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ORIGINAL ARTICLE

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A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19)

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Abstract

Objective: The pandemic coronavirus disease-19 (COVID-19) has pushed the global healthcare system to a crisis and amounted to a huge economic burden. 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 preventing the spread of COVID-19.

Methods: 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 30 March 2020. The available literature was critically appraised.

Results: A total of 45 articles were screened and 5 (3 in vitro pre-clinical studies and 2 clinical opinions) were included. 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.

Conclusion: Although pre-clinical results are promising, to date there is a dearth of evidence to support the efficacy of CQ or HCQ in preventing COVID-19. Considering potential safety issues and the likelihood of imparting a false sense of security, prophylaxis with CQ or HCQ against COVID-19 needs to be thoroughly evaluated in observational studies or high-quality randomized controlled studies.

KEYWORDS

chloroquine, COVID-19, high-risk, hydroxychloroquine, prevention, SARS-CoV-2

1 | INTRODUCTION

The present world is experiencing a pandemic (coronavirus disease-19 or COVID-19) caused by a novel strain of coronavirus, called SARS-CoV-2, previously called 2019-CoV. At the time of writing this article, 3 72 757 cases spanning over 195 countries and territories and 1 international conveyance have been reported.[1] 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%[2]; however, this could be an overestimate as the exact denominator of actual number of cases is underreported. Diversion of all healthcare facilities toward the COVID-19 pandemic is likely to increase the morbidity and mortality due to other health problems.

In such a scenario, understanding the impact on the economy is beyond the confines of a medical expert.

Another conundrum faced is a high secondary infection rate among high-risk healthcare workers annexing the already burdened healthcare system.[3] This would not only compound the impending shortage of healthcare facilities but would also mean more pervasive spread. Prevention is thus the best strategy to not only prevent more spread and deaths but also to unburden the healthcare system. However, there are challenges involved. Although methods like mitigation, quarantine, isolation, social distancing, and so on are being employed, these are not infallible. Contact tracing for the spread of infection from asymptomatic or mild undiagnosed cases, transition to community spread, and factors such as uncertainty regarding the survival of the virus in air or fomites are cumulatively adding to the mammoth task.[4] Hence, the focus has now been shifted toward evaluating and implementing other strategies like chemoprophylaxis and vaccination besides the continued use of the barrier system. Vaccine development will take time, between 12-18 months, as human trials are under way. There is a lot of speculation on chemoprophylaxis stemming from the available data on the use of some antimalarial drugs, such as chloroquine (CQ) and hydroxychloroquine (HCQ), which have been tried for the treatment of this disease.[5]

The potential drug targets depend on the natural cycle of this virus. The virus depends on pH-dependent internalization and fusion with lysosomes. HCQ and CQ target this pathway by increasing the pH as they get concentrated into the lysosome and endosomes. This, in turn, affects viral replication and also helps in immune regulation and prevention of a cytokine storm as the antigen presentation is affected. But the challenge is the translational impact of in vitro models to in vivo ones. There are studies from China and other countries highlighting the use of antimalarial anthraquinones including mention of the same in the latest guidelines.[6,7] Recent advice issued by a national body from a South-Asian country suggested the use of prophylactic HCQ at a dose of 400 mg twice daily, followed by once weekly, for healthcare workers managing patients with COVID-19 and close contacts of proven COVID-19 cases.[8] However, these studies and guidelines differ on the prophylactic use of these drugs causing further dilemma among healthcare professionals. Hence, we aimed to systematically review the literature on the role of CQ or HCQ in preventing the spread of COVID-19.

2 | METHODS

2.1 | Study design

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, reviews, viewpoints, or opinions if original clinical studies were not available. Studies which evaluated the therapeutic effects of CQ or HCQ were excluded.

