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The effect of hydroxychloroquine on mortality in hospitalized COVID-19 patients

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ABSTRACT

As of October 2020, there are no commonly accepted or proven effective treatments for coronavirus disease 2019 (COVID-19). Hydroxychloroquine (HCQ) is an established anti-malarial drug with demonstrated action against SARS-CoV-2 (the virus that causes COVID-19) in-vitro and early observational studies and anecdotal evidence supported its use in treatment of COVID-19. In this review, three of largest and most statistically powerful studies to date (two cohort studies and one randomized controlled trial [RCT]) are synthesized for the purpose of determining whether HCQ is effective in reducing mortality in patients hospitalized with COVID-19. All three studies found no statistically significant difference in mortality between patients treated with HCQ and patients in a control group (receiving only standard care). Although evidence on the use of HCQ to treat COVID-19 has been conflicting and controversial, this review finds no evidence to support its continued use.

INTRODUCTION

In October 2020, seven months after the World Health Organization declared the SARS-CoV-2 outbreak a global pandemic, infections and deaths from the virus continue to rise. As of early October 2020, there have been over 37 million SARS-CoV-2 infections reported worldwide and over one million deaths. The United States (U.S.) alone has seen over 200,000 COVID-19-related deaths.[i] There is still no cure; although, several promising vaccines are on the horizon. There are also no commonly accepted or proven effective COVID-19 treatments.

Chloroquine (CQ) and HCQ, both established anti-malarial drugs with similar mechanisms of action, were among the first drugs tested against SARS-CoV-2. Both drugs have demonstrated action against the virus in-vitro and studies conducted early in the outbreak suggest both are effective in treating COVID-19.[ii,iii,iv,v,vi,vii,viii] However, larger and more recent studies suggest HCQ is ineffective against COVID-19 and even dangerous, considering the side effects.[ix,x,xi,xii,xiii,xiv,xv,xvi,xvii]

Yet, the use of hydroxychloroquine for the treatment of COVID-19 patients in the U.S. continues to be controversial; pundits, politicians, and medical professionals have lined up on both sides of the debate. The president of the U.S., Donald Trump, along with his political supporters, including some medical professionals, have touted the effectiveness of HCQ against COVID-19.[xviii,xix,xx,xxi,xxii,xxiii] President Trump even went so far as to take the controversial as prophylaxis against SARS-CoV-2.[xxiv]

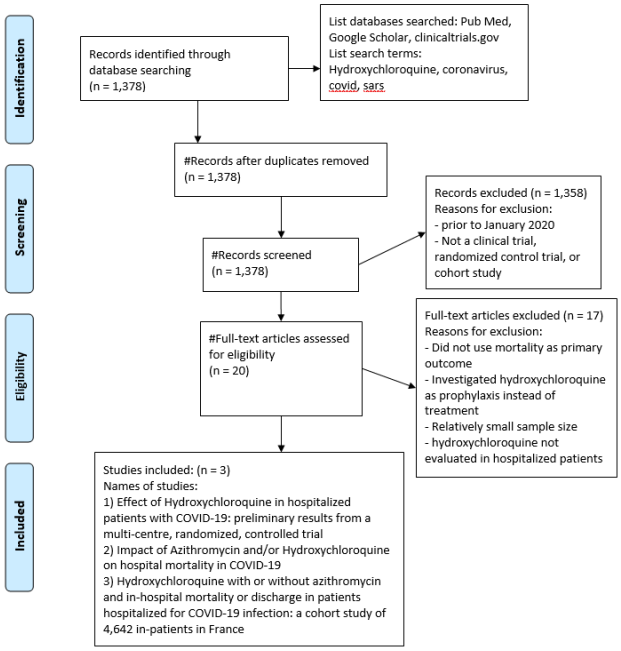
Given the controversy and dramatic publicity HCQ continues to receive, medical professionals may feel pressure from patients to administer the drug to treat or prevent COVID-19. In this review, three of the most recent and statistically powerful studies addressing HCQ as a treatment for COVID-19 are synthesized. The purpose is to arm readers with an understanding of the current state of the research and to determine whether HCQ is an effective treatment for patients hospitalized with COVID-19.

Clinical question: is HCQ effective in reducing mortality in patients hospitalized with COVID-19?

