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EFFICACY OF HYDROXYCHLOROQUINE OR CHLOROQUINE AS ANTI-COVID-19; A SYSTEMATIC REVIEW

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Abstract
Chloroquine (CQ) and hydroxychloroquine (HCQ) have shown mixed effects in clinical studies of COVID-19 disease. We aimed to comprehensively assess how CQ and HCQ affected COVID-19 patient outcomes.
Methods: We combed through a wide range of archives, preprints, and grey literature up through the date of November 17, 2022. Using a random-effects model, we combined only the mortality estimates that had their effects accounted for. We summed up how CQ or HCQ affected viral clearance, ICU admission, and the need for mechanical ventilation.
All of the database's MEDLINE, CINAHL, EMBASE, Web of Science, Google scholar, LILACS, and Scopus were searched electronically from their inceptions in the 1950s without regard to publication date or language availability up until November 2022. In total, 6 articles were used for the evaluation. Patients who are subjected to be treated with Chloroquine or Hydroxychloroquine against Corona viral infections.
Six randomized clinical trials (RCTs) met the criteria; therefore these findings can be considered. There is some evidence to show that HCQ is effective in lowering short-term mortality in COVID-19 hospitalised patients or the risk of hospitalisation in COVID-19 outpatients. Finally, these results should be taken into account in the follow-up care of patients who will be admitted for COVID-19 treatment and may help in their clinical management.

Keywords Hydroxychloroquine, COVID-19, SARS-CoV-2, Treatment, Efficacy

INTRODUCTION

The virus known as COVID-19 is an enclosed coronavirus, which is a positive single-strand RNA

virus.Because of its "crown-like" spikes, this virus is classified in the subfamily Orthocoronavirinae. viruses like SARS- CoV that have been found in bats and other animals are part of the beta-coronavirus genus. COVID-19, which is caused by the 2019- nCoV virus, was added to the fifth category of infectious disorders that must be reported on January 15, 2019. The beta-coronavirus genus can be further subdivided into several distinct groups (Khan et al., 2020). Three distinct but related Sarbecoviruses—the 2019-nCoV, SARS-CoV, and SARS-like bat CoV—have recently been identified (Wu et al., 2020). In December of 2019, researchers in Wuhan, China, discovered the first symptoms of a new outbreak of Coronavirus Disease 2019 (COVID-19). Quickly reaching other nations, the WHO issued a worldwide health alert on January 30, 2020. More than 2.5 million individuals have been killed by this epidemic as of March 1, 2021 (Gubernot etal., 2021).

Although various recommendations have been made to eliminate the spread of COVID-19 and boost the health and well-being of those infected, the effectiveness of these strategies remains debatable (QoL). Sincehydroxychloroquine can reduce inflammation and has shown antiviral action in vitro, it has been proposed as a treatment for COVID-19 (Wunsch, 2020).
Many hospitals are integrating the use of hydroxychloroquine into their standard treatment for thehospitalisedpeople with COVID-19 and several clinical trials to assess hydroxychloroquine as a powerful treatment for patients infected with COVID-19 (Kashour et al., 2021)have been recommended by numerous bodies, including the National Institutes of Health (NIH) and the Infectious Diseases Society of America, despite an evidence lackong on safety andefficacy (Valent et al., 2020).

More than half a century after the antiviral properties of hydroxychloroquine (HCQ) and chloroquine (CQ) were discovered, researchers have continued to explore their therapeutic potential against a wide spectrum of viral infections.CQ/HCQhas been tested against many different viruses, including HIV-1, dengue, SARS, influenza, Ebola, MERS- CoV, Chikungunya, and Zika (Horby et al., 2021).
Multiple hypothesised mechanisms underlie the effects of CQ/anti-SARS-CoV-2 HCQ. All of these things happen as a byproduct of their main impact, which is to increase intracellular pH and hence alter endosome activity. CQ/HCQ can interfere to disrupt the life cycle of the viruses at multiple points (Sinha and Balayla, 2020).
Glycosylation inhibition of ACE2 may decrease the protein's binding affinity to SARS-CoV-2, hence reducing the virus's capacity to bind to ACE2 in the cell membrane. Viruses can be stopped from entering cells if CQ/HCQ can prevent their membranes from fusing with the host cell membrane. CQ/HCQ also inhibits viral assembly thenrelease from host cells, as well as the reproduction of viruses (Brown et al., 2021).
By affecting endosomal antigen processing, CQ/HCQ also impact both the adaptive immune responses as well as innate one. This leads to a decrease in the production of inflammatory cytokines such IL-1b, TNF-a, and IL-
6. Endothelial function is improved alongside the reduction of the prothrombotic condition thanks to CQ/HCQ.Potentially very important to be used for patients with severe COVID-19 disease (Skipper et al., 2020).

