South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: CHLOROQUINE AND HYDROXYCHLOROQUINE FOR TREATMENT OF COVID-19: EVIDENCE REVIEW OF CLINICAL BENEFITS AND HARMS

Date: 9 April 2020

Key findings

- We conducted a rapid review of available published clinical evidence regarding use of chloroquine or hydroxychloroquine with or without other medicines for patients with COVID-19.
- We found one systematic review, which included two small randomised controlled trials from China in adult COVID-19 patients. Both trials compared oral hydroxychloroquine 200 mg 12 hourly for 5 days with standard treatment.
- It is unclear whether the use of chloroquine or hydroxychloroquine as part of the treatment of COVID-19 has any effect on outcomes critical for decision-making (e.g. mortality or decreased need for mechanical ventilation).
- Adding chloroquine or hydroxychloroquine to standard treatment may increase the risk of serious adverse effects, including cardiovascular events, but this is also low certainty evidence.
- The addition of chloroquine or hydroxychloroquine had no effect on the proportion of patients achieving a negative SARS-CoV-2 PCR on nasopharyngeal swab seven days after starting treatment, but the certainty of the available evidence was low.

THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

There is currently insufficient evidence to recommend routine use of chloroquine or hydroxychloroquine in children or adult patients with COVID-19.
Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.

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Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

The novel human respiratory coronavirus (SARS-CoV-2), which is the cause of COVID-2019, was declared a pandemic on 11 March 2020. There are currently more than 1 000 000 confirmed COVID-19 cases in over 200 countries and SARs-C0V-2 has caused more than 50,000 deaths (WHO 2020; as at 10.30pm 2 April, 1,002,159 confirmed cases, 51,485 deaths; https://coronavirus.jhu.edu/map.html). Effective therapeutic options to manage hospitalised patients with COVID-19 need to be identified urgently.

Chloroquine and its derivative hydroxychloroquine were used for the treatment of malaria, before the development of widespread resistance and is generally well tolerated. Hydroxychloroquine is more soluble and better tolerated than chloroquine but is not readily available in South Africa at present. Chloroquine is used to modulate immunity in rheumatoid arthritis and systemic lupus erythematosus patients.

There is *in vitro* evidence that chloroquine inhibits replication of SARS-CoV-2. Mechanisms include increasing pH in the intracellular endosome required for fusion of the virus with the cell, and inhibition of the entry of SARS-CoV-2 into cells through an effect on the ACE2 receptor (Liu 2020). In addition to suppression of viral replication, it is hypothesised that chloroquine's immunomodulatory effects may be of benefit in the treatment of COVID-19, (Wang 2020). Based on this theoretical benefit, during the current COVID-19 pandemic, chloroquine and hydroxychloroquine have been included in treatment guidelines for COVID-19 in some countries, including China, Italy and India (Frie et al; https://covid-nma.com/recommendations/).

Chloroquine and hydroxychloroquine may cause serious adverse reactions, including QT interval prolongation. This may put patients at risk of drug-induced torsades de pointes and sudden cardiac death. This risk is higher in elderly patients, those with congenital long QT syndrome and those taking other drugs which prolong the QT interval, such as azithromycin and lopinavir/ritonavir (Giudicessi 2020). Recommendations exist for the screening and management of QTc prolongation in patients on chloroquine and hydroxychloroquine (Giudicessi 2020).

The Liverpool has developed a prescribing resource specific for COVID-19 experimental medicines that is being updated regularly (https://www.covid19-druginteractions.org/). Below a table of features of CQ and HCQ update as of 9 April 2020:

Chloroquine and Hydroxychloroquine	
Note	*Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine.*
Metabolism	Chloroquine and hydroxychloroquine undergo CYP mediated metabolism by CYPs 2C8, 3A4 and 2D6. Co-administration with inhibitors or inducers of these isoenzymes may increase or decrease exposure to chloroquine respectively and dose changes or additional monitoring could be considered. Mean urinary recovery of chloroquine (within 3-13 weeks) is ~50% of the administered dose, most being unchanged drug and the remainder as metabolite. Hydroxychloroquine and its metabolites are widely distributed in the body and elimination is mainly via the urine, with 3% of the administered dose recovered over 24 hours.
Interaction Potential	• Chloroquine and hydroxychloroquine are moderate inhibitors of CYP2D6 and P-gp and caution may be required when co-administering co-medications metabolized or transported by these pathways with a narrow therapeutic index.
Cardiac effects	Chloroquine and hydroxychloroquine have been shown to prolong the QTc interval in some patients and should therefore be used with caution in patients receiving concomitant drugs known to prolong the QT interval or where a drug interaction may increase chloroquine exposure. ECG monitoring would be recommended in these instances.