METHODS

A search of PubMed, clinicaltrials.gov, and Google Scholar was performed using the following search terms: "hydroxychloroquine," "coronavirus," "covid," and "sars." Studies published before the global outbreak began in January 2020 were excluded from the search, which resulted in 1,378 records. Further studies were excluded if they were not randomized controlled trials or cohort studies, which brought the number of records down to 20. Of the 20 records, 17 were excluded because they either 1) did not use mortality as a primary outcome, 2) had a relatively small sample size, 3) examined the use of HCQ as prophylaxis, or 4) did not evaluate HCQ in hospitalized patients (see **Figure 1**). The three studies chosen for examination, two cohort studies and one randomized controlled trial, all evaluated the association between mortality and treatment with HQ. Two studies used 28-day mortality as a primary endpoint while the third used in-hospital mortality.

Figure 1 – PRISMA flow diagram



RESULTS

Study #1

Effect of hydroxychloroquine in hospitalized patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial[xxv]

Objective

To evaluate the efficacy of HCQ in reducing 28-day mortality, vs. "usual care" alone, in patients hospitalized with COVID-19.

Design

The results of this study are part of the RECOVERY trial, an individually randomized, open-label, platform trial that compares treatments for hospitalized patients with COVID-19.[1] The trial incorporates patients who are at least 18 years old[2] and admitted to one of 176 hospitals across the United Kingdom with either a suspected or confirmed SARS-CoV-2 infection. For the HCQ trial, patients were excluded if they had a known prolonged QTc interval. Other patients were excluded, at the attending physician's discretion, for inability to tolerate treatment.

Patients were randomized to receive HCQ (1,561) or "usual care" (3,155) at a ratio of 2:1; the investigators were blinded to the allocation of treatment, but patients and local health care staff were not. Patients in the HCQ arm received an 800 mg loading dose of HCQ sulfate (in 200 mg tablets) at zero and six hours, then 400 mg every 12 hours for the next nine days or until discharge.

The primary outcome for the HCQ trial was 28-day all-cause mortality. Secondary outcomes included time to discharge and invasive mechanical ventilation. The investigators also tracked data on major cardiac arrhythmia, use of hemodialysis, and cause of death. Results of the trial were recorded through an online form that was completed when patients died, were discharged, or 28 days after assignment to an intervention arm.

Investigators used the log-rank statistic and its variance to test the 28-day mortality null hypothesis (that HCQ provided no survival benefit) and to compare the two intervention arms by estimating an average mortality rate ratio.[3] For secondary outcomes, Kaplan-Meier survival curves were used to analyze time to discharge and a risk ratio was estimated for invasive mechanical ventilation. Subgroup analysis was performed based on sex, age, level of respiratory support, time since symptom onset, and predicted 28-day mortality risk; a chi-

[1] https://www.recoverytrial.net/

[2] This age restriction was in place until May 2020; now there is no age limitation.

[3] Rate of death for patients in the HCQ arm / rate of death for patients in the usual treatment only arm

squared test for trend was used to compare subgroups. Subgroup analysis based on ethnicity is to be conducted soon.

Results

For the primary outcome of 28-day mortality, investigators found no significant difference between the two intervention arms. In the HCQ arm, 418/1561 patients died (26.8%) and in the "usual care" arm, 788/3155 patients died (25.0%); the rate ratio is 1.09 with a 95% confidence interval of 0.96 to 1.23 (P=0.18). These results were largely unchanged across subgroups. Additionally, no significant difference in the occurrence of major cardiac arrhythmia[4] was found between the HCQ and "usual care" arms (44.7% in the HCQ arm vs. 43.0% in the "usual care" arm).

However, regarding secondary outcomes, patients in the HCQ arm were more likely to spend more time in the hospital and had a lower probability of being discharged alive compared to the usual treatment arm; patients in the HCQ arm spent a median of 16 days in the hospital vs. 13 days for the usual treatment arm. The ratio for rate of discharged alive in the HCQ vs. usual treatment arms was 0.92, with a 95% confidence interval of 0.85 to 0.99.

Critique

The RECOVERY trial is one of the few randomized controlled trials that has been conducted so far on HCQ as a treatment for COVID-19. It stands out as being one of the largest and most statistically powerful trials to date. It is also the largest of *any* HCQ treatment study (cohort, observational, etc.) that uses mortality as a primary outcome. As a result, this study arguably presents the most meaningful results and conclusions concerning HCQ as a treatment for COVID-19 of any study, to date.