Because the SARS-CoV-2 virus emerged and spread quickly around the world, research into the properties ofCQ/antiviral HCQ became necessary. These compounds are now widely used in the treatment of COVID-19 disease, with their popularity spurred by initial research reporting their effective in vitro antimicrobial effects against SARS- CoV-2 virus (Linsell and Bell, 2020).
Many randomised controlled trials have tested the hypothesis that hospitalised patients with COVID-19 benefit more from treatment with hydroxychloroquine than placebo (Bhattacharyya et al., 2021).

MATERIALS AND METHODS

Protocol

According to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)

guidelines, established and revised previously for formulating systematic reviews (Hutton et al., 2016), the included studies werechosen to answer a predetermined question using the Participants, Intervention, Control, and Outcome (PICO) model:

- (P) Participants: patients with COVID-19 being hospitalized or non hospitalized.
- (I) Intervention: Hydroxychloroquine or Chloroquine.
- (C) Control: patients with COVID-19 who did not receive a Hydroxychloroquine or Chloroquine as treatmentfor COVID-19.
- (O) Outcome: good and efficient quality of life (QoL) income for patients who received one of these twodrugs.

The research question was: "Does the mechanical ventilation intervention will improve the COVID-19 patients'QoL?".

Data Sources and Search Strategy

The databases sources used for this systematic review were the National Library of Medicine (NLM), Cochrane Central Register of Controlled Trials (CENTRAL), the PubMedCentral (PMC), and the Web of Science (WOS) electronic databases. These databases sources were obtained with a time period, in the last 3 years until November 2022. TheMeSH terms (Medical Subject Headings) used in NLM, CENTRAL, PMC data bases were: "Quality of life"[MeSH Terms] and "COVID-19"[MeSH Terms] and "recovery"[MeSH Terms] and "Hydroxychloroquine"[MeSH Terms] and "Chloroquine" [MeSH Terms] and "Efficacy"[MeSH Terms]. In the WOS, the search terms were Quality of life, COVID-19,recovery, Hydroxychloroquine, Chloroquine, and Efficacy.

The following table presents the database search terms in this systematic review.

Table 1 Database search terms

Database	Search terms
National Library of Medicine (NLM), the Cochrane Central Register of Controlled Trials (CENTRAL), thePubMed Central (PMC).	"Quality of life"[MeSH Terms] and "COVID- 19"[MeSH Terms] and "recovery"[MeSH Terms] and "Hydroxychloroquine"[MeSH Terms] and "Chloroquine"[MeSH Terms] and "Efficacy"[MeSH Terms].
WOS	Quality of life, COVID-19, recovery, Hydroxychloroquine, Chloroquine, and Efficacy.

*MeSH, Medical Subject Headings.

Inclusion and exclusion criteria

The inclusion criteria for this systematic study selections were:

1. In the last two years studies;
2. Studies where were carried out in the hospitals;
3. Studies were performed according to IDSA and COVID-19 treatment guidelines:
4. Studies that included all patients admitted and received mechanical ventilation;
5. Studies have quality of life assessment tools.

While the exclusion criteria for this systematic study selections were:

1. Studies out of hospitals;
2. Studies treated COVID-19 without mechanical ventilation
3. Narrative, literature, and systematic reviews;
4. Studies that did not involve any of quality of life (QoL) for COVID-19 patients;
5. Studies out of healthcare settings application;
6. Studies older than 2020.

Data Extraction and Analysis

The reviewer efficiently and firstly read abstracts of the studies and extracted only data that is related to the desired aim from full tests of the included and selected articles, including background information, introduction, study sites, criteria for selecting the quality management system and authority relied upon throughout the study, analytical methods, guideline types, discussion of these

data conclusions, future perspectives, and limitations. The uncertainty around the studies' eligibility was resolved during conversation between the two reviewers, allowing for the most trustworthy and appropriate results to be discussed subsequently (Tamil and Srinivas, 2015).

Risk of Bias (RoB) of Articles

The author used Agency for Healthcare Research and Quality (AHRQ) checklist for RioB assessment in ComparativeEffectiveness Reviews, to ensure that assumptions and limits are recognized and taken into consideration when assessing validity and generalizability, this checklist might be employed to what?. The AHRQ Evidence-based Practice Centers (EPCs) risk of bias evaluation for assessing the quality of research included in Comparative Effectiveness reviews.

