [2].' The 2019-nCoV share close similarity to bat corona viruses giving rise to the possibility that the disease started due to transmission from bats, though the investigation is still going on. It started in the Hubei province of Wuhan city in the Huanan Seafood market and within 1 week it infected thousands of people leaving many dead, forcing authorities to place the nearby area under quarantine [3].' On 30 January 2020, World Health Organization (WHO) officially declared the COVID-19 epidemic as a public health emergency of international concern. The emergence of SARS-CoV-2, since the severe acute respiratory syndrome corona virus (SARS-CoV) in 2002 and Middle East respiratory syndrome corona virus (MERS-CoV) in 2012 marked the third introduction of a highly pathogenic and large-scale epidemic corona virus into the human population in the twenty-first century. As of 6th May 3,588,773 cases have been recognized worldwide in 210 countries with more than 247,503 deaths and going [4].' The first case of COVID19 was detected in India on 30th January and till 6th May India amounts for 35,902 confirmed cases with 1,783 deaths [5].' This could be an underestimate due to the lower number of diagnostic tests and case identification partly due to poor health services in most countries. The mortality rate stands at 0.5-4.4%.

\* Corresponding author: Kumar Surendra

However, this could be an overestimate as the exact denominator of the actual number of cases is underreported. A lot of research has been undertaken to develop a vaccine, but with little chance of success in the foreseeable future. A lot of medicines are under research like Ribavirin, Lopinavir, Ritonavir, Antimalarials (Chloroquine and Hydroxychloroquine) and Interferones (INF). Of these drugs the particular interest is on Chloroquine and Hydroxychloroquine. The antiviral activity of chloroquine has been studied extensively in both in-vitro and in-vivo models and it is found that chloroquine as well as hydroxychloroquine is effective for both prophylaxis as well as treatment of COVID-19 infection. A 2005 study done by Martin J Vincent et al first raised the possibility that chloroquine and its derivative hydroxychloroquine might be effective at treating Coronavirus infection [6]. Chloroquine interferes with the virus's ability to replicate in two ways. First, the drug enters compartments called endosomes within the cell membrane. Endosomes tend to be slightly acidic, but the chemical structure of the drug boosts their pH, making the compartments more basic. Many viruses, including SARS-CoV, acidify endosomes in order to breach the cell membrane, release their genetic material and begin replication; chloroquine blocks this critical step [7]. The drug also prevents SARS-CoV from plugging into a receptor called angiotensin-converting enzyme 2, or ACE2, on primate cells. When the virus inserts its spike protein into the ACE2 receptor, it sets off a chemical process that alters the structure of the receptor and allows the virus to infect [7]. An adequate dose of chloroquine appears to undermine this process, and in turn, viral replication in general.

The objective of present work was to study the role and effectiveness of Hydroxychloroquine or Chloroquine for prophylaxis against COVID-19 infection.

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## 2. Material and methods

We aimed to include all completed and published pre-clinical as well as clinical studies, without limitations, which evaluated the prophylactic role of CQ or HCQ on SARS-CoV-2 (pre-clinical studies) or COVID-19 (clinical studies). We also looked for commentaries, re-views, viewpoints, or opinions if original clinical studies were not available. PubMed, EM-BASE, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials [CENTRAL], and Cochrane Methodology Register) were searched from inception until 27th April 2020. The search terms used in various combinations were: "chloroquine", "hydroxychloroquine", "anthraquinone", "CQ", "HCQ", "corona virus", "corona virus disease", "corona virus disease-19", "COVID-19", "severe acute respiratory syndrome", "SARS-CoV-2", "prophylaxis", and "preventive". These search terms were adapted for use with different bibliographic databases in combination with database-specific filters for studies, if available.

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## 3. Results

A total of 36 articles were screened and 4 *in vitro* pre-clinical studies and 2 clinical opines, 4 clinical studies and promising clinical trials registered at clinicaltrials.gov were included in the analysis. No original clinical study on the prophylactic role of CQ and HCQ on COVID-19 were available.

### 3.1. *In vitro* Studies

After the SARS epidemic in 2003 numerous scientific trials were carried to find a cure or prophylaxis against the Corona viruses. The earliest and most promising result came from a research done by Vincent MJ et al (2005) to study the use of chloroquine as potent inhibitor of Coronavirus infection and spread and found that chloroquine significantly inhibited the growth of viruses in cell lines in both Pre-infection and Post-infection models[6]. While Yao et al showed that HCQ exhibited a better *in vitro* anti-SARS-CoV-2 activity than CQ in Vero cells derived from the African green monkey kidney [8], Liu et al exhibited a higher potency of CQ over HCQ in the same cell line[9]. Xiao et al enumerated that CQ and remdesivir (which inhibits RNA polymerase), as compared to five other drugs, had a better *in vitro* potency in inhibiting SARS-CoV-2 in Vero cell lines [10]. Zhou et al[11] and Colson et al[12] gave their clinical opinions advocating the possible prophylactic use of CQ and HCQ against COVID-19.