One drawback to the RECOVERY trial is that it is open-label; patients and local health care staff are not blinded to the interventions and the placebo effect was not tested. Although, the placebo effect would likely only serve to further support HCQ's lack of efficacy in treating COVID-19, so this is not a substantial drawback. Additionally, it is unclear what "usual care" entails; this could vary among hospitals. A trial where "usual care" is standardized across hospitals would be more informative.

Study #2

Hydroxychloroquine with or without azithromycin and in-hospital mortality or discharge in patients hospitalized for COVID-19 infection: a cohort study of 4,642 in-patients in France[xxvi]

[4] Major cardiac arrhythmia included supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, or atrioventricular block that required intervention.

Objective

To assess the effectiveness of oral hydroxychloroquine with or without azithromycin in preventing death or leading to hospital discharge in adult inpatients with polymerase chain reaction (PCR)-documented SARS-CoV-2.

Design

This was a retrospective cohort study incorporating 4,642 patients from 39 public hospitals in Ile-de-France, France. **Table 1**, below, outlines the inclusion criteria. This study utilized the Corona OMOP database which contains electronic medical records and administration records for public hospitals in the area to identify patients with prescriptions for HCQ. The "Entrepot de Nonnees de Sante" (EDS) is where they received electronic health records, biology and imaging results, and drug prescriptions.

Table 1 – Patient inclusion criteria

Adult inpatients
Minimum 18 years old
PCR documented SARS-CoV-2RNA from nasopharyngeal swab
Patients who were not receiving COVID treatments from other trials
Hydroxychloroquine and Azithromycin naive patients
Excluded: patients who died or were discharged within 24 hours of admission

Out of the 4,642 total patients studied, 623 received HCQ alone, 227 received HCQ and azithromycin (AZI), and 3,792 received neither drug. The primary outcome assessed was 28-day all-cause mortality as a time-to-event endpoint. If they were discharged before day 28, subsequent re-admissions were evaluated to determine health status at day 28. The secondary outcome was 28-day discharge home.

The locally-proposed regimen for HCQ was a loading dose of 600 mg on day one followed by 400 mg daily for the next nine days. The suggested AZI regimen was 500 mg on day one followed by 250 mg daily for the next four days (with or without concomitant HCQ use). However, dosages were left to the discretion of physicians.

Statistical analysis was performed to compare groups using the Chi-square test, Kruskal-Wallis, and Mann-Whitney rank sum tests. Time-to-event analyses were done with non-parametric Nelson-Aelen estimator. They created cause-specific Cox proportional hazards regression

models as the primary means of analyzing all-cause mortality and hospital discharge. They minimized bias by measuring the average treatment effect (ATE) via doubly robust estimators to come up with the augmented inverse probability of treatment weighting (AIPTW). They also performed sensitivity analyses to recheck their results. They considered a two-tailed p-value less than 0.05 to be significant.

Results

Looking at the whole population of patients and confounding variables, there was no significant difference noted between the HCQ and the neither drug groups. Additionally, there was no statistically significant difference in the ATE between the HCQ and neither drug groups for 28-day mortality.

Differences in the mortality rates were found within each group with 111 deaths (17.8%) in the HCQ group, 54 deaths (23.8%) in the HCQ + AZI group, and 830 deaths (21.9%) in the neither drug group with a $p<0.001$ across all the results. However, there were more patients transferred to the ICU within 24 hours of admission in the HCQ + AZI group (27.3%, $p<0.001$).

These results demonstrate a lack of efficacy of HCQ or HCQ + AZI in treating COVID-19. The results showed a possible association of HCQ + AZI treatment with a greater risk of mortality than the neither drug group. A higher rate of patients discharged home was found with competing risks survival analysis in the HCQ arm. There was no significant difference in mortality of the patients receiving HCQ compared to patients receiving neither drug.

Critique

Strengths of the study include their statistical analysis using causal inference to consider both time-to-event survival analyses and binary endpoints at a single time point. They also conducted many sensitivity analyses to account for confounding variables and ensure stability of their results. They used double robust estimations and varying missing data imputation techniques as well. Additionally, they had a very large sample size of over 4000 patients' data to analyze.

The primary drawback to this study is that it is observational, so causation could not be established. Another major drawback is the uneven size of the treatment groups, only 13.4% of patients received HCQ, 5.9% received HCQ + AZI, and a whole 81.7% received neither drug. Additionally, patients received doses of HCQ that were not uniform across hospitals making the results of the study less informative. Their findings should be replicated before they are regarded as well-backed recommendations.