Quality of the Reports in the study's Articles

There were a total of 13 factors included in this evaluation of published research, including studies and authors' recommendations. Following is a table displaying how each item on the checklist was graded by the reviewer (0 for not reported, 1 for reported).

Table 2 The studies checklist reported by authors

	Reis et al.(2021),	**Avezum et al. (2022),**	**Self et al.(2020)**	**Brown et al. (2021)**	**RECOVERY Collaborative Group. (2020)**	**Mitjà et al. (2020)**
1. Title	1	1	1	1	1	1
Abstract	1					1
2. Species	0	0	0	0	0	0
3. Key finding	1	1	1	1	1	1
4. Background	1	1	1	1	1	1
5. Reasons for making this study	0	0	0	0	0	0
6. Objectives	1	1	1	1	1	1
Methods						
7. Quality of life assessment tool	1	1	1	1	1	1
8. Study design	1	1	1	1	1	1
12. Sample size	1	1	1	1	1	1
15. Statisticalmethods	1	1	1	1	1	1
Results						
16. Experimental results	1	1	1	1	1	1
17. Results and estimation	1	1	1	1	1	1
Discussion						
18. Interpretation and scientific implications	1	1	0	1	1	1
21. Study limitations	0	0	1	1	0	1
22. Generalization/applicability	0	1	0	1	1	1
23. Funding	0	0	1	0	1	0
24. Ethicalapproval	1		1	1		1
Total score	13	11	9	14	9	15

Mode Value: 11.8± 1.06. Items were ranked on a scale from 0 (not reported) to 1 (reported). Every study's aggregatescore was also recorded.

RESULTS

Characteristics of the Studies

A total of 492 studies were selected, read, identified, and assessed by the reviewer between 2020 and October2022. The initial screening helped eliminate 45 studies that were duplicates. Forty-one studies were deemed insufficient after a second screening revealed that they did not fully or properly meet

the inclusion criteria and the following figure shows the flowchart of the screening The rest of following tables providing a general description of the studies' details.