2.2 | Search strategy

PubMed, EMBASE, 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 30 March 2020. The search terms used in various combinations were: "chloroquine", "hydroxychloroquine", "anthraquinone", "CQ", "HCQ", "coronavirus", "coronavirus disease", "coronavirus 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. The search strategy was used to obtain the titles and the abstracts of the relevant studies in English, and they were independently screened by 2 authors, who subsequently retrieved abstracts, and if necessary, the full text of articles to determine the suitability. Disagreement resolution was done with a third author. The systematic review protocol could not be pre-registered as the current pandemic is an ongoing public health emergency, thereby resulting in a paucity of time to permit pre-registration.

2.3 | Appraisal of the selected articles

The clinical opinions were critically appraised following the checklist of McArthur et al (2015).[9] The characteristics of the pre-clinical studies were also critically appraised. This was performed independently by 2 authors, and disagreement resolution was done with a third author. No assumptions or simplifications were made during the process.

3 | RESULTS

At total of 45 articles were screened and 3 in vitro pre-clinical studies[10-12] and 2 clinical opinions[13,14] were included in the analysis. No original clinical studies on the prophylactic role of CQ or HCQ on COVID-19 were available (Figure 1). Table 1 enumerates the findings of the in vitro pre-clinical studies and Table 2 denotes the critical appraisal of the clinical opinions. The pre-clinical studies showed the prophylactic effects of CQ and HCQ against SARS-CoV-2. 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, Liu et al exhibited a higher potency of CQ over HCQ in the same cell line. 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. On the other hand, both Zhou et al and Colson et al provided their

