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COMMENTARY

Hydroxychloroquine in COVID-19: The Study Points to Premature Decisions on Efficacy While Bells Ringing for Safety

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Abstract: Coronavirus disease (COVID-19) pandemic has been a global disease burden. It has affected more than sixteen million people in the world within seven months of its first outbreak in Wuhan. Different treatment modalities, therapeutic and prophylactic agents for its therapy are underway. Until the proven therapy gets available, repurposing of drugs is a better way out. Hydroxychloroquine (HCQ) has been a potential recourse of treatment in this regard for COVID-19 management. As different episodes of cardiac adverse events of HCQ are reported, safety concerns are now a prime objective. The risk-benefit analysis is mandatory to address rational drug therapy even in such a global health crisis. In this article, we want to evaluate the safety and efficacy of HCQ in COVID-19 management.

Keywords: cardiac arrhythmia, COVID-19, drug repositioning, hydroxychloroquine, severe acute respiratory syndrome coronavirus-2

Introduction

Coronavirus disease (COVID-19) pandemic has created strain over all the system on the globe. It has constituted a huge hurdle affecting millions of human beings.[1] Though it has spread mostly around the developed world, the situation is worse in low- and middle-income countries (LMICs). The crawling progress in the health-care system and economy to thrive can be the factors behind this. No known treatment on hand leads to the reuse of the old concept of drug repurposing. In repurposing studies of drugs, anti-malarial agent, especially hydroxychloroquine (HCQ), is found to be significant as a potential treatment option.[2,3] Its property to inhibit virus entry into the cells and to reduce the cytokine storm is considered a prime factor for COVID-19 management.[4] More than 200 trials on this drug are going on all over the world.[5] Meanwhile, a question on its clinical efficacy and safety concern is raised by larger studies regarding the treatment of COVID-19 cases. HCQ's use can give rise to severe arrhythmias affecting multiple systems.[6] QT-prolongation is the commonest cardiac consequence of HCQ, for which patients need to be monitored, especially if there is concomitant use of other QT-prolonging medications. Thus, COVID-19 cases under HCQ need to evaluate and monitor prior to the development of further consequences like ventricular arrhythmias.[7]

We searched databases like PubMed, Medline, Google Scholar, MedRxiv, Research Square, Cochrane Library, and Clinicaltrials.gov to find different articles regarding the use of HCQ in patients with COVID-19. We built search builder using

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appropriate medical search headings words and bullions as: ("coronavirus"[mh] OR "COVID 19"[tw] OR "SARS CoV 2"[All Fields] OR "novel coronavirus"[tw]) AND ("Hydroxychloroquine"[mh] OR "HCQ"[All Fields] OR "hydroxychloroquine"[tw]) for relevant papers in PubMed, Medline, and Cochrane Library. For search in Google Scholar, preprint sites and Clinicaltrials.gov "Hydroxychloroquine" and "COVID 19" used to search relevant papers. We included randomized controlled trials (RCTs), retrospective and prospective studies for our study that compared the use of HCQ with or without azithromycin in addition to standard of care compared to the patients receiving standard of care alone. We excluded reviews, commentaries, protocols, letter to editors, and editorials for this study.

Hydroxychloroquine – at a Glance

It is a synthetic derivative of 4-aminoquinoline which was synthesized as a drug in the mid-1940s.[8] It has chemotherapeutic and antibiotic characteristics. It also has anti-inflammatory activity and is being used to treat autoimmune diseases like rheumatoid arthritis and lupus erythematosus.[9] Being a weak base, it is supposed to elevate endosomal pH in host intracellular organelles thus prevent autophagosome-lysosome fusion and inactivate the enzymes required by the virus for replication.[10] By increasing endosomal pH, it also affects the terminal glycosylation of the receptor angiotensin-converting enzyme-2. This results in the prevention of virus entry into the cells as this receptor is utilized by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to enter the cell.[11] Significant cardiac adverse effects associated with HCQ such as QT-prolongation, ventricular arrhythmias, torsade de pointes (TdP), and cardiomyopathy are the prime concerns that require risk-benefit judgment in COVID-19 management.[12–14]

Apart from cardiac side effects, it has also the potential to cause bone marrow failure, hemolysis in glucose-6-phosphate dehydrogenase deficiency cases, retinopathy, gastrointestinal disorders, hepatobiliary disorders, metabolic disorders like hypoglycemia, skeletal muscle myopathy, neuromyopathy, psychiatric disorders, and exfoliative dermatitis.[15]