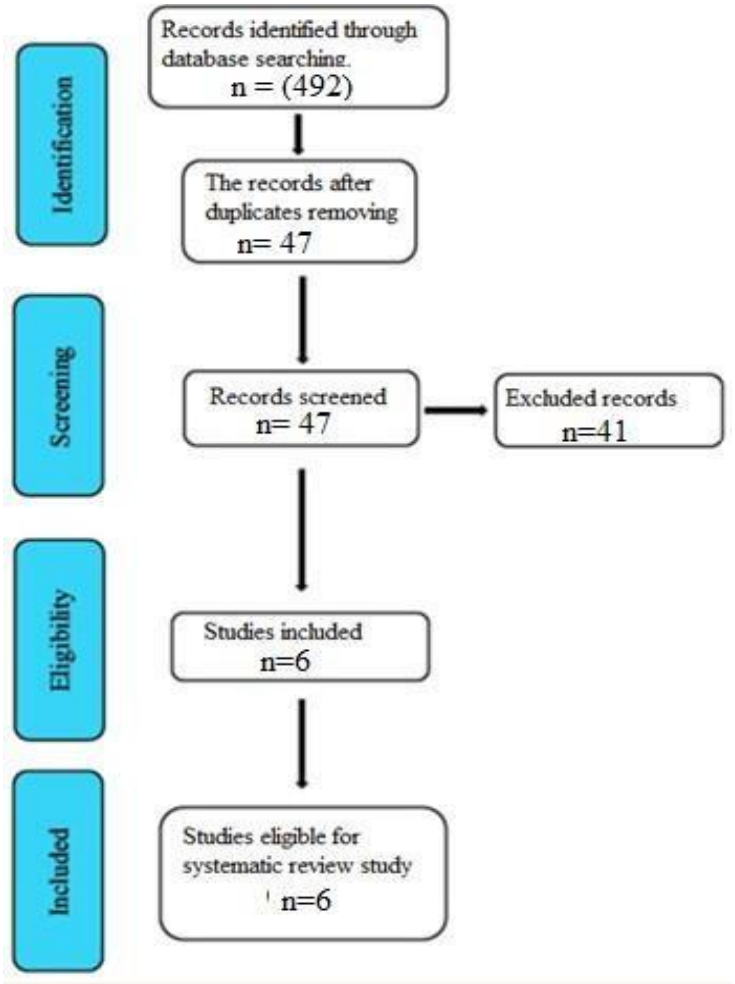

Figure 1 The systematic review flowchart

Table 3 Characteristics of included studies

Studies	Study Sample	Analysis Methods	Conclusions
Reis et al. (2021),	In a randomised clinical trial performed in Brazil, the expected number of participants was 1476 patients.	After 500 individuals were selected and tested between June 2, 2020, and September 30, 2020, for whom a recentdiagnosis of SARS-CoV-2 infection was made due to respiratory symptoms, interim analyses were planned. Based on the preliminary results, the 685-person experiment was stopped before completion because it was pointless. In December of the following year, the data was tallied to determine the study's findings. INTERVENTIONS In this study, patients were randomly selected to receive either a lopinavir-ritonavir combination (800 and 200 mg, respectively, every 12 hours for the first 24 hours, then 400 mg and 100 mg, respectively, twice daily for another 9 days), hydroxychloroquine (800 mgloading dose, then 400 mg daily for 9 days), or a placebo.	Hospitalization rates and other secondary clinical outcomes related to COVID-19 were not significantly reduced by hydroxychloroquine in this randomised clinical trial. Rapid clinical trialslike the one presented here may be feasible in low-resource areas even during COVID-19 pandemic, as this study demonstrates.
Avezum et al. (2022),	In a randomised-controlled, multicenter trial, 510 patients were expected to participate from 34 institutions across the United States.	Adults hospitalised due to SAR-Cov syndrome coronavirus and infection were assigned between April 2 and June 19, at year of 2020 and they will be evaluated for their final outcome on July 17, 2020. After every 102 participants,interim analyses were scheduled to take place. The	Clinical status at day 14 did not substantially improve with hydroxychloroquine treatment versus placebo among adults hospitalisedwith respiratory disease due to COVID-19.ccording to these results, hydroxychloroquine

		trial was terminated due to futility at the fourth interim analysis, which involved 479individuals. INTERVENTIONS Patients (n = 242) were given either hydroxychloroquine (400 mg twice day for 2 doses, then 200 mg twice daily for 8 doses) or a placebo (n = 237).	should not be used totreat COVID-19 in hospitalised adults.
Self et al. (2020),	A total of 34 US hospitals were involved in the multicenter, blinded, placebo- controlled randomised trial, with 510 patients as the target sample size.	Adults hospitalised of = participants, interim analyses were scheduled to take place. In the fourth interim analysis,which included 479 participants. INTERVENTIONS Both hydroxychloroquine (n = 237) and a placebo (n = 242) were administered to patients.	In adults hospitalised with respiratory disease due to COVID-19, treatment with hydroxy chloroquine compared to placebo didnot significantly improveclinical status at day 14. This study's findings do not support using hydroxychloroquine to treat COVID-19 in hospitalised adolescents.
Brown et al. (2021),	enrollment of 85 patients when another clinical trial found hydroxychloroquine to have a significant advantage over placebo	Evaluation of hydroxychloroquine versus chloroquine in a randomisedcontrolled trial for COVID- 19 patients hospitalized. Themedication was taken for a total of 5 days. The primary outcome measure was the COVID ordinal outcomes scale onday 14.	Despite the fact that theirstudy was cut short before completion, they still found no evidence favouring hydroxychloroquine's superiority to chloroquine. It's possible that hydroxychloroquine's association with increased rates of acute kidney injury is simply amatter of chance. Their findings may have been skewed toward hydroxychloroquine due to the differential use of remdesivir. These findings corroborate those of other trials showing that HCQ is showing less effectiveness for treating COVID-19 in hospitalised patients;
RECOVERY Collaborative Group. (2020),	Total of 1561 were given hydroxychloroquine and 3155 were given standard care	In this randomised, controlled, open-label platform study, they compared a number of potential therapies with usualcare in patients hospitalised with Covid-19. Primary endpoint of this trial was 28-day mortality.	Death rates at 28 days were not significantly different between patients treated with hydroxychloroquine and those treated with standard care among those hospitalised with Covid-19.
Mitjà et al. (2020)	About 239 individuals in a multi-center, open- label, randomised controlled study in Catalonia. Covid-19 included only outpatient adults with confirmed SARS-CoV-2 infection who had not been hospitalised for more than five days.	Both HCQ (800 mg on day 1,then 400 mg once day for 6 days) and no antiviral medication were randomly assigned to patients (not- placebo controlled). Nasopharyngeal swab viral RNA load reduction at 7 days post-treatment initiation, WHO disease progression at 28 days post-treatment initiation, and time to complete symptom relief were the primary objectives of the study. Up to 28 days ofadverse events were evaluated.	Patients with mild COVID-19 did not benefit more from HCQthan they would have from receiving standard care.