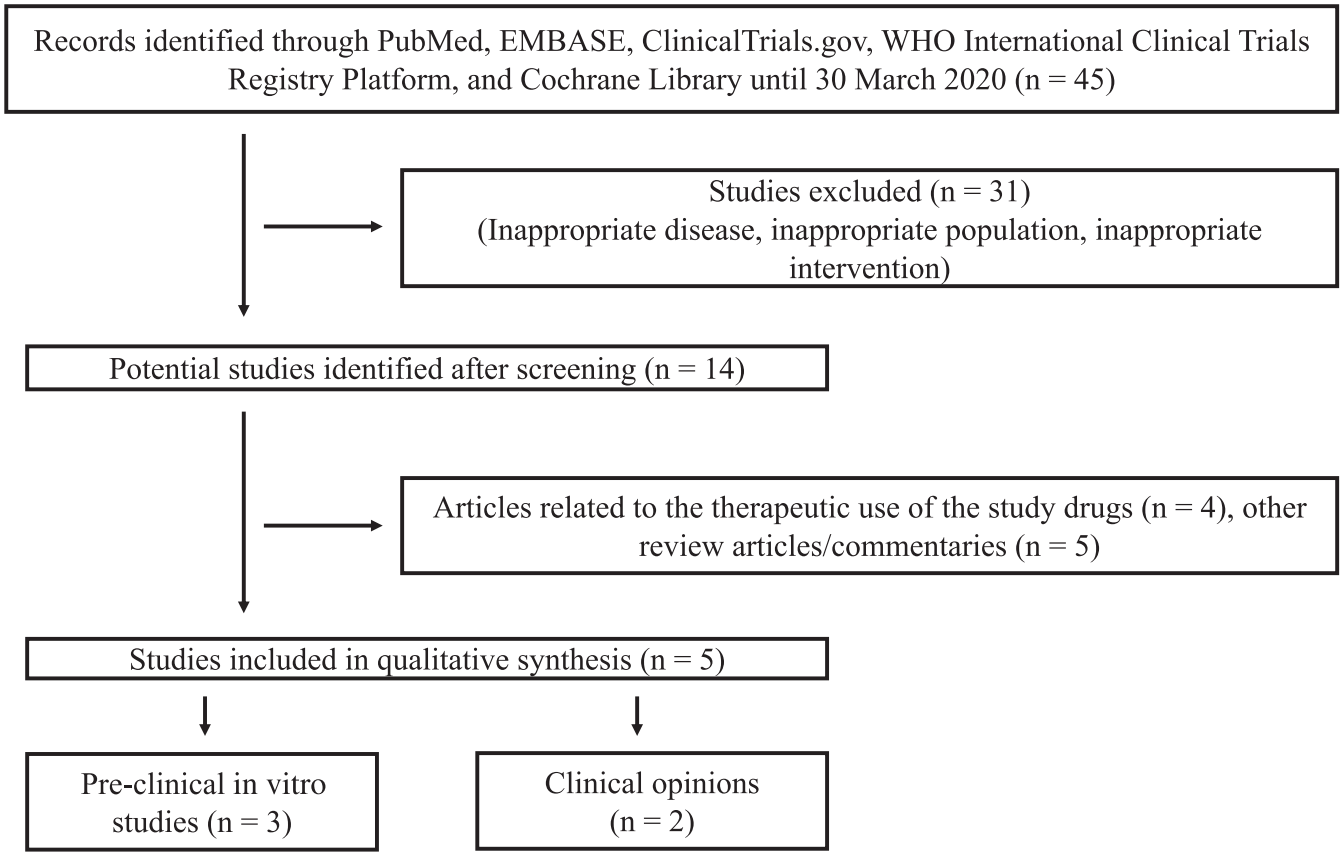

FIGURE 1 Flowchart depicting the steps of qualitative synthesis of evidence from the literature

clinical opinions advocating the possible prophylactic use of CQ and HCQ against COVID-19. On appraisal, both the articles were found to be of reasonable quality.

4 | 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[10] Vero cell lines derived from African green monkey kidney were treated with CQ or HCQ before exposing to a clinically isolated novel coronavirus 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 (EC_{50}) (6.25 and 5.85 μmol/L at 24 and 48 hours, respectively). The concentration to achieve EC_{50} was >100 and 18.01 μmol/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 (Table 3). 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. Another in vitro study by a different group of researchers from China compared HCQ to CQ at 4 different MOI.[11] The results were contradictory to that of the previous study showing a lower EC_{50} 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. This also puts a question mark on the preventive role where the therapeutic effect of CQ might not be adequate. In another published study, Xiao et al assessed the role of multiple US Food and Drug Administration-approved antiviral drugs, including CQ (Table 2).[12] Their time-of-addition assay demonstrated that CQ functioned at both entry and post-entry stages of the SARS-CoV-2 infection in Vero E6 cells. The concentration to achieve EC_{50} and EC_{90} were 1.13 and 6.90 μmol/L, respectively.

Based on these in vitro results, some authors have adjudicated the prophylactic use of CQ and HCQ against COVID-19. Following the concept of drug repositioning, CQ and HCQ were proposed to be used against SARS-CoV-2 in an editorial published by a French group in February 2020.[14] It was also supported with the already established in vitro antiviral efficacy of CQ in other viruses, as well as against SARS-CoV-2. They emphasized the potential cost-benefit ratio of this prophylactic approach as a hope for the overburdened healthcare system during this pandemic. On 20 March 2020, researchers from China published a concise report emphasizing the role of HCQ over CQ as a prophylactic drug.[13] The report highlighted the in vitro prophylactic effects of HCQ and elaborated the molecular mechanisms of its antiviral activity. The maximum daily dose of CQ is 500 mg, while HCQ can be given at a higher daily dose