### 3.2. *In vivo* studies

A study in France by Raoult et al [13] evaluated the efficacy of hydroxychloroquine in 26 patients with COVID-19 and found that administration of hydroxychloroquine 200 mg, three times a day led to a significant reduction in viral carriage on day 6 post-treatment compared to that in the control group, which did not receive hydroxychloroquine. That study also revealed that adding azithromycin to hydroxychloroquine appears to more efficiently clear the virus. A subsequent study by Raoult et al. [14] involving 80 patients with COVID-19 found that treatment with hydroxychloroquine and azithromycin resulted in a rapid decline in the nasopharyngeal viral load, with a virus-negative

rate of 83% on day 7 and a rate of 93% on day 8.’ Although a control group was not included in that study, its results suggest the potential of hydroxychloroquine to treat COVID-19 given that the recorded median duration of viral shedding is 20 days in survivors.

In addition to the studies cited above, a Chinese team recently released the results of a clinical study on hydroxychloroquine to treat COVID-19 [15].’ That study divided 62 patients into a hydroxychloroquine group and a control group at a ratio of 1:1. Patients in the control group received standard treatment including oxygen therapy, antivirals, antibacterials, and immunoglobulin with or without corticosteroids. Patients in the hydroxychloroquine group received hydroxychloroquine sulfate 200 mg, twice a day for 5 days in addition to the standard treatment. Results indicated that hydroxychloroquine helped reduce the time until body temperature returned to normal, it decreased the duration of cough, and it improved lung imaging findings [15].’ The above studies together favor the usefulness of hydroxychloroquine in treating COVID-19.

Chen et al, Shanghai China conducted a randomised controlled trial to test the effectiveness of HCQ in 30 adult patients who tested positive for COVID-19 [16].’ Patients in the treatment group received 400mg HCQ for 5 days, while the control group received usual care. The result of a nasopharyngeal swab on Day 7 was used as the primary outcome. The authors report three adverse events in the control group (one patient with abnormal liver function and anaemia, and one patient with abnormal renal function), and four adverse events in the treatment group (two patients with diarrhoea, one with lethargy, and one patient with abnormal liver function tests), which they argue were not linked to treatment with HCQ [16].’ One patient in the treatment group deteriorated significantly and thus HCQ was stopped on Day 4 of the treatment. The intention-to-treat analysis revealed that the treatment group did not differ from the control group in the number of patients testing negative for COVID-19 on Day 7 (13 versus 14 patients), nor the duration of illness (all  $P > 0.05$ ) [16].’

### 3.3. Clinical Trails

Currently, around 142 trials that have been registered in various national and international databases involving chloroquine and hydroxychloroquine, alone or in combination with other drugs in the prevention or treatment of COVID-19. Most of them are non-blinded trials. The most promising clinical trials are mentioned in the table-1.

**Table 1** The most promising clinical trials

NCT04308668 (USA)	Recruiting	Multi-center randomized parallel group trial	1500 participants (Healthcare workers and contacts)	HCQ	Placebo	Incidence and severity of COVID-19
NCT04304053 (Spain)	Recruiting	Multi-center cluster randomized trial	3040 participants (COVID19 contacts)	Antiviral treatment and prophylaxis with HCQ	Standard public health measures	Incidence of secondary COVID-19 cases
NCT04303507 (Europe & Asia)	Not yet recruiting	Multi-center randomized parallel group trial	40000 participants (COVID19 contacts)	CQ or HCQ	Placebo	Number of symptomatic COVID-19 infections
NCT04318444 (USA)	Not yet recruiting	Community-Based Randomized Clinical Trial	1600 participants (COVID 19 contacts)	HCQ	Placebo	Number of participants with symptomatic, lab-confirmed COVID-19
NCT04318015 (Mexico)	Not yet recruiting	Parallel group RCT	400 participants (healthcare workers contact with COVID19)	HCQ	Placebo	Symptomatic COVID-19

#### 4. Limitations of the current empirical data

The *in vivo* studies reported have methodological deficiencies. The trials by Chen et al and Gautret and colleagues were both underpowered according to their own calculations, which may have led to an exaggeration of effect sizes and false positive results. Moreover, whilst viral status at Day 6/Day 7 were the primary outcomes, no medium- or long-term follow-up data were presented in either study. Gautret and colleagues reported that one patient tested negative for the virus on Day 6, but subsequently tested positive on Day 8. This highlights the need for long-term follow-up data. Chen et al reported that most patients included in their trial (both control and treatment group) recovered quickly from COVID-19, indicating that the researchers had recruited a sample with mild symptoms. The authors argue that the lack of severe cases may have caused a ceiling effect, which may explain the non-significant results. Gautret et al did not perform intention-to-treat analysis, excluding six patients from their analyses who had dropped out at follow-up, which may have introduced bias. Finally, Gautret and colleagues did not randomise patients to the control and treatment group, potentially introducing allocation bias.