Study #3

Impact of Azithromycin and/or Hydroxychloroquine on Hospitality Mortality in COVID-19[xxvii]

Objective

To evaluate the effect of hydroxychloroquine, azithromycin, both, or neither on the mortality of patients with confirmed SARS-Cov-2 infections.

Design

This was a retrospective cohort study incorporating 1,376 patients who were admitted between February 20th and May 10th, 2020 to a tertiary referral hospital in Lombardy. 11,671 patients total were admitted to the ED in the time frame. 2075 had a positive real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 from a biological sample. 1,403 patients were hospitalized patients in the COVID-19 wards. Out of those, 27 patients were excluded from the analysis; 27 with an "outcome not available" and one was under 18 years of age.

The patients were divided into groups based on the treatment(s) they received: HCQ only (211 patients, 15%), azithromycin (AZI) only (421, 30%), HCQ + AZI (166 patients, 12%), and neither drug (605 patients, 43%). The regimen for HCQ was 200mg twice daily for five to seven days. The primary outcome measured was hospital mortality. Secondary outcomes included admission to the ICU and hospital length of stay. They chose a 12 week follow up so that 97% of the patients would have been discharged or died by the end of the study.

Fisher's test was to analyze the factorial variables and the Kruskal-Wallis test for continuous variables. They also analyzed a propensity score to check the probability of treatment assignment based on characteristics such as age, sex, PaO2/FiO2, lactate, CRP, ICUE admission, and platelet count. That score was overlapped with the primary outcome of mortality and reported odds ratios with 95% confidence intervals. For any statistically significant associations, they calculated the point estimate with E-values and the confidence interval limit closer to the null to address confounding variables that had gone unmeasured. They also performed two sensitivity analyses to exclude patients admitted to the ICU and to analyze complete cases. The results were updated by including patients who were admitted to the hospital after May 10.

Results

For the primary outcome of in-hospital mortality, there was no significant difference between the HCQ and neither-drug groups (OR 0.76, 95% CI 0.53-1.09). Mortality rates in the HCQ group was 28% and 28% in the neither-drug group. Additionally, for the secondary outcome of ICU admission, there was no significant difference between the HCQ and neither-drug groups (OR 1.10, 95% CI 0.69-1.760). However, the HCQ group was associated with longer hospital stays (OR 1.15, 95% CI,1.06-1.24) compared to the neither-drug group.

Critique

Strengths of the study include using a propensity score to account for confounding variables and the large sample size. Some of their findings, however, could have been influenced by other factors. It was found that patients in the HCQ group had longer hospital stays than the neither drug group. However, survivors of the illness might have a longer hospital stay. In addition, their length of hospitalization was longer than in hospitals from other studies, so their discharge criteria might be different. Another drawback was that the investigators did not include specific dosages and the timing of therapy in their analysis; sub-analyses based on dosage and timing could potentially show HCQ to be more efficacious.

DISCUSSION

For the RCT and two cohort studies synthesized in this review, the effect on mortality of HCQ in treating COVID-19 was consistent and no different from standard care. Although the two cohort studies indicate a strong association between HCQ and the null hypothesis, their results are not definitive. The Horby et al RCT provides the strongest evidence for HCQ's inefficacy in treating COVID-19 but additional results from ongoing RCTs around the world are needed to confirm (or refute) these results. **Table 2**, below, summarizes the three studies in this review.

Table 2 – Summary of the three studies

	Study #1: Horby et al	**Study #2: Sbidian et al**	**Study #3: Albani et al**
Study type	Randomized controlled trial	Retrospective cohort	Retrospective cohort
# of participants	4,716	4,642	1376
Patients receiving HCQ	1,561	623	211
Population	Hospitalized COVID-19 pts >18yrs	Hospitalized COVID-19 patients >18yrs	Hospitalized COVID-19 pts >18yrs
Treatment	HCQ v std care	HCQ v std care v HCQ + AZI	HCQ v std care v AZI v HCQ + AZI
Primary outcome	28-day all-cause mortality	28-day all-cause mortality	Hospital mortality
Primary data interpretation	No difference between HCQ v std care	No evidence for HCQ efficacy	No difference between HCQ v std care
Statistics	P-value = 0.18	P-value = 0.723	OR 0.76, 95% CI 0.53-1.09
Critiques	• Open label (placebo effect) • Tested moderate/severe cases only	• No standard HCQ regimen (proposed regimen but ultimately up to physician) • Observational	• Smaller sample size + multiple treatment arms • No standard HCQ regimen (proposed regimen but ultimately up to physician)

