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Abstract

As anti-malarial drugs have been found to inhibit Corona viruses in vitro, studies have evaluated the effect of these drugs in COVID-19 infection. We conducted an updated meta-analysis of clinical trials and observational studies published till June 2020. Patients with reverse transcription polymerase chain reaction (RT-PCR) confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (COVID-19) infection were included. The drugs used in the intervention group are Chloroquine (CQ)/Hydroxychloroquine (HCQ) with or without Azithromycin. The primary outcome is time to achieve virological cure. Of 1040 citations, 11 studies provided data of 1215 patients. Compared to control, CQ/HCQ has no significant effect on the time to negative COVID-19 RT-PCR results, neither in clinical trials (mean difference [MD] 1.55; 95% confidence interval [CI] -0.7 to 3.79; P = 0.18; n = 180), nor in observational studies (MD 1.14; 95%CI - 11.98 to 14.26; P = 0.86, n = 407). CQ/HCQ did not affect the virological cure after day 3, 7, 10, 14, 21 and 28; except after day 5, as shown by a single small non-randomised trial (odds ratio [OR] 9.33; 95% CI 1.51 to 57.65; P = 0.02, n = 30). Pooled data from 2 observational studies showed a significant effect of CQ/HCQ on virological cure by after day 10 (OR 7.86; 95% CI 4.4 to 14.04, P < 0.001, n = 373) and day 14 (OR 6.37; 95% CI 3.01 to 13.48, P < 0.001, n = 407). The GRADE evidence generated was of “very low-quality/certainty”. To conclude, CQ/HCQ does not affect the time to virological cure compared to usual/standard of care in COVID-19 infection. Recurrent infection in a smaller number of patients was noted in the CQ/HCQ group. As the evidence generated was of “very low-quality/certainty”, large good quality studies are needed to confirm the present findings.

Keywords: Aminoquinoline, azithromycin, COVID-19, evidence-based medicine, hydroxychloroquine, severe acute respiratory syndrome coronavirus 2

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19, a highly contagious disease emerged in Wuhan, China, in late 2019. Till date, it has infected millions of patients globally. India has a rising number of cases but the mortality is low. As there is no specific anti-viral drugs, pharmaceutical agents (antiviral agents, antibiotics, immune-modulators and convalescent plasma) are being tried with variable success.

Two aminoquinoline anti-malarial drugs (chloroquine [CQ] and hydroxychloroquine [HCQ]) were in the news for treatment of COVID-19 infection, after publication of one study from France. Subsequently, large studies (mainly observational) have been published. Both the drugs have been found to inhibit other corona viruses, such as SARS-CoV-1. The mechanisms of action include – inhibition of angiotensin converting enzyme 2 (ACE-2) used by the virus for entry into the cell, inhibition of release of viral particles into intra-cellular space, and a non-specific anti-inflammatory action (inhibition of interleukin-6 [IL-6], tumour necrosis factor, aberrant interferon and other pro-inflammatory cytokines that cause lung injury leading to acute respiratory distress syndrome). Both the drugs are cheap, and considered safe, as per their approved indications. Compared to CQ, HCQ is more soluble and less toxic and is considered safer.

There have been published studies evaluating the safety and/or efficacy of these agents (alone or in combination).
compared to a control arm or parallel intervention, to treat patients with COVID-19.\[4,15-24\] However, the results have been contradictory. A published rapid systematic review including data from three studies found no role of anti-malarial drugs on the virological outcomes in patients with COVID-19 infection.\[25\] After publication of this review, many studies (both observational studies and clinical trials) with larger sample sizes have been published. The present updated meta-analysis has included these larger studies to evaluate the effect of the anti-malarial drugs (CQ and HCQ) to inform clinical practice, and guide the international agencies to formulate recommendation.

**Materials and Methods**

**Types of studies**

Both clinical trials and observational studies comparing anti-malarial drugs (CQ and HCQ) alone or in combination with other drugs versus control (standard of care) or other treatment were included.

**Types of participants**

Children (age >12 years) and adults with reverse transcription-polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 (COVID-19) cases treated in the hospital were included. Exclusion criteria were allergy to these anti-malarial drugs, hearing loss, retinopathy and severe neuro-psychiatric diseases.

