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Editorial

Caution Needed on the Use of Chloroquine and Hydroxychloroquine for Coronavirus Disease 2019

Stephan D. Fihn, MD, MPH; Eli Perencevich, MD, MS; Steven M. Bradley, MD, MPH

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Author affiliations and article information are listed at the end of this article.

The coronavirus disease 2019 (COVID-19) pandemic has propagated global shock waves that have disrupted nearly every aspect of human endeavor. Nowhere has this been more evident than in health care. Health care delivery systems in some locations have been overwhelmed, and even those not so severely affected have had to reorganize and restructure to concentrate resources to meet an anticipated surge of patients who are critically ill. In the absence of rapid and reliable testing, proven therapies, or even standard protocols for treatment, physicians and other clinicians have been forced to improvise, in some cases relying on the thinnest of evidence, to treat patients who are desperately ill.

The response of the medical research community has been remarkable. Investigators have rapidly pivoted to fill the enormous gap in knowledge the pandemic has laid bare. While nearly all medical research not directly related to COVID-19 or otherwise deemed essential has been paused, laboratories around the world have refocused on elucidating the biological characteristics of the severe acute respiratory syndrome coronavirus 2 in support of efforts to develop treatments and vaccines. In addition to the phenomenal investment in basic research, clinical investigators have collected massive amounts of data and launched nearly 1000 clinical trials worldwide.[1]

In this study by Borba et al,[2] results are presented from a preliminary study that tested a compound, chloroquine sulfate, that has been widely touted in the lay press as an effective treatment for COVID-19. Hydroxychloroquine, which was initially used widely as an antimalarial drug, has also long been used as an effective treatment of chronic rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus. In addition, earlier research on this drug suggested that it had potential antiviral properties. In 2 small, uncontrolled studies, hydroxychloroquine and its congener, chloroquine, were reported to be effective against COVID-19, although the publishing journal's society subsequently declared that the trial did "not meet the Society's expected standard."[3-5] These weak findings, bolstered by anecdotal reports and media attention, have fostered widespread belief in the efficacy of these agents. In response, concerns have been raised about the lack of reliable efficacy data and about potential toxic effects. In short-term use, chloroquine can prolong the QT interval and induce arrhythmias. This is especially concerning in elderly patients with underlying heart disease who are at highest risk for COVID-19. Nonetheless, in many hospitals, patients with known or suspected COVID-19 infection are routinely being treated with chloroquine, and it is often being coadministered with other agents, such as azithromycin, that might synergistically cause QT interval prolongation.[6] At least 1 death in the general population has resulted from unintentional poisoning due to ill-advised use of chloroquine.[7]

Borba and colleagues[2] performed a parallel, double-blind, randomized clinical trial in a Brazilian population designed to assess the safety of chloroquine in dosages that, based on earlier research, were thought to be sufficient to exert antiviral effects.[2] They compared a high dose of chloroquine, 600 mg twice daily for 10 days (total dosage, 12.0 g), with a lower-dose regimen, initially 450 mg twice daily on the first day, tapering to 450 mg once daily for 4 days (total dosage, 2.7 g). Patients enrolled in the trial exhibited fever and respiratory symptoms, along with tachypnea, tachycardia, hypoxemia, or hypotension. The primary outcome was death, originally planned to be assessed at 28 days after entry to the trial. Secondary outcomes included death at 13 days, electrocardiographic anomalies, recovery of viral RNA, and a number of clinical events, such as duration of mechanical

ventilation and clinical status. Because of delays in testing for the virus, treatment was initiated based on suspicion of COVID-19. Ultimately, 31 of 40 patients (77.5%) in the low-dose group and 31 of 41 patients (75.6%) in the high-dose group had test results positive for COVID-19. This should not be viewed as a problem, as it accurately reflects the conditions under which many patients are being treated in the absence of a definitive diagnosis.

