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COMMENTARY

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# Does pandemic justify the use of hydroxychloroquine for treatment and prevention of COVID-19 in India?

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The world is witnessing a pandemic never seen before which has engulfed more than 200 countries in a matter of few weeks and claimed more than 0.1 million lives, still counting. Do we have any cure for this deadly virus? The answer is No. As the Corona pandemic grows, the need for an effective treatment is mounting as the doctors are running out of options to help the infected. Recently, Hydroxychloroquine (HCQ) has been widely used off-label for treatment and prevention of COVID-19. However, many gaps exist in our understanding of if and how hydroxychloroquine works against COVID-19. Most of the favorable data come from in-vitro studies in Petri dishes.[1,2] Chloroquine (CQ) was shown to inhibit the replication and spread of coronavirus (CoV) in vitro and to prevent infection with CoV in newborn mice as well. Since the suppressive effect of CQ was also present when the cells were treated before the infection, a prophylactic advantage of CQ use was also suggested.[3-5] Chloroquine exerts direct antiviral effects, inhibiting pH-dependent steps such as endosome-mediated viral entry or the late stages of replication of enveloped viruses including members of the flaviviruses, retroviruses, and coronaviruses. Chloroquine also has immunomodulatory effects, suppressing the production/release of tumor necrosis factor α and interleukin 6, thereby mediating the symptoms as a result of an inflammatory response or immune hyperactivation.[6] However, in vitro activity of these drugs should not be interpreted as proof of clinical efficacy against COVID- 19. Similar in vitro activity of CQ and HCQ was identified against other viruses, but subsequent clinical trials did not show significant clinical benefit of these drugs against Ebola, chikungunya, influenza, and dengue viruses.[7-10] Another mechanism of action of CQ is that it inhibits severe acute respiratory syndrome (SARS)-CoV replication and spread in cell culture, possibly through reducing glycosylation of the angiotensin-converting enzyme 2 receptor, which appears to be the primary receptor for entry of SARS-CoV-2 into various epithelial tissues.[3,11] The action of CQ in the reduction of hyperglycemia, which is a significant risk factor for disease severity also needs to be explored further.[11]

Human trials of HCQ against COVID-19 have so far yielded mixed results. A study among hospitalized patients with confirmed COVID-19 in Marseille, France, showed significant reduction/disappearance in viral load with HCQ and azithromycin treatment.[12] However, these results are widely debated due to some methodological issues primarily related to smaller sample size, unmeasured viral load in a majority of the control cohort, and nonrandomized nature of the trial that might end up cherry-picking patients, potentially biasing the results. A randomized trial of HCQ in 30 COVID confirmed patients in China yielded no better clinical benefit compared to the control arm which received standard treatment.[13] Another prospective single-arm study of 11 hospitalized patients in France treated with HCQ and azithromycin (same dosing regimen reported by Gautret et al[12]) showed no evidence of viral clearance or clinical benefit with one death and two transferred to the Intensive Care Unit. In another patient, the treatment regimen was discontinued after 4 days due to QT prolongation.[14]

On the other hand, a preliminary result from a trial from 10 hospitals in China involving 100 patients demonstrated that chloroquine phosphate is superior to the control treatment in preventing the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course.[15] Significant time to clinical recovery and radiological recovery was also seen in another randomized controlled trial (RCT) from Wuhan, China with 62 patients (31 in each arm).[16] Another large cohort of 1061 patients also demonstrated good clinical outcome and virological cure in 92% of cases within 10 days.[17] There have been some instances of the use of HCQ among patients in Jaipur, India, with reasonable success. A recent meta-analysis by Sarma et al[18] showed no difference in the virological cure, death, clinical worsening of the disease, and safety when compared to the control/conventional treatment arm, although more robust data are needed to reach a definite conclusion.

So, with the current body of evidence, which is at best suggestive, we definitely need more evidence for establishing its therapeutic benefit through well-designed powered RCTs. But, at the same time, we feel that in the current crisis, the curative use of this drug in a subset of the patients with no contraindications might do more good than harm.