**Types of interventions**

Anti-malarial drugs (CQ and HCQ) administered (with or without Azithromycin) in various dose schedules to patients with SARS-CoV-2 (COVID-19) infection.\[13\] Control group patients received usual/standard of care as per the hospital/ institute policy or government guideline. Studies comparing different doses (high-dose versus low-dose of anti-malarial drugs) were also included.

**Types of outcome measures**

**Primary**

1. Time to virological cure (days).

**Secondary**

1. Proportion of patients with virological cure after days 3, 5, 7, 10, 14, 21 and 28
2. Proportion of patients with recurrence of infection.

Definition of outcome measures: Virological cure is defined as non-detection (negative report) of COVID-19 by RT-PCR in two consecutive respiratory specimens (naso-pharyngeal swabs, throat swabs, nasal swab, broncho-alveolar lavage fluid and tracheal aspirate) taken 24 h apart. Recurrence of infection is defined as detection (positive report) of COVID-19 by RT-PCR in any of the above specimens collected from a patient at any time point after documentation of virological cure.\[26\]

**Search methodology**

Major databases (PubMed/MEDLINE, Cochrane Central Register of Controlled Trials [CENTRAL], EMBASE, Google Scholar and Pre-print servers [medRxiv, bioRxiv, OSF preprints, preprints.org]) were searched systematically from 1970 to 5\textsuperscript{th} June 2020 [Appendix 1]. No language restrictions were applied. Two reviewers (SSN, BB) reviewed the search results to identify relevant studies.

**Data extraction**

Data extraction was done using a data extraction form that was designed and pilot tested \textit{a priori}. Two authors (BB and BM) independently extracted the following information from each study: author year, country, study design, setting (hospital or community), method of recruitment, inclusion criteria, risk of bias, participants (age, sex, sample size, disease severity), intervention (dosage, duration, frequency, and co-intervention if any), outcomes (outcome definition, valid unit of measurement, time points of collection, and reporting), loss to follow-up and key conclusions. Any disagreements between the two review authors were resolved through discussion with the third author (RRD).

**Assessment of risk of bias in the included studies**

Two review authors independently (BB, SSN) assessed the methodological quality of the selected trials by using Cochrane Handbook,\[27\] and of observational studies by Newcastle Ottawa Scale.\[28\] Quality assessment was undertaken using the ROBINS-I tool for non-randomised trials.\[29\] Any disagreements between the two review authors were resolved through discussion with the third author (RRD).

**Data synthesis**

Data were analysed using Review Manager (RevMan) V.5.1.\[30\] Data were pooled and expressed as mean difference (MD) with 95% confidence interval (CI), if continuous; odds ratio (OR) with 95% CI, if categorical. All the analyses were by Generic Inverse Variance method using random effects weighting.\[31\] where the log RR s for cohort studies or log OR s for case–control studies were weighted by the inverse of the variance to obtain a pooled RR estimate. A $P < 0.05$ was considered statistically significant. Inter-study heterogeneity was assessed by Cochrane’s Q (Chi-square $P < 0.10$) and quantified by $I^2$. An $I^2 \geq 50\%$ indicated ‘substantial’ heterogeneity and $\geq 75\%$ indicated ‘considerable’ heterogeneity.\[32\]

**Grade of evidence**

To assess the quality of evidence, we used GRADE Profiler software (V.3.2) (Hamilton, Canada).\[33,34\] The software uses five parameters for rating the quality of evidence (risk of bias, inconsistency of results, indirectness of evidence, imprecision of results and publication bias), and does rating as-no, serious and very serious limitation.

**Results**

**Description of studies**

Of 1040 total citations retrieved, the full text of 15 papers was assessed for eligibility, and 4 studies were excluded [Figure 1]. Of the remaining 11 eligible studies ($n = 1215$), 6 were published in peer-reviewed journals,\[4,15-19\] and 5 in pre-print servers (not peer-reviewed).\[20-24\] We contacted the authors of
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Effect of interventions

Primary outcomes

1. Time to virological cure (days): The pooled result from 2 RCTs showed no significant difference between the HCQ group and control group [MD 1.55 (95% CI -0.7 to 3.79), P = 0.18] [Figure 2]. The pooled result from two observational studies also showed no significant difference between the HCQ group and control group [MD 1.14 (95% CI -11.98 to 14.26), P = 0.86] [Figure 3].