DISCUSSION

In December of 2019, researchers discovered the 2019 coronavirus illness (COVID-19). SARS-CoV-2 was the coronavirus in question (Wunsch, 2020), and it affected a population that was immunologically naive but well connected around the world. In the face of a novel infectious agent causing acute respiratory failure for which no effective medicines were available, it was necessary to conduct rapid, often pragmatic trials of prospective treatments,often starting with pharmaceuticals already marketed for other reasons. Initial treatment choices included chloroquine and hydroxychloroquine.

In this systematic review, a collection of scientific based selection procedures consisted of six different studies of Reis et al. (2021), Avezum et al. (2022), Self et al. (2020), Brown et al. (2021), RECOVERY CollaborativeGroup. (2020), and Mitjà et al. (2020), all of these studies were included and discussed.

It was noting that Reis et al. (2021) reported that duration to hospitalisation, hospitalizations, and viral clearance rates associated with COVID-19 were not significantly different between the

hydroxychloroquine, placebo,and lopinavir-ritonavir groups. Overall, neither trial cohort or subgroup saw statistically significant improvements in clinical outcomes from the use of hydroxychloroquine or lopinavir-ritonavir, according to both ITT and PP analyses. The independent DSMB stopped enrolling participants in the hydroxychloroquine and lopinavir-ritonavir groups based on data from interim analyses. All patients randomised to hydroxychloroquine or lopinavir-ritonavir followingthe data cut for the interim analysis but before the DSMB conference are included in this report.

Throughout this pandemic, medications that have demonstrated promise in preventing viral replication in preclinical investigations and experimental models of SARS-CoV and SARS-CoV-2 infection have garnered a lot ofattention. Repurposed medications appear to be a substantial option in the event of the introduction of a new disease with significant morbidity and fatality rates. These medications are perfect for the COVID-19 scenario since they arereasonably priced, widely available, and have a history of minimal risk. Research efforts are currently focused on evaluating these options in patients with mild, early disease in the expectation that early viral load treatment will haltthe spread of more severe COVID-19. Research involving mild to severe disease has not yielded any repurposed drugs that have shown promise so far. In spite of this, the presence of political and ideological undertones in this discussionhas made it more challenging to undertake this research, expanding the issue outside the sphere of science. Two Brazilian health ministers resigned because of public pressure to employ experimental treatments for COVID-19 before any evidence of their effectiveness had accumulated. In this courtroom, the legal proceedings of the aforementioned lawsuit have begun. They designed an adaptive clinical trial to speed things up by using a centralised randomisation system, quadruple masking, independent data analysis, and adherence to the Consolidated Standards of Reporting Trials standards.

Since there was an abundance of curiosity about the efficacy of hydroxychloroquine and lopinavir-ritonavir as treatments at the outset of the pandemic, and since both drugs were being widely used off-label, they were chosenfor evaluation. The effectiveness of these medications in treating COVID-19, as well as the scientific discussion and political support that hydroxychloroquine has received, have been the subject of numerous articles. Information on the efficacy of hydroxychloroquine and lopinavir-ritonavir in inpatients from the RECOVERY trial became available throughout their investigation. In hospitalised terminally ill patients, neither medication was effective. Additionally, hydroxychloroquine's efficacy outside of clinical trials has not been shown. Two, it was unclear whether or not thesemedications would be useful in preventing or treating early-stage COVID-19 infection. Their research suggests that in the initial stages of treating COVID-19, lopinavir-ritonavir and hydroxychloroquine should be avoided. There hasn'tbeen a larger study like theirs before, and it looks at these medicines from the very beginning of the care process.

Regarding Avezum et al. (2022), who reported that between May 12, 2020 and July 7, 2021, 1,372 people were randomly randomised to receive either hydroxychloroquine or a placebo. There was no statistically significant difference between the hospitalisation rates in the hydroxychloroquine and placebo groups (p=0.16): 44/689 and 57/683, respectively (95% CI 0.52-1.12). When administered according to the study's dosage and schedule, there wereno incidences of severe cardiac arrhythmias, sudden death, or retinopathy, and there was no statistically significant difference in the frequency of prespecified serious adverse events between the two groups. The COPE trial's findingswere in line with those of the updated meta-analysis of all previous RCTs.