  

Now, let us talk about the prophylactic use of HCQ. There is no study that evaluated HCQ as prophylaxis for COVID-19, which is a different ball-game altogether. Chloroquine blocks immune activation by inhibiting the production of interferon-α, which is a key part of the body's defense against viruses. In doing so, it could hamper a person's ability to fight off coronavirus. This makes it a bad choice for prophylaxis. Paradoxically, the same mechanism of HCQ could help sicker patients with COVID-19 recover early as it tames down the overzealous immune response, thus making it a potential candidate for therapeutic use.

India's apex medical research agency, the Indian Council of Medical Research (ICMR), recommended the use of hydroxychloroquine as a prophylactic against COVID-19 among healthcare workers and asymptomatic contacts of laboratory-confirmed cases of COVID since March this year. This is widely criticized as a hastily taken step with minimal evidence backing.

In the current scenario where there is mass fear against COVID-19, this recommendation has made the people to believe that it will kill the viruses. Better communication should have been planned to ensure everyone does not go out and buy it. Yet, as social media buzzes with news of people stocking up on hydroxychloroquine, it seems many do believe it will protect them.

The ICMR warned against injudicious use of HCQ without a medical prescription due to the known adverse effects of HCQ. Probably the message did not get across effectively, not to blame the agency though, but the psychology of mass fear prevailing in the society. Everyone, irrespective of the indications started looking for the drug, majority without medical consultation. This can have significant public health implications in terms of adverse effects of the drug which can show up widely despite being rare, drug resistance, shortage of the drug in the market depriving those indicated (both COVID and non-COVID indications such as malaria, lupus, rheumatoid arthritis). Anecdotal findings and media reports suggest that there is, in fact, acute shortage of the drug in several parts of the country probably due to artificial scarcity created by drug traders as a result of hoarding and panic buying by customers. However, the government was quick to react and placed the drug under the Schedule H category to restrict the sale and distribution of the drug. Although the ICMR warned against any false sense of protection as a result of intake of the drug, this is inevitable and runs the risk of downplaying public health measures such as social distancing, use of masks and sanitizers, etc.

There are also concerns regarding the dosage of the drug to be given, its side effects, and the evidence behind it. The dosage schedule recommended by the ICMR also has no support from the literature. Even though some trials are underway on the post- and pre-exposure chloroquine prophylaxis for healthcare workers and asymptomatic contacts of laboratory-confirmed cases of COVID-19, the dosages being tested in the trials are different from those recommended by the ICMR (Clinical Trial Registry Number: NCT04331834, NCT04308668, and NCT04318444 registered with ClinicalTrials.gov).

Hospitals and state governments around the country have been implementing ICMR's recommendations in different ways. For example, healthcare workers in several states were given the drug without screening for risk factors. Many individual doctors or other healthcare workers are also popping the drug on their own. In contrast, a government medical college in Kerala evaluated all individuals taking the drug for risks including an electrocardiogram to look for heart-related abnormalities.

Thus, although the intention was to protect the high-risk groups from getting infected, the delivery of the message and implementation could have been better. Rather than discouraging this move by the ICMR, I think all healthcare workers taking this drug should volunteer themselves to be part of a trial or an observational study to generate evidence related to its safety and efficacy and guide future recommendations. This could have been planned as a multicentric trial or a large observational study with an online recruitment platform where health staff could register and fill their sociodemographic and clinical details, details regarding drug intake and its side effects, and COVID exposure and infection. The other risk group that includes asymptomatic contacts of laboratory-confirmed patients with COVID-19 are under active surveillance by the state and local health authorities for 28 days and could also be roped into this study to generate robust evidence. As a nation of 1.3 billion, we need to capitalize on this opportunity to generate data and valuable evidence on the use of HCQ in beating this pandemic. Of course, pandemic does not just justify the use of HCQ, but pandemic is the time to innovate, think out of the box and generate evidence to prove the same so that we can lives.

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## CONFLICT OF INTEREST

The author declares that there is no conflict of interest

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