Secondary outcomes

1. Proportion of patients with virological cure after days 3, 5, 7, 10, 14, 21 and 28: Compared to control, CQ/HCQ did not affect the virological cure after days 3, 7, 21 and 28 [Table 3]. However, the pooled data from 2 observational studies showed a significant effect of CQ/HCQ on virological cure after 10 and 14 days [Table 4].

Grade of evidence

The evidence generated was of ‘very low-quality’ for all the outcomes (primary and secondary). A detailed analysis of the summary of evidence is provided in Table 5.

Discussion

Summary of evidence

After an extensive search of the literature we could find 11 studies (n = 1215) eligible for inclusion in the review. Compared to control, CQ/HCQ has no significant effect on the time to negative COVID-19 RT-PCR results. CQ/HCQ does not affect the virological cure after days 3, 7, 10, 14, 21 and 28 (except after day 5 as shown by a single, small non-RCT). However, pooled data from 2 observational studies showed a significant effect of CQ/HCQ on virological cure after 10 and 14 days.

It has to be kept in mind that, the anti-viral action of anti-malarial drugs against COVID-19 is still largely unknown. The dose schedule of CQ was nearly uniform, however, the dose schedule of HCQ varied widely among the included studies (except one large study, the cumulative dose in remaining of the studies was equal to or higher than the recommended). The median time from onset of symptom to admission or treatment initiation was nearly ≤8 days in all but 2 studies. Except one study, others

Risk of bias in included studies

The details have been provided in Supplemental file [Appendix 2]. Except one trial, others had low to high-risk of bias in different domains. One non-RCT had serious risk of biases in all the domains. All the observational studies were at a high risk of bias for selection of controls, and a low risk of bias for the exposure parameters.
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Table 1: Characteristics of included studies

| Study author, Country | Number of patients | Age (year) of patients (Mean ± SD) | Disease severity | Dose schedule of CQ/HCQ | Time from symptom onset to treatment (d) | Additional information |
|-----------------------|--------------------|-----------------------------------|------------------|-------------------------|-----------------------------------------|-----------------------|
| Gautret 2020, France  | N: 36 (HCQ=14; HCQ + AZM=6; Control=16) | HCQ=51.2±18.7; Control=37.3±24 | All severity included | HCQ: 600 mg/d (200 mg TID) for 10 days; HCQ+AZM: AZM 500mg on day 1 followed by 250 mg OD for 4 days in addition to HCQ. | HCQ group recruited in one centre and control group in another. Attrition rate 23% in HCQ group. Funded study. There were protocol deviations. |
| Chen 2020, China     | N: 30 (HCQ=15; Control=15) | HCQ=50.5±3.8; Control=46.7±3.6 | Asymptomatic: 16.7%; URTI: 61.1%; LRTI: 22.2%; Not defined. | HCQ: 400 mg/d (OD) for 5 days. | Not mentioned |
| Huang 2020, China    | N: 22 (CQ=10; Control=12) | CQ (median, IQR)=41.5 (33.8-50); Control (median, IQR)=53 (41.8-63.5) | Moderate: 84%; Severe: 1.3% | HCQ: 1200 mg/d for 3 days followed by 800 mg/d for the remaining days (total treatment duration: 2 weeks for mild/moderate, and 3 weeks for severe cases) | Mean: 16.6 (HCQ started within 24 h of randomization) |
| Borba 2020, Brazil   | N: 81 (CQ high-dose=41; CQ low-dose=40) | CQ (median, IQR)=54.7±13.3; CQ low-dose=47.4±13.3 | Severe: 89% (33% were critical) | High-dose CQ: 600mg BID for 10 days (total dose 12 g); Low-dose CQ: 450mg BID on day 1 followed by OD for 4 days (total dose 2.7 g) | Underlying co-morbidities: hypertension (18.2%), diabetes (9.1%), and cerebro-vascular disease (4.5%). No protocol deviation. Funding status not mentioned |
| Huang 2020, China    | N: 373 (CQ=197; Control=176) | median (IQR): [CQ=43 (33-55); Control=47.5 (35.8-56)] | Mid: 3.8%; Moderate: 91.4%; Severe: 4.8% | CQ: 500 mg/d to 1000 mg/d (OD or BID) for 10 days | Major co-morbidities: hypertension (6.4%), diabetes (2.4%). Funded study |
| Mallat 2020, UAE     | N: 34 (HCQ=23; Control=11) | median (IQR): [HCQ=33 (31-48); Control=41 (30-55)] | Mild and moderate (100%) | HCQ: 800 mg/d (400 mg BID) on day 1 400 mg/d for 10 days | Major co-morbidities: hypertension (14.7%), asthma (8.8%), and diabetes (5.9%). |

