May 22, 2020

No Improvement in Death Rate for COVID-19 Patients who Received Hydroxychloroquine

Official Statement - 6/4

My research intentions have always been to contribute to scientific discussion and to ensure that the practice of medicine is based on the best evidence available. During this pandemic, I have felt this even more keenly, and believe that it is imperative to provide timely data that informs both the scientific field and the care of our patients.

*In that pursuit, through an association with one of my co-authors, I was introduced to and partnered with Dr. Sapan Desai and his company Surgisphere, a privately held company that purported to have data from hospitals around the world that could be leveraged to answer important public health questions I posed in the face of the COVID-19 pandemic. To answer these questions, Dr. Desai, who served as a co-author and whose team maintained this observational database, conducted various analyses. As first author, these were provided to me, and on the basis of these analyses, we published two peer-reviewed papers, one in the **New England Journal of Medicine** (NEJM) and the other in **The Lancet**.*

*When discrepancies in the data started to arise, I and the remaining co-authors immediately asked for a re-analysis from Surgisphere and then proactively contracted **Medical Technology & Practice Patterns Institute** (MTPPI) to conduct an independent peer review. On June 3, MTPPI informed us that Surgisphere would not be able to transfer the data required to conduct this audit "because of agreements with its clients and the fact that the documents contain confidential information." Since we do not have the ability to verify the primary data or primary data source, I no longer have confidence in the origination and veracity of the data, nor the findings they have led to. I have notified the editors at NEJM and The Lancet of our intention to retract these papers.*

I have always performed my research in accordance with the highest ethical and professional guidelines. However, we can never forget the responsibility we have as researchers to scrupulously ensure that we rely on data sources that adhere to our high standards. It is now clear to me that in my hope to contribute this research during a time of great need, I did not do enough to ensure that the data source was appropriate for this use. For that, and for all the disruptions – both directly and indirectly – I am truly sorry.

Mandeep R. Mehra, MD, MSC

Retraction: **https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31324-6/fulltext**

Press Release 5/22

A research team led by investigators from Brigham and Women's Hospital has evaluated real-world evidence related to outcomes for COVID-19 patients who were treated with hydroxychloroquine or chloroquine analogues (with or without a macrolide). Investigators found no evidence that either drug regimen reduced the death rate among patients. Patients treated with hydroxychloroquine or chloroquine regimens were far more likely to experience abnormal, rapid heart rhythms (known as ventricular arrhythmias) than their counterparts who had not received the drugs. The team's findings are published in ***The Lancet***.

"No matter which way you examine the data, use of these drug regimens did not help," said corresponding author Mandeep R. Mehra, MD, executive director of the Brigham's Center for Advanced Heart Disease. "If anything, patients had a higher likelihood of death. We also saw a quadrupling in the rate of significant ventricular arrhythmias in patients with COVID-19 who had been treated with hydroxychloroquine or chloroquine regimens."

Mehra and colleagues conducted their study using the Surgical Outcomes Collaborative database, an international registry comprised of de-identified data from 671 hospitals across six continents. The analysis included data on more than 96,000 patients hospitalized with COVID-19. This included almost 15,000 patients who had received the anti-malarial drug chloroquine or its analog hydroxyquinone with or without an antibiotic (macrolides such as azithromycin and clarithromycin) early after COVID-19 diagnosis. The study's primary endpoint was death or discharge from the hospital.

Mehra and colleagues found that 10,698 patients died in the hospital (11.1 percent) and 85,334 survived to discharge. The team compared death rates for those taking one of the drug regimens to that of a control group, after accounting for confounding variables, such as age, sex and underlying risk factors. The death rate among the control group was 9.3 percent. Each of the drug regimens of chloroquine or hydroxychloroquine alone, or in combination with a macrolide, was associated with an increased risk of in-hospital death with COVID-19.

In addition, each of the drug regimens was associated with an increase in the risk of ventricular arrhythmia. Among the treatment groups, between 4 and 8 percent of patients experienced a new ventricular arrhythmia, compared to 0.3 percent of patients in the control group.

Chloroquine and hydroxychloroquine have been known to cause cardiovascular toxicity and previous studies have shown that macrolides can increase the risk of sudden cardiac death. A preliminary analysis of patients in Brazil treated with chloroquine and an antibiotic has suggested a high dose of chloroquine may be a safety hazard. Results from randomized, controlled clinical trials are not expected until the summer.

The authors caution that the current study is observational in nature — this means that it cannot absolutely answer the question of whether the drug regimens were solely responsible for the changes in survival. Randomized clinical trials will be required before any conclusion can be reached regarding harm.

"These findings suggest that these drug regimens should not be used outside of the realm of clinical trials and urgent confirmation from randomized clinical trials is needed," the authors conclude.

The development and maintenance of the Surgical Outcomes Collaborative database was funded by the Surgisphere Corporation. The present analysis was supported by the William Harvey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital, Boston. Mehra reports no direct conflicts pertinent to the development of this paper. Other general conflicts include consulting relationships with Abbott, Medtronic, Janssen, Mesoblast, Portola, Bayer, NupulseCV, FineHeart, Leviticus, Roivant and Triple Gene. Dr. Desai is the founder of Surgisphere Corporation, Chicago. The other authors have no pertinent conflicts to report.

Paper cited: Mehra M *et al*. "Hydroxychloroquine or Chloroquine with or without a Macrolide and Outcome in COVID-19: A Multinational Registry Analysis" *The Lancet* DOI: 10.1016/S0140-6736(20)31180-6

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