The intended sample size was 440 individuals, but based on occurrence of serious adverse events, the data safety monitoring board terminated the trial after only 81 individuals had been enrolled, preceding even the first planned interim analysis at 25% of enrollment. By day 13 of enrollment, 6 of 40 patients (15.0%) in the low-dose group had died, compared with 16 of 41 patients (39.0%) in the high-dose group. Prolongation of QTc interval was observed in 4 of 36 patients (11.1%) in the low-dose group and 7 of 37 patients (18.9%) in the high-dose group. In addition, 2 patients in the high-dose group (2.7%) experienced ventricular tachycardia. Three of 5 patients (60.0%) in the high-dose group with underlying heart disease died.

Despite these discouraging findings, several other observations prevent concluding categorically that high-dose chloroquine was toxic and that the likely mechanism was arrhythmogenesis. First, Borba et al[2] found no apparent association of the appearance of QTc interval prolongation and subsequent death. There was also no witnessed torsade de pointes, an arrhythmia that is characteristically induced by QTc interval prolongation. Second, all patients were also receiving azithromycin, and nearly all were receiving oseltamivir (for possible influenza), which can also prolong the QTc interval. Thus, one can only conclude from this trial that high-dose chloroquine (and by close association, hydroxychloroquine) in combination and azithromycin and possibly oseltamivir, is potentially associated with increased mortality among patients with severe, suspected COVID-19.

Several other trials, including a large multicenter trial in the US, are ongoing and hopefully will provide additional crucial information about the efficacy and safety of hydroxychloroquine. In the interim, the results of this trial by Borba et al[2] should prompt some degree of skepticism toward the enthusiastic claims about chloroquine and perhaps serve to curb the exuberant use. For the time being, prudent clinicians should discuss with patients and their families, when feasible, the potential risks of this drug and the uncertain benefits before initiating it.

This trial by Borba et al[2] also illustrates some of the successes and challenges that the COVID-19 pandemic has created for publication of research results. The mechanisms to design, approve, fund, and execute important research have dramatically accelerated. The first patient was enrolled in this trial on March 26, 2020, and the first submission of this manuscript to the JAMA Network was on April 13, 2020. The rapidity with which clinical data have been issuing forth through traditional medical journals and other conduits is unsurpassed. Journals, including *JAMA Network Open*, have been receiving hundreds of submissions from around the globe. In response to the urgency of disseminating information, *JAMA Network Open* has adapted processes to expedite triage, review, and publication of important studies while still maintaining high-quality peer review. This is all the more difficult in the present environment, when the most qualified reviewers are busily engaged in dealing with the epidemic in their own institutions and their larger communities. Nevertheless, it remains critically important that a commitment not only to high-quality science, but also to accurate and unbiased reporting, remains intact as we seek to publish results as rapidly as possible. Science poorly conducted or poorly reported is counter to the public interest.

In the current torrent of data, the half-life of information is short. A novel observation from a week earlier rapidly becomes common knowledge or is superseded by more definitive studies. That so much research is being conducted and published underscores the robustness of the scientific publishing enterprise and should be heartening to the world population as we all wait anxiously for information and signs of progress.

ARTICLE INFORMATION

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Correction: This article was corrected on April 27, 2020, to fix an incorrect drug name in the third paragraph.

Corresponding Author: Stephan D. Fihn, MD, MPH, Department of Medicine, Harborview Medical Center, University of Washington, 325 Ninth Ave, PO Box 359780, Seattle, WA 98104 (sfihn@uw.edu).

Author Affiliations: Department of Medicine, Harborview Medical Center, University of Washington, Seattle (Fihn); Department of Health Services, Harborview Medical Center, University of Washington, Seattle (Fihn); Deputy Editor, *JAMA Network Open* (Fihn); Center for Access an Delivery Research and Evaluation, Iowa City VA Health Care System, Iowa City, Iowa (Perencevich); Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City (Perencevich); Associate Editor, *JAMA Network Open* (Perencevich, Bradley); Healthcare Delivery Innovation Center, Minneapolis Heart Institute, Minneapolis, Minnesota (Bradley).

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