Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial

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BACKGROUND – THE STUDY QUESTION?	
Background	• At of the time of this study there are no specific, evidence-supported agents for use in coronavirus infection • This study aims to determine if hydroxychloroquine pharmacotherapy reduces the time to clinical improvement in coronavirus disease patients • Hydroxychloroquine regulates pro-inflammatory cytokines in SLE and other rheumatic conditions. COVID-19 patients who are critical go through a cytokine storm. Hydroxychloroquine has shown efficacy as both an antiviral (SARS 2003-2004, MERS, chloroquine *in vitro*) as well as an autoimmune modulator (SLE, rheumatic diseases), and may have a role in the treatment of patients with COVID-19
Previous trials	• There have been promising studies showing the activity of chloroquine against SARS-CoV-2 in vitro • A number of antivirals including chloroquine and remdesivir were cited by the study as being effective against coronaviruses, all of which were conducted in cellular assays • At the time in which this trial was conducted, there was very little information about proven efficacy against COVID
Null Hypothesis	• Hydroxychloroquine is **not statistically efficacious** in the treatment of patients with COVID-19.

GENERAL STUDY OVERVIEW		
	Summary	Critique
Funding	• Not specified in the article, but the Chinese Ministry of Health likely funded the study and provided supplies to the hospital during the early stages of the epidemic in February	• Not specified in the article, though it may be disclosed in future versions/once officially published
Trial design	• Parallel-group, randomized controlled trial • Double-blinded (neither the patients nor the prescribers knew who was getting the hydroxychloroquine) • Treatment group received hydroxychloroquine 400 mg/d (200 mg BID) x5 days in addition to standard care • Control group received only standard care (oxygen, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids)	• Randomized, controlled trials are generally a standard for preliminary drug testing • Study observations such as body temperature were taken at standardized intervals • Cough was self-reported • Variations in 'standard care' – lack of detail or specification on what additional antiviral agents and other adjuncts patients received
Objectives	• Assessing the following areas in the treatment of coronavirus disease: • Time to clinical recovery (TTCR) defined as return of body temperature to ≤37.2°C (axilla, oral) or ≤37.8°C (rectum, tympanic membrane) and cough relief, maintained for more than 72h	• It's worth noting per the CDC COCA call on 4/2/20, a US observational study found that only 50% of ICU coronavirus disease patients initially present with fever. So, coronavirus patients who did not present with fever may have been excluded from this study

	• Clinical characteristics (fever, cough, progression to severe illness, and adverse effects) • Absorption of pneumonia on chest CT scan	
Enrollment	• Enrolled 62 patients with mild respiratory illness attributable to COVID	• Generalizability of results to patients with moderate to severe disease
METHODS		
Inclusion criteria	• Age of 18 or over • Positive PCR test for COVID-19 • Diagnosed with pneumonia per chest CT scan • SaO_2/SPO_2 >93% or PaO_2/FIO_2 >300 mmHg (<300 indicates acute respiratory injury or distress) **mild respiratory illness** • Willing to be randomized – informed consent	• Duration of symptoms prior to hospitalization and enrollment not known • Sampling procedures (e.g, nasopharyngeal swabs) not specified • IRB procedures followed
Exclusion criteria	• Severe critical illness or does not meet criteria for safe follow-up • Retinopathy or retinal disease history • Conduction block or arrhythmias • Severe liver disease (based on AST/ALT) • Pregnant or breastfeeding • Severe renal failure or currently on renal replacement therapy (eGFR > 30) • Possibility of transfer to another hospital within 72 hours • Previous participation in a COVID-related trial in the previous 30 days	• Hydroxychloroquine was only tested on patients suffering from mild illness in this study, so the efficacy of the drug on patients who are experiencing COVID related ARDS is difficult to determine • Likewise, patients who may not have acute illness but suffer from comorbidities which dissuade them from using hydroxychloroquine therapy (renal or hepatic disease) limits the applicability of the study to a wider population • Retinopathy generally only occurs after long-term use of hydroxychloroquine, unclear if necessary to exclude these patients given short duration of study treatment • Results cannot be extrapolated to pediatric patients

Interventions	• Treatment group received hydroxychloroquine 400 mg/day, given as 200 mg BID, in addition to standard care, for five days
	• Control group received standard care only
	• Standard care could include
	  • Supplemental oxygen
	  • Noninvasive/invasive ventilation
	  • Antiviral and Antibiotic agents
	  • Corticosteroids
	• Randomization performed using a statistical computer program
		• Variation in the standard of care within and between groups