HCQ: Hydroxychloroquine, CQ: Chloroquine, AZM: Azithromycin, RT-PCR: Reverse transcription polymerase chain reaction, URTI: Upper respiratory tract infection, LRTI: Lower respiratory tract infection, IQR: Inter-quartile range, ICU: Intensive care unit, OD: Once daily, BID: Twice daily, RCT: Randomised controlled trial, SD: Standard deviation

used CQ/HCQ within 48 h of admission/hospitalization. This might be due to the fact that starting anti-viral drugs (including HCQ/CQ) after 48 h of symptom onset might not be beneficial as the golden window for antiviral treatment (e.g. in influenza) is lost. However, this is difficult in a hospitalised setting (may be possible in outpatient or community setting). Another important point is that, the patients included in the present study were having comorbidities, and were on multiple drugs. The interactions between these drugs, and CQ/HCQ in affecting the action of the later on COVID-19 are unknown at present. Moreover, as none of the studies measured the blood level of these drugs, it is difficult to conclude this (at least to some extent). In two studies, recurrent COVID-19...
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Infection was noted (from faecal samples in one study). The authors could not explain the reason for the same as none of the patients in the control group was positive. Future studies with larger samples might provide insight into the causation.

**Limitations**

The studies were variable in many aspects (blinding of participants and outcome assessors, patient selection, severity of illness, dose schedule of the anti-malarial drugs, timing of

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**Table 2: Characteristics of studies published in pre-print server (not peer-reviewed)**

| Study author (Year) | Country     | Study design     | Number of participants (disease severity) | Dose schedule of CQ/HCQ | Viral outcome measures |
|---------------------|-------------|------------------|-------------------------------------------|-------------------------|-----------------------|
| Chen 2020[21]       | China       | RCT              | 62 (nonsevere cases)                      | HCQ 200 mg BID for 5 days | None                  |
| Chen 2020[22]       | China       | Observational study | 284 (all severity)                       | CQ for 7 days            | CQ does not enhance viral clearance |
| Feng 2020[23]       | China       | Observational study | 50 (all severity)                        | CQ for 7 days            | Chloroquine deserves further investigation |
| Shabrawishi 2020[24] | Saudi-Arabia | Observational study | 93 (mild and moderate cases)            | Group 1: CQ/HCQ Group 2: CQ/HCQ + azithromycin Group 3: CQ/HCQ + antiviral drugs |

CQ: Chloroquine, HCQ: Hydroxy-chloroquine, RCT: Randomised controlled trial

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**Table 3: Outcome measures from clinical trials (randomised, quazi-randomised and nonrandomised)**

**HCQ/CQ versus control**

| Outcome measures | Number of trial(s) | Sample size | Effect estimate               | P       |
|------------------|--------------------|-------------|------------------------------|---------|
| Time to negative COVID-19 RT-PCR (d) | 2[14,15] | 180 | MD 1.55; 95% CI 0.7-3.79 (I²=0%) | 0.18    |
| Proportion with negative COVID-19 RT-PCR | | ] |                           |         |
| After day 3 | 2[14,15] | 180 | OR 1.02; 95% CI 0.16-6.6 (I²=78%) | 0.98    |
| After day 5 | 1[13] | 30 | OR 9.33; 95% CI 1.51-57.65 | 0.02*    |
| After day 7 | 3[14-16] | 202 | OR 0.65; 95% CI 0.36-1.17 (I²=0%) | 0.15    |
| After day 10 | 1[15] | 150 | OR 0.73; 95% CI 0.37-1.47 | 0.38    |
| After day 14 | 3[14-16] | 202 | OR 0.98; 95% CI 0.44-2.15 (I²=0%) | 0.95    |
| After day 21 | 1[15] | 150 | OR 1.49; 95% CI 0.62-3.61 | 0.37    |
| After day 28 | 1[15] | 150 | Not pooled (event NE in HCQ group) |         |

