Hydroxychloroquine and COVID-19: Recent High Quality Randomized Trials

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In any field of science, published trials provide data. Often if not usually, trials of the same or similar agent or method will get different results. To sort those results, we look for some criteria that may indicate more or less reliable data in the trial.

Is the method a single case report, or report of a few cases?

This data is unreliable, and especially in the COVID-19 pandemic because most people will recover no matter what you do. Even the majority of hospitalized patient recover regardless of any particular treatment, and the current mean stay in the hospital is about 5 days This kind of evidence is not evidence. You can't say it was your drug rather than other treatments or the healing power of nature that effected the cure.

Is is a controlled clinical trial?

In other words, is the problem in the first case above addressed by giving the drug to half the patients, using normal methods on the other half? We could theoretically then conclude that, if the patients receiving the drug had fewer symptoms, less hospitalization, less death, etc, then the success must be due to the drug.

Is the trial controlled?

But what if the patients receiving the drug were all young with mild illness, and the ones on standard care were diabetic cardiovascular disease patients? Oh oh. Now the data is unreliable. This occurred in one trial claiming that hydroxychloroquine was superior to standard care in a clinical trial. The patients in the standard care group has a lot more cardiovascular disease so more of them were going to die anyway. It happened in another trial where the patients receiving the HCQ were all more severely ill, and thus it looked as if it had no benefit simply because the group that got the drug were sicker and were going to die regardless of any treatment. So researchers, editors, peer reviewers, and the public have to try to control for such factors that can confound the outcomes.

Is the trial Peer Reviewed?

Controlling for such confounding factors, and design of a trial with integrity are very complex, experts don't always agree, and thus we have the process of peer review by journals. A group of scientists in the field look for weaknesses in the trial, before it is allowed to be published.

Is the above process perfect?

By no means, in fact it is often or even usually flawed in some way. Therefore, we try not to look at any one single trial, no matter how successful it looks. We want to see an emerging consensus of results from more than one trial and more than one group of researchers.

Is the process *then* perfect?

No, still flawed, subject to prejudice, financial interests, political interests. But, the end product produces a set of data that cannot be ignored. It is not necessarily perfect. But if, as below, the four best-designed trials of hydroxychloroquine for COVID-19 reach exactly the same conclusion, then it will be very difficult for you to claim positively that HCQ “cures” or “prevents” COVID-19. You can't simply ignore the results. You will need to use “maybe” “might” “or in my opinion.” You can't use single practitioners “clinical experience.” Or a single case study, or a lab dish study, or an un-peer-reviewed preprint, or even a single randomized controlled trial to make your point. And you can't cherry pick your favorite badly designed trials because you like the results, and then ignore completely the rest of the information you don't like. Or argue that some guy in a white coat who hasn't seen a patient in the last three years standing in front of a camera in front of the Supreme court has any kind of reliable information that might actually help save lives.

Below I have selected the four most ***recent, well-designed, randomized, controlled clinical trials*** on the use of hydroxychloroquine for prophylaxis in exposed practitioners, for outpatients with mild disease, for hospitalized patients with mild disease, or hospitalized patients with any stage of disease. These come from 3 different continents with teams of researchers rather than individual authors. Is this “cherry-picking”? No, selection of only well-designed trials, and leaving uncontrolled and unpeer-reviewed information behind is a reasonable and standard method of science. Is this the final word? No, other trials are ongoing. ***But this data cannot simply be ignored.***

Compiled 7/31/20 Paul Bergner

July	RCT. Mild disease in hospitalized patients	HCQ Plus antibiotic	"Among patients hospitalized with mild-to-moderate Covid-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care."

1. Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without azithromycin in Mild-to-Moderate Covid-19. https://www.nejm.org/doi/full/10.1056/NEJMoa2019014

July	RCT Mild disease in outpatients.	HCQ	"Hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19. Side effects were double in the HCQ group."

2. Rajasingham R et al. Hydroxychloroquine in Non-hospitalized Adults With Early COVID-19.After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as post-exposure prophylaxis within 4 days after exposure. https://www.acpjournals.org/doi/10.7326/M20-4207?fbclid=IwAR2qkb75luMEU1QsMALMl8XGGDMoU-DW73zLKNMNSISpflJ-Vtp-ORmXJfE

June	RCT Massive study in hospitalized patients	HCQ	"Hydroxychloroquine does not reduce the risk of death among hospitalised patients with this new disease."

3. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19?fbclid=IwAR2SysNzVqw6Crfmqfyar2yDB6CA8F_hW1JpUVOOxEQ5Se-7xJQl93Y2lP0

June	Exposed hospital workers for prophylaxis after exposure	HCQ	After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as post-exposure prophylaxis within 4 days after exposure.

4. https://www.nejm.org/doi/full/10.1056/NEJMoa2016638?fbclid=IwAR0DPXqqO5I6nT9KAIbyHU65M8MbIi0Axm4csRvDlM0Vpe3JNjfuzEG6pGg

Addendum

Some people have asked why I did not include the recent study on this topic from the Henry Ford Health system. That trial was not randomized, it was retrospective, and was not blinded. No rationale was given for why a patient may have received HCQ or not. And also the patients receiving HCQ were more likely also to receive steroids – 77% of the HCQ patients and only 36% of the controls, and steroids are today recognized as beneficial in critical COVID-19 illness. It is impossible to tell if the benefit was from the HCQ or from the steroids. I didn't include it because it is not a randomized controlled clinical trial. You can see the full study https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7330574/pdf/main.pdf And see discussion here: https://www.statnews.com/2020/07/08/a-flawed-covid-19-study-gets-the-white-houses-attention-and-the-fda-may-pay-the-price/