There are variable reports from laboratory to human use in RCTs regarding the effects of such 4-aminoquinolines in some viruses like the influenza virus, Zika virus, ebola virus, dengue virus, and chikungunya virus. Though showing somehow effective results in laboratory experiments, the insignificant result is reported in most of the human use. Such a response may be attributable to the drug's complex pharmacokinetics that makes it difficult to extrapolate to humans.[10]

Outcome of HCQ

HCQ and standard of care in COVID-19 patients versus standard of care alone studies reported no significant differences in overall virological clearance between the two arms. The effectiveness of HCQ for such action drew attention by the study conducted by Gautret et al.[16] While subsequent studies by Chen J. et al, Mallat et al and Tang et al did not demonstrate virological clearance.[17–19] A similar type of study reported significant differences in radiological progression between two arms. The study by Chen Z. et al showed improvement in CT findings, while another study by Chen J. et al did not support such findings.[17,20]

Regarding mortality, a mixed type of result obtained with HCQ use. Rosenberg et al, Magagnoli et al, and Geleris et al showed increased risk of mortality among HCQ groups.[21–23] In contrast to that, Yu et al, and Membrillo et al[24,25] showed a decrease in mortality rate while the reports by Gautret et al, Lee et al, Mahevas et al, and Barbosa et al were inconclusive.[16,26-28]

Rosenberg et al, Geleris et al, and Barbosa et al reported an increase in intubation rate and mechanical ventilation.[21,23,28] Whereas Magagnoli et al, Yu et al, and Lee et al demonstrated inconclusive results comparing hydroxychloroquine with the standard of care.[22,24,26]

Table 1: Studies regarding safety and efficacy of hydroxychloroquine with or without azithromycin in patients diagnosed with COVID-19.

Safety Profile

Tang et al, Rosenberg et al, and Mahevas et al[19,21,27] notified an increased risk of overall adverse effects. While Gautret et al, Chen J et al, Chen Z et al, and Lee et al claimed less adverse profile of this agent.[16,17,20,26] On top of that, Tang et al, Lee et al, and Mahevas et al advocated that there is no severe adverse effect of such agent.[19,26,27]

The significantly higher risk of cardiac adverse events like QT prolongation is found to be associated with the use of HCQ. Studies conducted by Rosenberg et al and Mahevas et al demonstrated such effects to a greater extent.[21,27] The de-novo arrhythmias and QT prolongation are found to be aggravated by concomitant administration of azithromycin.[7]

Table 1 Studies Regarding Safety and Efficacy of Hydroxychloroquine with or Without Azithromycin in Patients Diagnosed with COVID-19

Study	Study Type	Outcomes	Dosing and Duration of HCQ Therapy	Safety Profiles
Barbosa et al[28]	Quasi-randomized trial	The HCQ group had a significantly higher respiratory support need at 5 days compared to the only support group (p=0.013).	HCQ 400 mg BD for 1–2 days followed by 200mg OD for 4 days in the treatment group	No side effects mentioned.
Chen Jun et al[17]	RCT	The median time from hospitalization to virus nucleic acid negative conversion was 4 (1, 9) days in HCQ group, which is comparable to that in the control group [2 (1, 4) days, Z=1.27, *P*>0.05]. The median duration for normalization of body temperature in HCQ group was 1 (0, 2) day after hospitalization, which was also comparable to that in the control group [1 (0, 3) day]. Radiological progression was shown on CT images in 5 cases (33.3%) of the HCQ group and 7 cases (46.7%) of the control group, and all patients showed improvement in follow-up examinations.	HCQ 400 mg BD for 5 days in the treatment group	No severe side effects. 27% (4/15) patients receiving HCQ developed side effects.
Chen et al[20]	RCT	The time to clinical recovery (body temperature recovery time and the cough remission time) were significantly shortened in the HCQ treatment group. Patients had improved pneumonia in the HCQ treatment group (80.6%, 25 of 31) compared with the control group (54.8%, 17 of 31).	HCQ 400 mg BD for 5 days in the treatment group	No severe side effects. 6.5%(2/31) patients receiving HCQ developed mild side effects.
Gautret et al[16]	RCT	At day 6, 70% of HCQ patients were virologically cured compared to 12.5% in control group (p = 0.001).	HCQ 200 mg, TID for 10 days	No severe side effects. 0.8% (1/26) patients receiving HCQ experienced a side effect.
Geleris et al[23]	Observational study	There was no significant association between HCQ use and intubation or death (HR, 1.04, 95% CI, 0.82 to 1.32).	HCQ 600 mg BD on day 1, then 400 mg daily for a median of 5 days And AZT 500 mg on day 1 and then 250 mg daily for 4	Side effects not mentioned.
Lee et al[26]	Retrospective cohort Study	Switching therapy due to clinical failure was significantly more common in the HCQ group than in the LPV/r group [41% (11/27) and 2% (1/45), respectively, P=0.001]. There was a significant progression of disease in the HCQ group than in the LPV/r group [44% (12/27) and 18% (8/45), respectively, P=0.030].	HCQ (400 mg orally every 24 hours) Lopinavir in the control group	3.7% (1/27) patients experienced a severe side effect. 25.9% (7/27) patients receiving HCQ experienced side effects.