TABLE 1 Characteristics of the in vitro pre-clinical studies

Characteristics	Studies		
	Yao et al 2020	Liu et al 2020	Xiao et al 2020
Cell lines used	Vero cells derived from African green monkey kidney	Vero cells derived from African green monkey kidney	Vero E6 cells from African green monkey kidney and Huh7 human liver cancer cells[a]
Study drugs	CQ and HCQ	CQ and HCQ	CQ and others[b]
Drug concentrations and duration	0.032, 0.16, 0.80, 4, 20, and 100 μmol/L for 2 h	0.068, 0.21, 0.62, 1.85, 5.56, 16.67, and 50 μmol/L for 1 h	1.11, 3.33, and 10 μmol/L for 1 h
Comparator	None	Phosphate-buffered saline (control)	DMSO
50% maximal effective concentration (EC_{50})	Higher for CQ than that of HCQ	Lower for CQ than that of HCQ	Lower for CQ and remdesivir than others[b]
Key findings	HCQ exhibited a better in vitro anti-SARS-CoV-2 activity than CQ	The antiviral effects of HCQ seemed to be less potent than that of CQ, especially at a higher viral replication rate	CQ and remdesivir blocked virus infection at a low micromolar concentration
	Longer incubation time may provide a better antiviral effect	The entry step as well as the post-entry steps of virus infection were inhibited by HCQ	Full-time entry, as well as post-entry steps were inhibited by CQ and remdesivir

Abbreviations: CQ, chloroquine; DMSO, dimethyl sulfoxide; h, hour; HCQ, hydroxychloroquine.

[a]Remdesivir.

[b]Other drugs included ribavirin, penciclovir, nitazoxanide, nafamostat, remdesivir (GS-5734), and favipiravir (T-705).

TABLE 2 Critical appraisal of the clinical opinions[9]

Checklist	Studies	
	Zhou et al 2020	Colson et al 2020
Is the source of the opinion clearly identified?	Yes	Yes
Does the source of opinion have standing in the field of expertise?	Yes	Yes
Are the interests of the relevant population the central focus of the opinion?	Yes	Yes
Is the stated position the result of an analytical process, and is there logic in the opinion expressed?	Yes	Yes
Is there reference to the extant literature?	Unclear	Unclear
Is any incongruence with the literature/sources logically defended?	Yes	No
Is the opinion supported by peers?	Unclear	Unclear

of 1200 mg, which is equivalent to 750 mg of CQ. HCQ, at a higher dose, may have a more potent antiviral activity as compared to that of CQ. Furthermore, HCQ has a better safety profile due to lower tissue accumulation as compared to CQ. An additional advantage of HCQ is its safety in pregnancy unlike CQ.[15] Thus, if proven beneficial, HCQ may be a prophylactic drug against COVID-19.

Clinical trials are underway to assess the translational impact of the in vitro prophylactic benefits of CQ and HCQ against COVID-19. Five ongoing clinical trials are aiming to assess the prophylactic efficacy of CQ and HCQ, although there is no mention of any planned interim analysis. With the paucity of evidence on the prophylactic use of these drugs, there are additional essential concerns to address. Despite the in vitro antiviral efficacy, CQ has failed to show efficacy in an in vivo guinea pig model of Ebola,[16] and ferret model of Nipah virus[17] and influenza virus.[18] Clinical trials of CQ as prophylaxis failed in influenza[19] despite strong in vitro efficacy.[18] Even in Chikungunya, the viral replication paradoxically enhanced in animal models after CQ administration.[20] In a clinical trial, long-term musculoskeletal symptoms were more frequent in patients treated with CQ as compared to placebo.[20] Another critical concern is the toxicity of these

TABLE 3 Ongoing clinical studies evaluating the prophylactic role of CQ and HCQ against COVID-19 (search conducted on clinicaltrials.gov on 30 March 2020)

Study registration no. (country)	Recruitment status	No. of Centers and study design	Population (volunteers)	Interventional group(s)	Comparison Group(s)	Primary Outcomes
NCT04308668 (USA)	Recruiting	Multi-center randomized parallel group trial	1500 participants (contact or healthcare worker exposed to a patient with COVID-19)	HCQ	Placebo	Incidence and severity of COVID-19
NCT04304053 (Spain)	Recruiting	Multi-center cluster randomized trial	3040 participants (Contacts of patients with COVID-19)	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 (contact or healthcare worker exposed to a patient with COVID-19)	CQ or HCQ	Placebo	Number of symptomatic COVID-19 infections
NCT04318444 (USA)	Not yet recruiting	Community-Based Randomized Clinical Trial	1600 participants (adult household contacts of COVID-19 patients	HCQ	Placebo	Number of participants with symptomatic, lab-confirmed COVID-19
NCT04318015 (Mexico)	Not yet recruiting	Parallel group RCT	400 participants (healthcare workers attending to COVID-19 patients)	HCQ	Placebo	Symptomatic COVID-19