Prior randomised controlled studies investigating the same scientific question in analogous patient groups found no significant benefit with either hydroxychloroquine or choloroquine compared to the control. Neither the sample size nor the strength of the tests were enough. Early hydroxychloroquine treatment was investigated for its potential to lessen the likelihood of hospitalisation due to COVID-19, but the researchers observed no such benefit. There were 1,372 patients whose samples were taken to test for hydroxychloroquine, but only 441. Primary endpointdata was collected from 423 of 491 patients with confirmed or suspected COVID-19 who were not hospitalised. Hydrocychloroquine was associated with a higher rate of adverse effects, but it was found to have no impact on the severity of symptoms or the requirement for hospitalisation in patients with COVID-19. A meaningful ordinal

analysiswas not possible due to the relatively low incidence of hospitalisation (3%). Only 148 people with confirmed instances of COVID-19 were randomly assigned to receive the trial medication, representing a dropout rate of 16.2 percent fromaan initial sample size of 1,372.

The study was cut short because no evidence was found that hydrocychloroquine reduced the duration of symptoms or prevented serious outcomes. Because of the impracticality of continuing the study due to the low incidence rates, it was terminated early. In a study including 293 outpatients, researchers discovered that hydroxychloroquine did not hasten patients' recoveries or save unnecessary hospitalizations. None of the treatment'sside effects were serious enough to warrant stopping it.

Although there is a great evidence referring that drug hydroxychloroquine does has no activity in prophylaxisfor whom infected before with COVID-19, the possibility of benefits cannot be ruled out by the current trials. Hospitalized patients with respiratory illness due to COVID-19 did not show significant improvement in clinical status, death rates, or the need for invasive mechanical ventilation after 14 days of treatment with hydroxychloroquinecompared with placebo or control.

And Self et al. (2020) found that the results from a multi-center, randomised clinical trial conducted at 34 UShospitals found that patients hospitalised with respiratory disease caused by COVID-19 and treated with hydroxychloroquine had neither better or worse clinical outcomes. These findings were consistent regardless of the study population or end measure used (ordinal scale of clinical status, time on oxygen, or length of hospital stay, for example).

Hydroxychloroquine has shown promise as a treatment for COVID-19 in in vitro studies, where it has been shown to reduce endosome-mediated viral entry by blocking the glycosylation of cell receptors targeted by coronaviruses. 6-8 Hydroxychloroquine also inhibits the production of several proinflammatory cytokines responsiblefor the development of acute respiratory distress syndrome, another potentially lethal effect of COVID-19. Oxychloroquine has widespread clinical use for COVID-19 due to its efficacy, low toxicity, and long history of successful usage in treating malaria and rheumatologic diseases. For the treatment of COVID-19 in hospitalised patients, the FDA granted an EUA for hydroxychloroquine on March 28, 2020; the EUA was revoked on June 15, 2020.

Consistent with recent in vitro studies and open-label pragmatic trials in the UK and Brazil, this clinical trial found that hydroxychloroquine had no antiviral efficacy against COVID-19. When considered in conjunction with the aforementioned research, the results of this experiment lend credence to the notion that hospitalised COVID-19 patients would benefit little, if at all, from treatment with hydroxychloroquine.

This study's strengths include its blinded, placebo-controlled design; rapid recruitment from a large number of hospitals serving patients from a wide range of racial and ethnic backgrounds in the United States; and positive results. Mortality and illness from COVID-19 were measured using a patient-centered, clinically-relevant ordinal scale.

It has been noted that, Brown et al. (2021), found that the results of a clinical trial conducted in the early stages of the 2009 COVID-19 pandemic that compared two commonly utilised and much contested medications. When comparing the hydroxychloroquine and chloroquine groups, they found no statistically significant differences in the primary result. Their data give about the same probabilities that a treatment impact was insignificant, therefore this finding needs to be interpreted in light of the limitations imposed by the small sample size (0.48). They found that AKI more predominent in the hydroxychloroquine group, although this may have more to do with the large number of safety outcomes they analysed than with any real differences between the two groups. According to a post hoc sensitivity analysis, the difference in remdesivir usage between the hydroxychloroquine and chloroquine groups mayhave masked chloroquine's superiority over hydroxychloroquine.

A large open-label pragmatic trial using a higher dose of hydroxychloroquine than is typically used and withminimal safety monitoring was conducted in the United Kingdom, and its results were interpreted as suggesting a modest (1-2% absolute risk increase) harm associated with hydroxychloroquine compared to usual care. One study comparing the two dosages of chloroquine found that those given the higher dose had a higher death rate.

High rates of QTc prolongation or ventricular arrhythmia were found in clinical cohorts, but this wasn't

borneout by randomised controlled trials. Even if a kidney transplant or dialysis cannot account for the variation in stage 2AKI, this observation is important to keep in mind.

