Does hydroxychloroquine (HCQ) affect whether COVID-19 patients needed a ventilator or died?

Based on a national retrospective study of hospitalized VA patients, hydroxychloroquine (HCQ) did not reduce COVID-19 deaths and should be prescribed with great caution.

Key takeaways

- Hydroxychloroquine, typically used as an anti-malarial/immune suppressant medication, is unlikely to be the magic pill to cure COVID-19.
 Based on this one-month study of hospitalized veterans at <u>VA hospitals</u> across the United States, patients given hydroxychloroquine alone actually had a statistically greater risk of death compared to a control group that received just the standard of care.
- Patients given both hydroxychloroquine and azithromycin (an antibiotic)

did not have a greater risk of death relative to the control group, who received no HCQ.

- Given potential side effects like cardiac toxicity, HCQ should be prescribed with caution.
- This study has the caveat of being retrospective, which means certain key variables (namely, pre-existing conditions) could not be controlled between groups. Ongoing randomized control trials, which isolate the effect of the drug via randomizing what treatment patients receive, will help provide a more definitive answer on this topic.

Why is this important?

Political leaders, including President Trump, have touted hydroxychloroquine as a promising treatment after <u>an early French study</u> appeared to show impressive results in COVID-19 patients. However, that <u>study has been heavily criticized</u> for not including a control group in its experimental design. Without a control group, we have no way to tell whether patients recovered due to the drug or on their own. As a result, we have to take that study's conclusions with a heavy dose of skepticism.

However, despite the flawed evidence, people have started treating themselves with hydroxychloroquine or one of its chemical cousins, believing it will protect them from COVID-19. This has led to <u>at least one instance of death</u> and a shortage for those who actually need the drug for conditions including lupus and rheumatoid arthritis.

Combating rumors with solid evidence could have important medical consequences and save lives. This study is a preliminary but strong step towards understanding the

What did the study do?

SAMPLING



Collected COVID-19 patient data from the VA 1

OUR TAKE



VA database has detailed information on each patient

The authors had access to the VA's comprehensive database, a rich dataset that not only helped them identify COVID-19 patients but also gave them detailed information about each patient's medical background. Since they could not control anything about which patients went into which treatment category, they were able to use this extra information to statistically adjust for certain factors like pre-existing conditions.



A Retrospective study means patients were not randomized

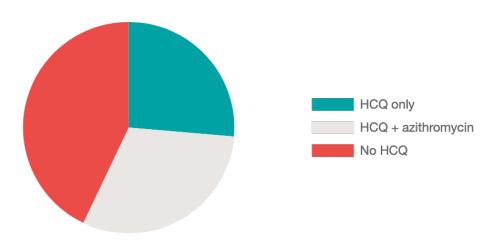
This was a retrospective study, meaning the data was collected before this study was conceived. Thus, when the authors wanted to ask a question about hydroxychloroquine efficacy, they had no ability to randomize which patients received which treatments (necessary for reducing bias). This has led to certain issues in the patient pool. For instance, all patients were elderly men (between ages 59-75), the majority were black², and those given hydroxychloroquine tended to be more sick.

Having said that, retrospective studies aren't necessarily "bad." They allow researchers to quickly analyze existing data and draw preliminary conclusions without having to wait months for prospective trials, which collect data in real time.

ANALYSIS



Divided VA data into 3 treatment groups



The researchers divided the patients into 3 groups: those who received hydroxychloroquine (HCQ), those who received both HCQ + azithromycin ³, and those who received no HCQ (the control group).

OUR TAKE



Adjusted for different patient sickness levels

Overall, the statistical methods used were reasonable given the type of data they were working with. The researchers used statistical techniques to adjust for how sick patients were when they started treatment.

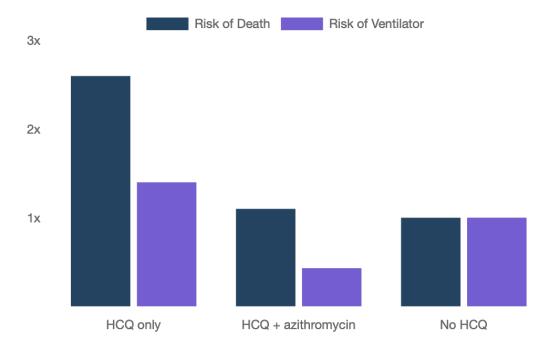
Lack of control for azithromycin

50 patients (~30%) in the "No HCQ" control group received azithromycin. As a result, we don't know whether azithromycin made a difference in how these patients did. The most common reason for researchers to lump these groups together is to maintain statistical power, which is a term for the ability of a study to determine whether a treatment (in this case, HCQ) makes a difference. Unfortunately, they did not explain their decision in the text.

RESULTS



Greatest risk of death in HCQ patients compared to other groups



Risk is relative to the control group. Patients in the HCQ only group were 2.6 times more likely to die than those who received no HCQ.

Even after accounting for pre-existing illness, patients who received HCQ were significantly more likely to die. Patients who received both HCQ and azithromycin faced a similar death rate as the control group who received no HCQ at all. Each treatment group was roughly equally likely to be placed on a ventilator.

OUR TAKE



HCQ adminstered as a hail mary

19 patients did not receive hydroxychloroquine until after they were put on a ventilator. It's possible that by this point it was too late and nothing was going to change how these patients did. By grouping them into the HCQ

group, it might have made that group look more fatal. In certain types of studies (called <u>randomized control trials</u>), researchers use something known as <u>intention-to-treat analysis</u> to avoid skewing the results in this fashion. In this study, the researchers could have done something similar and presented data based on the treatments patients got before going on the ventilator.

CONCLUSION



Exercise caution if prescribing HCQ for COVID-19, especially if it is not combined with azithromycin

OUR TAKE



Despite the issues with the analysis that we pointed out above, the authors made balanced conclusions that were grounded in the data and results. They also acknowledged the drawbacks of their study. Because this was a VA study, only male patients were included and in general, these patients were older (median age 65 years) and a majority were black. This makes it harder to generalize the findings to the rest of the population.

Fortunately, there are several ongoing randomized control trials (the gold standard of studying whether or not a treatment is effective) on HCQ. These will provide a more definitive answer on whether hydroxychloroquine has any use in treating COVID-19 patients.

How was it reported?

VERY GOOD

Anti-malarial drug Trump touted is linked to higher rates
of death in VA coronavirus patients, study says

WASHINGTON POST

Overall a complete summary though there could be more discussion of the limitations of the study.

GOOD

COVID-19 treatment hydroxychloroquine showed no benefit, more deaths in VA virus study

FOX NEWS

Good discussion of the limitations of the study. More detail on the study results and implications could have been provided.

Study finds no benefit, higher death rate in patients taking hydroxychloroquine for Covid-19

CNN

A reasonable summary of the research but does not mention any of the limitations or drawbacks of the study.

The original paper is a preprint study. It has *not* been certified by peer review from other researchers, and information presented may be erroneous. Do not use it to guide clinical practice! Learn more \rightarrow

Original Paper DOI: 10.1101/2020.04.16.20065920

Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19 [PDF]

Footnotes

- 1. U.S. Department of Veterans Affairs
- 2. This could actually be helpful given COVID-19 has disproportionately hit African-American communities.
- 3. Some people were speculating that the two drugs would work better together.

Updates and Corrections

If you see a mistake or want to suggest changes, please contact us.

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