We reviewed current published evidence for efficacy and harms of chloroquine and hydroxychloroquine in treating patients with confirmed COVID-19.

METHODS

We conducted a rapid review of the evidence including systematic searching on two electronic databases (Epistemonikos and the Cochrane Library). Five systematic reviews were identified: one high-quality review included a newly published trial and was dated 31 March 2020. We subsequently identified one additional study through twitter feeds on COVID-19 evidence on 4 April 2020. A further search on PubMed and www.covid-nma.com on 5 April did not identify any new studies.

One reviewer summarised the included systematic review and extracted the data from the primary studies into a narrative table (RD); two reviewers checked the results (KC, TK). MB reviewed the overall report. The search strategy is shown in Appendix 1.

Eligibility criteria for review

Population: Patients with confirmed COVID-19, no restriction to age or disease severity.

Intervention: Chloroquine or hydroxychloroquine either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator)

Outcomes: Mortality, duration of hospitalisation, time to negative SARS-CoV2 PCR on nasopharyngeal swab duration of ICU stay, duration of mechanical ventilation, adverse reactions.

Study designs: We sought systematic reviews of clinical trials in people with COVID-19, where evidence was limited, we also identified and report non-randomised studies.

RESULTS

Results of search: We summarised the findings from the systematic review and meta-analysis (updated on 31 Mar 2020) (Epistemonikos 2020). The systematic review identified two randomised controlled trials (RCTs) (Chen J 2020; Chen Z 2020). It excluded one non-randomised clinical trial (Gautret 2020). We identified an additional non-randomised study from France on 4 April (Molina 2020). Data in **Table 1** report the main characteristics and outcomes of the trials included in the systematic review. **Table 2** describes the excluded non-randomised studies.

Included studies: The two RCTs were conducted in hospitalised adult patients with COVID-19 in China. One trial excluded patients with moderate or severe disease; in the other, exclusion criteria were not ascertained (full text was available in Chinese only). Both excluded patients at high risk of adverse effects. Neither trial assessed mortality, duration of hospitalisation, duration of ICU stay, or duration of mechanical ventilation.

In the meta-analysis, the certainty of the evidence is downgraded due to 1) methodological issues with the trials, 2) imprecision with few events and the low numbers included, resulting in wide confidence intervals and 3) indirectness when surrogate markers were presented. This resulted in evidence that is of low or very low certainty for all outcomes. See **Table 3.** Summary of Findings Table and **Graph of forest plots** from the review.

Effectiveness of the intervention: None of the trials reported on whether the addition of antimalarials results in a lower risk of respiratory failure. They did report on the surrogate outcome 'progression to severe disease'. We are uncertain whether the addition of hydroxychloroquine affects the outcome, risk ratio 0.46 (95% confidence interval 0.15 to 1.39, very low certainty evidence, 2 trials, 92 patients).

Adding hydroxychloroquine may result in an increase in serious adverse effects. The trials reported on overall adverse effects and found an increase when hydroxychloroquine was given, risk ratio 1.65 (95% confidence interval 0.50 to 5.50, low certainty evidence, 2 trials, 92 patients).

Adding hydroxychloroquine may not increase the proportion of patients with negative SARS-CoV-2 PCR on nasopharyngeal swab on Day 7, risk ratio 0.93 (0.73 to 1.18, low certainty evidence, 1 trial, 30 patients).