Given the number of compared safety outcomes between groups, the observed difference is consistent with random fluctuation. Although there is theoretical concern that hydroxychloroquine may worsen kidney injury in COVID-19, it has been found to protect the kidneys in patients with chronic autoimmune disease. The RECOVERY experiment and the vast majority of earlier experiments lacked sufficient data collection to verify this result. Given that AKI during hospitalisation is typically associated with worse intermediate to long-term outcomes, this may be animportant safety signal to investigate in larger cohorts.

Their combined practical and theoretical research experience suggests that restricting hydroxychloroquine dosing to controlled clinical trials enhances population-level safety in Utah, but they are unable to provide definitive statistical evidence for this claim. They argue that clinical trials, especially open-label pragmatic trials, are crucial formitigating the social and cultural dangers of a pandemic.

Despite significant local pressure, they made the right decision to administer hydroxychloroquine "off label"in a clinical trial setting, which has advantages for public health because of its focus on patient autonomy and informedconsent, appropriate safety monitoring, and the possibility of contributing to generalizable knowledge.

And RECOVERY Collaborative Group. (2020) were studied in the RECOVERY trial found that treatment with hydroxychloroquine did not benefit hospitalised individuals with Covid-19. It was hard to determine whether ornot the mortality rate would decline much because the confidence range for the primary outcome was so tiny. Similarconclusions were drawn from trials that separated participants by age, sex, race, duration of sickness, need for supplemental oxygen, and assessed risk at the outset. Patients who were given hydroxychloroquine were more likelyto die and required more intrusive mechanical breathing than those who got standard care.

To determine whether or not potential therapy for Covid-19 reduce 28-day mortality, researchers devised RECOVERY, a large-scale pragmatic randomised controlled platform experiment. Hospitalized case fatality rates in the UK and abroad are roughly equivalent to the percentage of patients who died during the study period among the usual-care group (15%). The hospitals were only asked for the most essential details, while additional data (such as mortality rates over time) was collected from regular data connections. Neither physiological nor electrocardiographicnor laboratory nor virological information was obtained.

Hydroxychloroquine's antiviral effectiveness against SARS-CoV-2 in vitro and evidence from observationalstudies indicating successful reduction of viral levels have led to its consideration as a treatment for Covid-19. Drugsbased on the four-aminoquinoline structure, however, have limited success in combating viral infections. Rapid achievement of therapeutic levels of free drug in the blood and respiratory epithelium is required to demonstrate the therapeutic efficacy of hydroxychloroquine in severe cases of Covid-19. To increase the likelihood that therapy wouldbe administered for severe cases of Covid-19, the dosage schedule used in their experiment was created to swiftly acquire and maintain maximally effective plasma concentrations. predicted to be greater than the range seen with long-term hydroxychloroquine treatment for rheumatoid arthritis. Based on pharmacokinetic modelling, in which it was hypothesised that cytosolic levels in the respiratory epithelium are in dynamic equilibrium with blood levels and a 50% effective concentration of 0.72 M was used against SARS-CoV-2, an optimal dose of hydroxychloroquine was identified.

The risk of cardiovascular injury is substantial with high-dose, short-term 4-aminoquinoline regimens. When hydroxychloroquine is added to azithromycin, a common part of Covid-19 therapy, the expected lengthening of the corrected QT interval on electrocardiography is amplified. The combination of hydroxychloroquine and azithromycin is widely used, despite the fact that cardiovascular disease is common in hospitalised patients, myocarditis is commonamong Covid-19, and serious cases of cardiovascular toxicity are documented only occasionally. The RECOVERY study used a far lower dose than the standard amount used in the previous trial (600 mg twice day for 10 days). Theyconclude, using pharmacokinetic modelling and data on blood levels and death from

a case series including 302 persons with chloroquine overdose, that a chloroquine regimen equal to the hydroxychloroquine regimen employed in their trial should have a satisfactory safety profile. In the first two days after starting hydroxychloroquine, no dose-dependent toxicity was found; however, a small absolute excess of cardiac mortality of 0.4 percentage points in the hydroxychloroquine group was observed based on extremely few occurrences. Furthermore, the data reported here demonstrate that neither ventricular tachycardia nor ventricular fibrillation increased in the hydroxychloroquine group.

While these results show that hydroxychloroquine is ineffective in the treatment of Covid-19 in hospitalisedpatients, they do not address its usefulness as a preventative measure or in the treatment of less severe SARS-CoV-2 infections in the community. An FDA EUA would allow for the administration of chloroquine and hydroxychloroquine to certain inpatients in the United States (FDA). The FDA has withdrawn the EUA forchloroquineand hydroxychloroquine, and the WHO and the NIH have halted trials of its use in hospitalised patients since they revealed their preliminary findings on June 5, 2020.