Abbreviations: CQ, chloroquine; HCQ, hydroxychloroquine.

drugs. CQ has a narrow safety margin and may cause several cardiovascular adverse effects, including QT prolongation, as well other unforeseen adverse reactions.[21] HCQ is relatively safer. However, unrestricted acute overdosing of these drugs can lead to serious toxicities. Moreover, these adverse events may get augmented due to potential drug inhibitors like cytochrome P-450 system inhibitors, as well as with other drugs being advocated or evaluated in COVID-19 such as azithromycin[6] and protease inhibitors.[22,23]

In the absence of robust in vivo and clinical evidence, it seems premature to recommend CQ and HCQ as a panacea for prophylaxis of COVID-19. In the current COVID-19 pandemic, quarantine, social distancing, and personal hygiene seem the only proven preventive measures.[24] It is pertinent to mention here that from the regulatory point of view, there is a mixed opinion on the prophylactic use of CQ or HCQ in different countries. Injudicious use of CQ and HCQ in the light of scarcity of evidence may indulge a false sense of protection, hampering the essential precautionary measures by the common masses. Furthermore, the pandemic hysteria leading to unrestricted off-label use of these drugs by the common masses without adhering to the guidelines may lead to deprivation of these essential drugs to other legitimate patients of lupus and rheumatoid arthritis or malaria if production does not match the demand. There are already reports of adverse effects published in newspaper including death and hospitalization.[25] Thus, further prudency is warranted in this regard.

Re-emphasizing the fact that chemoprophylaxis against COVID-19 is the need of the hour, the related socioeconomic issues need to be addressed. There are reports of the ostracization of healthcare workers and other individuals from affected places.[26,27] Hence, targeted prophylaxis of high-risk individuals can serve the purpose of social security apart from health benefits. However, the primary objective of prophylaxis is defied if a drug use, without concrete scientific evidence, leads to mass hysteria and depriving the legitimate population, such as patients with lupus and rheumatoid arthritis, for the use of these drugs.[28] If CQ and HCQ show prophylactic efficacy in ongoing clinical trials, targeted prophylaxis may be recommended over mass prophylaxis in the future.

There are limitations to our study. To date, there is a dearth of adequate data on this topic of interest. Pre-clinical and clinical studies are ongoing, and most likely new information will be added to the existing literature in the near future necessitating updating this review. Notwithstanding these limitations, we have shown that there is absence of clear evidence to support the efficacy of CQ or HCQ in preventing COVID-19.

5 | CONCLUSION

The pandemic COVID-19 has pushed the global healthcare system to a crisis and amounted to a huge economic and societal burden. Prevention of transmission of the disease in the population, particularly among high-risk individuals, is the urgent need of the hour. Different drugs for prophylaxis against COVID-19 including CQ or HCQ have been tried. Although pre-clinical results are promising, to

date there is dearth of good-quality evidence to support the clinical efficacy of CQ or HCQ in preventing COVID-19. 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 patients 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.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

SS and VSN conceptualized the review; SS, SD, and AJ were involved in literature search and study selection; SS and DPM were involved in disagreement resolution and finalization of the included studies; SS, SD, and AJ have extracted data from the studies for qualitative synthesis of evidence; DPM, and VSN have interpreted the analyses; SS, SD, and AJ have drafted the review; DPM and VSN have provided expert inputs and updated the final review.

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