Two studies in France present conflicting results of the treatment of hospitalised patients with COVID-19 with a combination of azithromycin and chloroquine (Gautret 2020; Molina 2020). The studies' details are provided in Table 2 of Excluded Studies. Given the methodological limitations of the studies to infer causality, their results should be considered with caution and more weight given to results of randomised controlled studies.

Safety of the intervention: Preliminary safety results of a Brazilian randomised, double-blinded, phase IIb clinical trial of two different doses of chloroquine for hospitalised COVID-19 patients with severe respiratory syndrome, have recently been published[9]. The Data and Safety Monitoring Board had recommended the interruption of the high dose arm of chloroquine (12 g in total for 10 days) due to associated cardiotoxicity. QT prolongation and ventricular arrhythmia was more common in the high-dose vs low-dose arm (25% vs 10.71% and 7.1% vs 0.0%, respectively). Selection bias may have been present as older patients (>75 years) and patients with a history of cardiac disease were over-represented in the high-dose arm. The study is likely to be underpowered (n=81). The preprint provides a signal that high dose chloroquine is less safe than lower doses. Once published in a peer-reviewed journal, the RCT data will be reviewed and included in the meta-analysis, and this rapid review will be updated accordingly.

CONCLUSION

There is currently insufficient evidence to support inclusion of chloroquine or hydroxychloroquine in treatment guidelines for COVID-19 in South Africa until further evaluations are conducted and reported. There are currently at least 34 registered RCTs on this topic, some of which are already recruiting patients (https://clinicaltrials.gov/). Eligible patients in South Africa should be considered for enrolment in randomised clinical trials of potential therapies for COVID-19 (e.g. the SOLIDARITY trial), so that robust data on efficacy and safety of interventions can be generated to inform treatment policies going forward.

Reviewers: Tamara Kredo, Karen Cohen, Marc Blockman, Rene de Waal.

Declaration of interests: TK (Cochrane South Africa, South African Medical Research Council), KC and MB (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town) and RDW (Centre for Infectious Disease Epidemiology and Research, University of Cape Town) have no interests to declare in respect of chloroquine or hydroxychloroquine.

Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings
Chen Z et al, 2020[6] Full-text journal pre-print. Not peer-reviewed	Randomised controlled trial	China N = 62 Age >18 years (mean 44.7 years) Hospitalised SAR-CoV-2 PCR positive Pneumonia on chest CT Mild illness (SaO_2/SpO_2 >93% or PaO_2/FIO_2 >300 mmHg) Excluded: patients with severe illness, participants in other clinical trials, patients with liver and/or renal impairment	All received: Oxygen Antivirals, details not specified Antibacterials, details not specified Immunoglobulin, details not specified Intervention arm: Hydroxychloroquine sulfate 200 mg 12 hourly orally for 5 days (HCQ group)	Fever resolution time – normal body temperature for 72 hours (mean (SD): HCQ group 2.2 (0.4) days, control 3.2 (1.3) days Cough remission time (slight to no cough for 72 hours) 'significantly reduced' in HCQ group – results not reported. Progression to severe disease: 0/31 in HCQ group; 4/31 in control group Day 6 CT results (relative to pretreatment): Improved in 25/31 in HCQ group, and 17/31 in control group. Adverse events: 2 mild AEs in HCQ group (rash and headache)
Chen J et al, 2020[5] Published article (Chinese). Only abstract available in English.	Randomised controlled trial	China N = 30 Confirmed COVID-19, > 18 years old Exclusion criteria: allergic, pregnant,patients with serious disease or organ dysfunction, patients with retinal issues or hearing loss, or those with serious neurological or psychiatric disorders. Mean age 48 years (from McCormack review)	All received 'conventional treatment': all patients received inhaled interferons; 10 patients in experimental group and 12 in control group received Abidor; 2 patients in received lopinavir + ritinar (not clear which group). Intervention arm: Hydroxychloroquine sulphate 400 mg daily orally for 5 days (HCQ group)	SARS-CoV-2 nucleic acid conversion rate on pharyngeal swab at Day 7: negative in 13/15 in HCQ group, and 14/15 in control group ($p<0.05$) Time to body temperature normalisation (median (interquartile range)): 1 (0 to 2) day in HCQ group; 1 (0 to 3) day in control group. Progression to severe disease: 1/15 on HCQ group. Not stated for control group. Diarrhoea and abnormal liver function: 4/15 in HCQ group; 3/15 in control group.