Primary Endpoints	• Time to clinical improvement in COVID patients receiving HCQ versus patients only receiving standard care • Absorption of pneumonia per chest CT • Compared Day 0 CT scan (before treatment) to Day 6 to determine improvement	• Nice to include an objective measurement of pneumatic improvement • Percent of pneumonia absorption – computer or provider interpreted? • Details on how absorption of pneumonia was assessed was not provided
Secondary Endpoints	• None specified	• N/A
Statistical analyses	• t-test and chi-square test to compare groups (Graphpad Prism v.6.0) • Two sided p-value of less than 0.05 was deemed significant	• These statistical analyses were appropriate
RESULTS		

Enrollment	• Surveyed 142 patients with confirmed COVID-19
	• Excluded 80 patients who didn't meet the criteria
	• 62 patients were included in the study
	  • 31 patients in hydroxychloroquine group
	  • 31 patients in standard treatment group
	• No patients were lost over the course of the study
		• Demographics and underlying conditions not specified – see below

Baseline characteristics	• No major differences in sex or age	• Patients were not weighed/BMI was not assessed • It's known now that COVID patients who experience complications tend to be disproportionately obese • Dose was standardized to patients, although in certain disease states hydroxychloroquine dosing is weight based (over or under 50 kg is dosed differently). • Baseline demographics and comorbidities like diabetes, heart disease, pulmonary disease, were not provided
Monitoring	• Patients were monitored for temperature and cough three times per day • Temperature was recorded using various thermometers • Cough check was patient-reported • Radiology performed chest CT scans at baseline (Day 0) and one day after treatment was completed (Day 6)	• Consistent monitoring by medical professionals in a hospital setting • They adjusted the acceptable "improved" temperature of the patients based on which type of thermometer was used • Cough check is patient reported

<table>
<tr><td>Primary Outcome</td><td>

Time to clinical recovery

Body temperature recovery time was about 1 day faster in the hydroxychloroquine group compared to the control group (p = 0.0008)

HCQ: 2.2 days to recovery, SD: 1.3, n = 31
Control: 3.2 days to recovery, SD: 1.3, n = 31

Cough remission time was reduced in the hydroxychloroquine group as well, 3.1 days vs. 2.0 days to remission (p = 0.0016)

Pneumonia

Large proportion of patients with improved pneumonia in the HCQ treatment group
80.6% of patients showed significant improvement in HCQ group
54.8% in the standard treatment group

<table>
<tr><th>Group</th><th>All</th><th>Exacerbated</th><th>Unchanged</th><th colspan="3">Improved</th></tr>
<tr><th></th><th></th><th></th><th></th><th>Moderate</th><th>Significant</th><th>Total</th></tr>
<tr><td>All</td><td>62</td><td>11 (17.7 %)</td><td>9 (14.5 %)</td><td>18 (29.0 %)</td><td>24 (38.7 %)</td><td>42 (67.7 %)</td></tr>
<tr><td>Control, n (%)</td><td>31</td><td>9 (29.0 %)</td><td>5 (16.1%)</td><td>12 (38.7 %)</td><td>5 (16.1%)</td><td>17 (54.8%)</td></tr>
<tr><td>HCQ, n (%)</td><td>31</td><td>2 (6.5 %)</td><td>4 (12.9 %)</td><td>6 (19.4%)</td><td>19 (61.3%)</td><td>25 (80.6%)</td></tr>
<tr><td>P value</td><td>0.0476</td><td></td><td></td><td></td><td></td><td></td></tr>
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Table 2: Absorption of pneumonia on chest CT.
Abbreviations: HCQ, hydroxychloroquine.
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Statistical vs. clinical significance
Limited sample size

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<tr><td>Secondary Outcomes</td><td>

N/A

</td><td>

N/A

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<tr><td>Other Clinical events</td><td>

Two patients in the HCQ group developed adverse effects: 1 rash, 1 headache.
Four patients in the control group needed intensive care, none in the HCQ group had disease progression to this extent

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These ADRs were not specified, other than what may be considered common side effects of hydroxychloroquine. Regardless, the patients continued pharmacotherapy despite the ADRs

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<tr><td colspan="3">AUTHORS' CONCLUSIONS</td></tr>
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The authors suggest the probable efficacy of hydroxychloroquine in reducing the time to clinical recovery, specifically reducing fever and cough.

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<tr><td colspan="3">GENERALIZABILITY/CRITIQUE/DISCUSSION</td></tr>
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Limited population/homogenous demographics examined in only one hospital
We don't know significant baseline characteristics about these patients

No data on obesity, BMI, comorbidities like diabetes, underlying respiratory diseases like COPD, or modifiable risk factors like smoking
This makes the study difficult to generalize to a wider population

Only mild illness was examined – these patients might have improved anyway, regardless of the addition of hydroxychloroquine
Based on this study, hydroxychloroquine given 400 mg/day for 5 days seems to show statistical significance in terms of reducing time to clinical improvement, in terms of fever and cough, by roughly 1 day in comparison to standard measures.
The study is NOT generalizable to patient with moderate to severe COVID-19

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