(*Continued*)

Table 1 (Continued).

Study	Study Type	Outcomes	Dosing and Duration of HCQ Therapy	Safety Profiles
Magagnoli et al[22]	Retrospective analysis	The risk of death from any cause was higher in the HCQ group (adjusted HR, 2.61; 95% CI, 1.10 to 6.17; P=0.03) but not in the HCQ + AZ group (adjusted HR, 1.14; 95% CI, 0.56 to 2.32; P=0.72). There was similar risk of ventilation was in the HCQ group (adjusted HR, 1.43; 95% CI, 0.53 to 3.79; P=0.48) and in the HCQ+AZ group (adjusted HR, 0.43; 95% CI, 0.16 to 1.12; P=0.09), compared to the NHCQ group.	HCQ or HCQ + AZT in combination	Side effects not mentioned.
Mahevas et al[27]	Comparative observational study	Survival rate without transfer to the ICU at day 21 was 76% in HCQ group and 75% in the control group (weighted HR 0.9, 95% CI 0.4 to 2.1). Overall survival at day 21 was 89% in the treatment group and 91% in the control group (1.2, 0.4 to 3.3). At day 21, 82% of patients in the HCQ group had been weaned from oxygen compared with 76% in the control group (Weighted risk ratio 1.1, 95% CI 0.9 to 1.3).	HCQ 600 mg within 48 hours of a hospital visit	1.1% (1/84) receiving HCQ experienced severe side effects. 9.5% (8/84) receiving HCQ experienced side effects.
Mallat et al[18]	Retrospective observational study	Time to negative viral load was longer in HCQ group (17 [13–21] vs 10 [4–13] days in p=0.023). On day 14, 47.8% (14/23) patients tested negative in the HCQ group compared to 90.9% (10/11) in NHCQ group (p=0.016).	HCQ 400 mg BD for 1 day followed by 400 mg OD for 10 days	No side effects observed.
Membrillo et al[25]	Observational cohort study	Cumulative survival increased in HCQ treated group. Mild group: - 14.4 days (95% CI: 13.7–15.2 days) in those treated with HCQ and 8.2 days (95% CI: 6.5–9.9 days) in the untreated group. Moderate group: - 10.9 days (95% CI: 9.3–12.5 days) in those treated with HCQ and 7.7 days (95% CI: 4.4–10.9 days) in the untreated group. Severe group: - 6 days (95% CI: 3.3–8.5 days) in those treated with HCQ and 4 days (95% CI: 1.7–6.1 days) in NHCQ group.	A loading dose of 1200 mg HCQ followed by a maintenance dose of 400 mg OD	Not mentioned.

(*Continued*)

Table 1 (Continued).