Table 2. Characteristics of excluded studies

Citation	Study design	Population (n)	Treatment	Main findings
Gautret P et al. 2020 [7] Journal pre-print	Open-label, non-randomised clinical trial (all patients at 1 hospital received HCQ; patients at other participating hospitals didn't)	N = 42 (26 on HCQ; 16 controls) Hospitalised: but some were asymptomatic, some had upper respiratory tract symptoms only; some had pneumonia or bronchitis. SARS-CoV-2 PCR positive Age >12 years (mean age 45.1 years) Patients with contra-indications to chloroquine were excluded	All received symptomatic treatment and azithromycin given at the discretion of the investigators. Intervention arm: hydroxychloroquine sulfate 200 mg 8 hourly orally for 10 days (HCQ group)	Day 6 results presented for 36 patients; 6 HCQ patients were considered LTFU and were excluded from analysis (3 transferred to ICU, 1 died (cause not specified), 1 left hospital on Day 3, 1 stopped HCQ on Day 3). Negative SARS-CoV-2 on Day 6 nasopharyngeal swab: 70% in HCQ group and 12.5% in control group (p=0.001).
Molina JM, et al No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Médecine et Maladies Infectieuses. 2020. [8] Pre-proof publication	Open label, single arm cohort	N = 11 7 men, 4 women 10/11 had fever Mean age of 58.7 years (range: 20-77) 8 had significant comorbidities associated with poor outcomes (obesity: 2; solid cancer: 3; hematological cancer: 2; HIV-infection: 1)	All received same medical management as Gautret study: Hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg Day 1 and 250 mg days 2 to 5) – same as Gautret patients 10/11 with fever received nasal Oxygen when initiating treatment	Within 5 days, 1 died, 2 were in ICU. 1 patient discontinued hydroxychloroquine and azithromycin at 4 days because of prolonged QT (from 405 ms to 470 ms) Repeated nasal swabs in 10 that were alive were still PCR positive for SARS-CoV-RNA at days 5-6 after treatment started.

Table 3. GRADE table of the evidence from the included systematic review

ANTIMALARIALS FOR THE TREATMENT OF SARS-CoV-2 INFECTION						
Patients	SARS-CoV-2 infection					
Intervention	Addition of antimalarials (hydroxychloroquine or chloroquine) to standard treatment (as defined by the studies)					
Comparison	Placebo or no treatment (added to standard treatment as defined by the studies)					
Outcomes	**Relative effect (95% CI) -- Participants/ studies**	**Absolute effect***			**Certainty of evidence (GRADE)**	**Key messages**
		WITHOUT antimalarials	**WITH antimalarials**	**Difference (95% CI)**		
Mortality	-- 30 patients/ 1 trial [2]	On trial reported that all participants were still alive at 2 weeks of follow-up.			⨁◯◯◯[1,2] Very low	We are uncertain whether the addition of antimalarials to standard treatment decreases mortality as the certainty of the evidence has been assessed as very low.

Mechanical ventilation	The outcome mechanical ventilation or extracorporeal membrane oxygenation has not been reported by the analyzed evidence.				--	--
Extracorporeal membrane oxygenation	The outcome extracorporeal membrane oxygenation has not been reported by the analyzed evidence.				--	--
Length of hospital stay	The outcome length of hospital stay has not been reported in the evidence analyzed.				--	--
Respiratory failure	-- 92 patients/ 2 trials [2,3]	No studies were found evaluating respiratory failure or acute respiratory distress syndrome, however, indirect evidence was found: The trials reported that the group receiving antimalarials had less progression of lung disease*** compared to the control group (RR 0.46, 95% CI 0.15 to 1.39).			⨁◯◯◯[1,3,4] Very low	We are uncertain whether the addition of antimalarials to standard treatment decreases respiratory failure as the certainty of the evidence has been assessed as very low.
Serious adverse effects	-- 92 patients/ 2 trials [2,3]	No studies were found evaluating serious adverse effects, however indirect evidence was found: The trials reported that the group receiving antimalarials presented more total adverse effects**** compared to the control group (RR 1.65, 95% CI 0.50 to 5.50).			⨁⨁◯◯[1,3,4] Low	The addition of antimalarials to standard treatment may increase the incidence of serious adverse effects (low certainty of evidence)
SARS-CoV-2 clearance***	RR 0.93 (0.73 a 1.18) -- 30 patients/ 1 trial [2]	933 per 1000	**868 per 1000**	**65 less** (252 less to 168 more)	⨁⨁◯◯[1,3] Low	The addition of antimalarials to standard treatment may not increase SARS-CoV-2 clearance (low certainty of evidence)