#### 5. Discussion

The first *in vitro* study pointing toward the role of CQ and HCQ as pre-exposure prophylaxis against COVID-19 was published as a research letter by Yao et al. Vero cell lines derived from African green monkey kidney were treated with CQ or HCQ before exposing to a clinically isolated novel corona virus strain (C-Tan-nCoV Wuhan strain 01) at a multiplicity of infection (MOI) of 0.05. HCQ was more potent than CQ in achieving the 50% maximal effective concentration (EC50) (6.25 and 5.85  $\mu\text{mol/L}$  at 24 and 48 hours, respectively) [17]. The concentration to achieve EC50 was >100 and 18.01  $\mu\text{mol/L}$  for CQ, suggesting a higher loading dose. This study led to the enthusiasm of registration of clinical trials on the prophylactic role CQ and HCQ. The study also highlighted the use of a high loading dose of CQ followed by a low maintenance dose to support its pharmacokinetic property of higher cellular accumulation and prolonged elimination half-life [17]. Another *in vitro* study by a different group of researchers from China compared HCQ to CQ at 4 different MOI. The results were contradictory to that of the previous study showing a lower EC50 of CQ than that of HCQ. Importantly the difference was even more striking at higher MOI, suggesting that in the presence of faster multiplication of the virus, CQ may perform better than HCQ. The possible reasons for the conflicting results are challenging to explain; however, it cautiously points toward extrapolation of *in vitro* evidence to clinical practice without robust clinical data. The French study by Gautret et al shows promising result regarding the use of HCQ along with Azithromycin for treatment of SARS-CoV2 infection while another Chinese study by Chen et al shows no significant effect of chloroquine. Hence large randomised studies are required before the prophylactic effects of HCQ and CQ can be confirmed. Nevertheless, it's a low cost option, especially given that there is dearth of PPE kits and N95 masks. Thus Chemoprophylaxis along with measures like sanitization, social distancing and Quarantine can prove to be an effective way to prevent the front line workers from contracting this infection.

Expectedly, some precautions will be needed while using both these drugs that include frequent monitoring of hematological parameters (RBC, WBC and platelet counts), measurement of serum electrolytes, blood glucose (because of hypoglycemic potential of HCQ) and hepatic as well as renal functions. Since both these drugs have the potential to prolong QTc, routine electrocardiography is essential prior to starting these drugs. Co-administration of other drugs known to prolong the QTc interval (such as anti-arrhythmic, anti-depressants, anti-psychotics, anti-histaminic, teneligliptin, ondansetron and moxifloxacin etc.) must be avoided. Moreover, addition of azithromycin to HCQ as done in French trial by Gautret et al. may increase the risk of QTc prolongation. Perform ECG daily if QTc is 450–500 msec. Additionally, hypoglycemia must be looked for in patients with diabetes, especially with concurrent use of chloroquine/HCQ and lopinavir/ritonavir. Chloroquine and HCQ should not be used concurrently with lopinavir/ritonavir and remdesivir for anticipated QTc prolongation [18]. Finally, Pharmacovigilance on visual and mental disturbance is also closely required.

Although there are sporadic case reports of chloroquine-induced cardiomyopathy and reversible heart failure in the literature, many studies and large meta-analysis conducted in patients with rheumatoid arthritis pointed to a reduced cardiovascular risk with both these compounds [18]. Nevertheless, since both the drug has potential to prolong QTc, a baseline ECG should be done in patients with established cardiovascular disease.

All clinicians using these drugs must know contraindication to both these compounds; hypersensitivity to these agents, retinopathy, porphyria, epilepsy, pre-existing maculopathy, G6PD deficiency, recent myocardial infarction and QTc >500 msec [19].

## 6. Conclusion

The pandemic COVID-19 has pushed the world healthcare system in the abyss. It has caused a huge socio-economic burden on already strained medical system and also caused huge psycho-logical impact, the effects of which will last for several years to come. Thus, there is requirement to develop an effective prophylactic drug against COVID-19 and CQ/HCQ comes with some hope. HCQ and CQ have been used for decades in patients with RA and Malaria and there is plenty of experience in dealing with both the drugs and their complications. Although evidence of chloroquine and HCQ is limited (based on the experimental data and only few small human trials), it has emerged as a cheap and scientifically proven option for prophylaxis against COVID-19 in resource constrained and COVID-19 overburdened health care system in middle and low-income countries including India where there is a severe shortage of protective gear, masks and PPE predisposing the healthcare workers to infection. Chemoprophylaxis with CQ/HCQ along with other measures like social distancing, sanitisation and quarantine can prove to be an effective method to protect the workforce from contracting this infection. Because of the lack of robust clinical evidence to date and duly considering the questionable efficacy, safety concerns, danger of deprivation of these essential drugs to legitimate patient due to panic stocking and instilling a false sense of protection among the common masses, the prophylactic use of CQ or HCQ against COVID-19 needs to be further reviewed as more data pour in.

## Compliance with ethical standards

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### Disclosure of conflict of interest

The authors declare there is no conflict of interest associated with this manuscript.

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