**HCQ and AZM versus control**

| Outcome measures | Number of trial(s) | Sample size | Effect estimate | P       |
|------------------|--------------------|-------------|-----------------|---------|
| Proportion of patients with negative RT-PCR | 1[13] | 22 | OR 15.0; 95% CI 1.32-169.89 | 0.03*    |
| After day 3 | 1[13] | 22 | OR 0.45; 95% CI 0.02-10.67 | 0.62    |

**High-dose versus low-dose CQ**

| Outcome measures | Number of trial(s) | Sample size | Effect estimate | P       |
|------------------|--------------------|-------------|-----------------|---------|
| Proportion of patients with negative RT-PCR | 1[13] | 27 | No separate data (6 patients negative) | NE      |

*P<0.05 significant. OR: Odds ratio, MD: Mean difference, CI: Confidence interval, RT-PCR: Reverse transcription polymerase chain reaction, Heterogeneity: F, AZM: Azithromycin, NE: Not estimable, CQ: Chloroquine, HCQ: Hydroxy-chloroquine

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**Figure 2: Time to virological cure (hydroxychloroquine vs. control; result from randomised controlled trials)**

[Image of Figure 2: Time to virological cure]
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**Table 4: Outcome measures from observational studies**

| Outcome measures | Number of study (reference) | Sample size | Effect estimate | P |
|------------------|-----------------------------|-------------|-----------------|---|
| Time to negative PCR results for COVID-19 (days) | 2[23,25] | 407 | MD 1.14; 95% CI -11.98-14.26 ($I^2=89\%$) | 0.86 |
| Proportion of patients with negative COVID-19 PCR | 1[27] | 373 | OR 7.86; 95% CI 4.4-14.04 <0.001* |  |
| After day 10 | 2[23,25] | 407 | OR 6.37; 95% CI 3.01-13.48 ($I^2=0\%$) | <0.001* |

*P<0.05 significant. OR: Odds ratio, MD: Mean difference, CI: Confidence interval, PCR: Polymerase chain reaction, Heterogeneity: $I^2$, CQ: Chloroquine, HCQ: Hydroxy-chloroquine

**Figure 3:** Time to virological cure (hydroxychloroquine vs. control; result from observational studies)

**Table 5: GRADE evidence (Effect of Chloroquine/Hydroxy-chloroquine±Azithromycin vs. Standard of care on COVID-19 virological outcomes)**

| Outcomes | Number of Participants (studies) | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects* |
|----------|---------------------------------|---------------------------------|-------------------------|------------------------------|
| **Primary outcome measures** | | | | |
| Time to virological cure (d) | 180 (2 RCTs) | ⊕⊝⊝⊝ | MD 1.55 (-0.7 to 3.79) | The mean time to virological cure (d) in the intervention groups was 1.55 higher (0.7 lower to 3.79 higher) |
| Time to virological cure (d) | 407 (2 observational studies) | ⊕⊝⊝⊝ | MD 1.14 (-11.98 to 14.26) | The mean time to virological cure (d) in the intervention groups was 1.14 higher (11.98 lower to 14.26 higher) |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Secondary outcomes: pooled results from minimum 2 studies are reported here. GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. *Open label trials with difference in the dose schedule of intervention and time to start of intervention, 5Sample size was less with wider 95% CI that includes line of no effect, 6In one trial, all patients in both the groups were cured. CI: Confidence interval; OR: Odds ratio; MD: Mean difference, RCT: Randomised controlled trial
administration, etc). Due to lack of paediatric data, the results of present review cannot be extrapolated to this population.

Conclusions
CQ/HCQ does not affect the time to virological cure compared to usual/standard of care used in the treatment of COVID-19 infection at present. Recurrent infection in a smaller number of patients was noted in the CQ/HCQ group. Good quality and multi-centric RCTs are required for any firm conclusion to be drawn or recommendation to be made during the on-going pandemic.

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Conflicts of interest
There are no conflicts of interest.

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