Not surprisingly, Mitjà et al. (2020) found no virological or therapeutic advantage of HCQ in outpatients with mild Covid-19. The antiviral benefit of HCQ was nullified when administered within five days of symptom onset(median 3 days), when compared to no antiviral treatment at all. Proof that the treatment has the potential to impact the pathogen burden is provided by the ability to quantify the viral load in the upper respiratory tract. Despite the trial's lack of power, this kind of treatment did not decrease the likelihood of hospitalisation or speed up the rate at which symptoms improved.

Minor adverse events (AEs) were noted with the trial treatment, but a far larger percentage of participants inthe HCQ arm suffered side effects, suggesting intolerance to the medicine. Seventy percent of HCQ users reported experiencing stomach upset. Only eight patients reported having an SAE in the first 28 days of starting HCQ medication, and all of them were linked to a worsening of their condition. There were no reports of arrhythmia-relatedsyncope, palpitations, or dizziness. This data refutes the worry that HCQ therapy would be hazardous, especially in the context of cardiac illness.

However, there are caveats to their study that should be taken into consideration. To begin, unlike on day 3,clinical examinations on day 7 were not planned ahead of time, resulting in a reduced sample number being used to determine viral positive. The World Health Organization (WHO) has suggested measuring viral load as part of clinical research for Covid-19, but they haven't specified when this should be done or what constitutes a statistically significant drop in viral load. They recommend waiting at least 7 days and setting the criteria for a significant reduction in viral load at 0.5 Log10 or greater. Based on in silico molecular docking studies indicating that DRVc might have a therapeutic effect on SARS-CoV-2, they initially decided to combine HCQ with DRVc due to DRVc's superior safety profile compared to other HIV protease inhibitors. Unfortunately, once the research began, DRVc was discarded sinceit did not function in vitro. Giving both medications at once may increase HCQ's plasma levels and effect size in some persons since DRVc is a weak inhibitor of HCQ's metabolic enzyme, CYP2D6. As a result, they draw the conclusionthat DRVc treatment did not lessen HCQ's effectiveness. Third, a placebo-controlled trial couldn't be conducted due to time constraints, which may have resulted in a lower number of serious adverse events (SAEs) (AEs are less often reported in a control, non-placebo group).

In contrast, the rates of attrition in the control group were unaltered. In addition, to lessen detection bias of the primary outcome, the laboratory staff was kept in the dark regarding participant allocation (i.e., the viral load). Finally, the trial's geographical focus and the fact that healthcare professionals constituted more than 80% of participants may restrict the generalizability of their findings. As a result, these results should be taken with a grain ofsalt if being transferred to different geographical or cultural settings.

HCQ and chloroquine have received unusual attention as prospective therapeutic agents as a result of inconclusive clinical trials in conjunction or not with azithromycin, uncontrolled case series, and public figure endorsements. Although there is growing evidence opposing the use of HCQ due to anxiety for risk, particularly heartillness, its potential for treating mild Covid-19 has been investigated

in this work. They found no association between viral load and any outcome 7 days after diagnosis, including symptom resolution and hospitalisation frequency, or 28days after diagnosis. The study's key strengths are its randomised controlled design and its use of the approved minimal outcome set for Covid-19 clinical trials, which includes RT-PCR to definitively determine the viral burden. Their findings are significant because they indicate that HCQ is not a promising therapeutic candidate for SARS-CoV-2, atleast in settings that are comparable to ours.

Conclusion

In conclusion, if COVID-19 patients are admitted to be treated in hospitals and are just isolated in their homes, they must obey certain treatment guidelines. HCQ or CQ are the main two old and familiar drugs used to treat COVID-19. Many of the trials included in this systematic review found hydroxychloroquine or chloroquine to be effective in reducing short-term mortality in hospitalized patients with COVID-19 or in reducing the risk of hospitalization in outpatients, respectively; these studies concluded that HCQ and CQ are effective to limit and have positive impacts in many patients, but other studies concluded that HCQ monotherapy lacks efficacy in achieving these goals. Our research also indicates that hospitalized COVID-19 patients who take HCQ in addition to azithromycin are at a higher risk of experiencing a rapid decline in health.

Recommendations

More studies about quality of life (QoL) measurements in patients with post-COVID-19 syndromes are needed and more sample size are needed for cohort perspective studies in measuring efficacy and effectiveness of HCQ and CQ in combination with other antiviral or anti-COVID drugs, it is also crucial to study on many trials the effectiveness ofthese two drugs before and after getting infected with COVID-19.

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