			• Observational

The Sbidian et al and Albani et al studies were both retrospective cohorts, while the Horby et al study was a randomized controlled trial. The three studies are relatively similar to each other regarding the inclusion criteria as well as their outcome measure of all-cause mortality. The Horby et al and Sbidian et al studies were similar with large sample sizes, while the Albani et al had a significantly smaller number of patients. All three studies tested for mortality in patients who received the HCQ treatment versus patients given only standard care.

Participants in the Horby et al study were 62% male and had a mean age of 65 years; 27% of the participants had at least one major comorbidity. In Sbidian et al, 59% of participants were male and the mean age was 66 years, with those receiving HCQ having more co-morbidities. Participants in the Albani et al study had a mean age of 70 years with 66% of them being male.

The Horby et al study was the largest and most statistically powerful of the three studies that in this review. It included nearly 15% of all patients hospitalized with COVID-19 in the UK during that time period. This study was a randomized controlled trial which proposed a specific HCQ dosage regimen to test the drug's effectiveness at a certain dose. The other two studies in this review were observational, and therefore did not test concrete drug regimens. The study showed that there was no significant difference (p value = 0.18) between the HCQ treatment and standard care in mortality rate. The main critique was that the study was open label, which could have allowed for placebo effect. This study was also mainly concerned with hospitalized patients with moderate to severe illness, and therefore was unable to address HCQ's effectiveness as a treatment of mild cases.

The Sbidian et al study was a retrospective cohort study and also had a large sample size. Data from electronic medical records were extracted and analyzed. This study had a smaller population of patients who received only HCQ compared to the Horby et al study. Due to the observational nature of this study, there was a locally proposed regimen for HCQ but ultimately, the dosages were up to the discretion of administering physicians. There was no significant difference noted between the HCQ versus standard care groups regarding 28-day mortality, with a p value of 0.723. Thhe results of this study did not offer any further evidence supporting the efficacy of HCQ. The main limitation of the study is that it was observational and the HCQ regimens were not standardized across patients, making it difficult to replicate. In addition, the various treatment arms had very different sizes, which made it difficult to compare results.

The Albani et al study was also a retrospective cohort study but had a much smaller sample size. This study also had multiple treatment arms, which subdivided the sample size even further. There was a recommended standard dosage regimen for treatment unlike the Sbidian et al study, however, it was ultimately up to the physician's discretion. The specific dosages given per patient were not provided. There was no significant difference between the HCQ and

standard care groups (OR 0.76, 95% CI 0.53-1.09). The main limitation of this trial was the observational nature and the lack of data on the actual timing of treatment in relation to symptom onset, and dosages, which makes it difficult to replicate like the Sbidian et al study.

Regarding biases, the studies all stated that there were no conflicts of interest. Hornby et al received funding from numerous health and biomedical research grants. The Sbidian et al and Albani et al studies did not receive any specific grants from funding agencies. There has been a rush to get studies done on potential treatments as COVID-19 is a high priority, ongoing problem worldwide.

CONCLUSION

HCQ was initially proposed as a treatment for COVID-19 based on its antiviral activity in-vitro.[ii] Additionally, early observational studies and anecdotal evidence supported its use while the world waited for more definitive results from large RCTs.[iii,iv,v,vi,vii,viii] Early in the pandemic, evidence on the benefits and risks of using HCQ to treat COVID-19 was mixed; however, as of October 2020 there is little evidence to support its continued use. Based on the results of the three studies synthesized in this review, HCQ is ineffective in reducing mortality in patients hospitalized with COVID-19. Although none of the studies found an increased risk of cardiac arrythmias associated with HCQ use, two of the studies saw an increased risk of longer hospital stays. Furthermore, Horby et al found patients treated with HCQ had a lower probability of being discharged alive. Forthcoming results from ongoing RCTs evaluating HCQ in the treatment of COVID-19 are needed to better determine the balance of risks and benefits. HCQ in the treatment of a milder form of COVID-19, or as a prophylaxis, was not assessed in this review and is an area that could be evaluated in future RCTs.

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