95 CI%: 95% confidence interval
RR: Relative risk.
GRADE: Evidence grades *Grading of Recommendations Assessment, Development and Evaluation.*

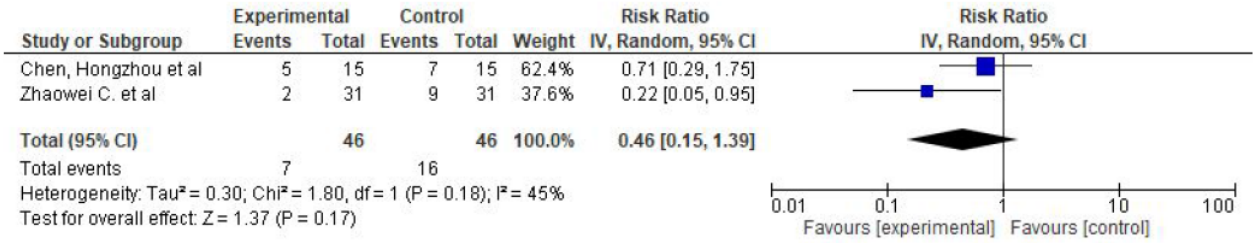
*The risk **WITHOUT antimalarials** is based on the risk in the control group of the trials. The risk **WITH antimalarials** (and its confidence interval) is calculated from relative effect (and its confidence interval).
** 2 weeks of follow-up.
*** Evaluated with CT scan at day 3 [2] and 6 [3].
**** Total adverse effects evaluated at 2 weeks [2] and 6 days [3] of follow-up, including diarrhea, anemia, elevated creatinine, transient AST elevation, rash and headache.
***** Defined as the proportion of patients with negative nasopharyngeal PCR at day 7.

[1] The certainty of the evidence was downgraded in one level for risk of bias, since there are limitations regarding the randomization process, administration of co-interventions and outcomes measurements. For the outcome serious adverse effects, we decided not to decrease the certainty of the evidence for this reason, since the absence of bias would reinforce the conclusion.
[2] The certainty of the evidence was downgraded in two levels for imprecision, since it cannot be ruled out that the observed effect is a product of chance, given the low number of events and sample size (n = 30).
[3] The certainty of the evidence was downgraded in one level for imprecision since different decisions would be taken at each end of the confidence interval.
[4] The certainty of the evidence was downgraded in one level for indirectness since the reported outcomes correspond to surrogates of respiratory failure and serious adverse effects. There is also controversy about indirectness regarding hydroxychloroquine therapeutic dose (400 mg qd). However, we did not downgrade for this factor because we did not find convincing evidence or consensus regarding the optimal dose.

Graphs. Forest plots of meta-analysis from the included systematic review

SARS-CoV-2 clearance

Lung disease progression (surrogate endpoint of respiratory failure)



Total adverse effects (surrogate endpoint of serious adverse effects)

Appendix 1: Search strategy

Epistemonikos (used in the systematic review)

((coronavir* OR coronovirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR "sars-coronavirus" OR hcov* OR (wuhan* AND (virus OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR cv19 OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR "mers-cov" OR "mers cov" OR "sars-cov" OR "sars cov"))

AND ((antimalari* OR "anti-malarial" OR "anti-malarials" OR "anti-malaria") OR (chloroquine* OR CQ OR Aralen) OR (hydroxychloroquine* OR HCQ OR Plaquenil))

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