Study	Study Type	Outcomes	Dosing and Duration of HCQ Therapy	Safety Profiles
Rosenberg et al[21]	Retrospective cohort study	The probability of mortality for patients receiving HCQ+ AZT was 189/735 [25.7% (95% CI, 22.3%-28.9%)], HCQ alone, 54/271 [19.9% (95% CI, 15.2%-24.7%)], AZT alone, 21/211 [10.0% (95% CI, 5.9%-14.0%)], and neither drug, 28/221 [12.7% (95% CI, 8.3%-17.1%)]. In adjusted Cox proportional hazards models, there were no significant differences in deaths for patients receiving HCQ + AZT [HR, 1.35 (95% CI, 0.76–2.40)], HCQ alone [HR, 1.08 (95% CI, 0.63–1.85)], or AZT [HR, 0.56 (95% CI, 0.26–1.21)] compared to patients receiving no drug. In logistic models, cardiac arrest was significantly more likely in patients receiving HCQ + AZT [adjusted OR, 2.13 (95% CI, 1.12–4.05)], but not HCQ alone [adjusted OR, 1.91 (95% CI, 0.96–3.81)] or AZT alone [adjusted OR, 0.64 (95% CI, 0.27–1.56)] compared to patients receiving no drug.	HCQ + AZT, HCQ alone, AZT alone	No serious side effects. 56.1% (565/1006) patients receiving HCQ experienced side effects.
Tang et al[19]	RCT	The probability of negative conversion by 28 days in the standard of care plus HCQ group was 85.4% (95% CI 73.8% to 93.8%), similar to that in the standard of care group (81.3%, 71.2% to 89.6%).	HCQ 1200 mg OD for 3 days followed by 800 mg OD for 2–3 weeks in the treatment group	2.85% (2/70) patients receiving HCQ experienced severe side effects. 30% (21/70) patients receiving HCQ experienced side effects. In the safety population, adverse events were recorded in 7/80 (9%). The most common adverse event in the HCQ recipients was diarrhea, reported in 7/70 (10%) patients.
Yu et al[24]	Retrospective study	Fatalities were 18.8% (9/48) in HCQ group, which is significantly lower than 47.4% (238/502) in the NHCQ group (P<0.05). The LoHS before patient death was 15 (10–21) days and 8 (4–14) days for the HCQ and NHCQ groups, respectively (P<0.05).	HCQ 200 mg BD for 7–10 days in the treatment group	Not mentioned.

Abbreviations: AZT, azithromycin; BD, twice a day; CI, confidence interval; CT, computed tomography; HCQ, hydroxychloroquine; HR, hazard ratio; ICU, intensive care unit; LoHS, length of hospital stay; LPV/r, lopinavir/ritonavir; NHCQ, non-hydroxychloroquine; OD, once a day; OR, odds ratio; RCT, randomized controlled trial; TID, three times a day.

Mild types of adverse reactions are reported in Chen Z et al study where one patient developed a rash and another one experienced headache.[20] Similarly, transient diarrhea with abnormal liver function tests is reported by Chen J et al along with one severe case.[17] Tang et al reported diarrhea, blurred vision, and thirst as adverse events in 30% of patients in his study and two of them reported severe events due to disease progression to upper respiratory tract infection.[19] The cardiac adverse event is found significant among adverse reactions. QT prolongation and de novo

ventricular arrhythmia are reported by many studies.[7,21,27,29,30] In some studies, fewer adverse events are reported in the treatment group than the control group.[26] Six patients on HCQ were lost in follow-up in a study conducted by Gautret et al.[16] In this regard, HCQ cannot be considered safe to use for COVID-19 patients without evaluating risk–benefit ratio.

One a recent multinational registry-based cohort study by Mehra et al is not discussed above though it is of good size being it is kept under retraction notice because of methodical flaws and not meeting the basic requirement of the committee of publication ethics.[31]

Furthermore, with the revocation of the emergency use authorization for HCQ by the United States – Food and Drug Administration on 15 June 2020, its use in a clinical settings for COVID-19 management has been limited. It has been practiced in case of clear benefits that outweigh the risks to the patients.[32]

Conclusion

From the different studies, it can be concluded that the use of HCQ for COVID-19 is not free of associated risks. In such a global health crisis without approved treatment modalities, therapeutic or prophylactic agents, the use of HCQ as a possible treatment option is not an irrational choice. However, different studies report the increased risk of overall de-novo arrhythmias and significant QT-prolongation and mortality with the use of HCQ. Such incidences are more severe with its combination with a macrolide. Moreover, there was no improvement in survival, need for intubation following treatment. Despite some improvement in radiological progression in some studies, there were increased overall and severe adverse effects, though not statistically significant, among all studies. There is a need for the completion of ongoing substantial RCTs for the apropos evaluation of HCQ as a treatment option for COVID-19.

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Disclosure

The authors report no conflicts of interest in this work.

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