

Prophylactic Medications Taken by Healthcare Workers for COVID-19; A Mixed Methods Study from South India

Abstract

Background: COVID-19 is an unprecedented pandemic that has taken the modern world under seize. In spite of lack of solid evidence, certain federal governments had recommended the use of hydroxychloroquine (HCQ), chloroquine, and azithromycin as prophylactic medications either for contacts or for healthcare providers in particular. The objective of this study is to assess the issues related to intake of prophylactic medications in view of COVID-19 and the proportion and pattern of side effects. **Methods:** A descriptive cross-sectional study was conducted using mixed methods approach among healthcare workers in Puducherry, India. **Results:** HCQ was the prophylactic drug taken by all the participants ($n = 26$). Of the 26, 15.4% had a baseline ECG, 26.9% took HCQ based on the recommended Day 1 dose of 800 mg and 61.5% of the participants had the drug provided by the hospital where they work. Reasons for taking prophylaxis were sense of vulnerability (due to co-morbidities, lack of PPE kits) and peer practice. However, the participants did not recommend prophylactic medication to others due to lack of evidence, death claims related to prophylactic drugs in media, hospitals not taking responsibility of baseline monitoring and need for long follow-up. **Conclusions:** The data on assessment of HCQ prophylaxis indicates only minor side-effects, though limited by sample size. Evidence-based recommendations on prophylactic drugs for COVID-19, effective risk communication, peer education and support, accountability, ease of baseline, and follow-up investigations were the need of the hour to improve intake and adherence to prophylactic regime for COVID-19.

Keywords: Adverse effects, COVID-19, healthcare workers, hydroxychloroquine

Introduction

COVID-19 is an unprecedented pandemic that has taken the modern world under seize. Healthcare providers and other front line workers are trying to serve under difficult circumstances with the constant threat of getting infected.^[1,2] Researchers on the other hand are making sure that they provide the best evidence to healthcare providers in controlling the pandemic.^[3] The debate on the role of hydroxychloroquine (HCQ), chloroquine, and azithromycin as prophylactic medications are going on since many months. In spite of lack of solid evidence, certain federal governments had recommended the use of HCQ, chloroquine, and azithromycin as prophylactic medications either for contacts or for healthcare providers in particular. Many withdrew these recommendations later on.^[4,5] The two main concerns that emerged from these debates are their effectiveness and side-effects.

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Government of India (GoI) on 23rd March 2020 issued through the National Task Force for COVID-19 recommendation for using HCQ as prophylaxis for SARS CoV-2. The asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19 and asymptomatic household contacts of laboratory confirmed cases were eligible for HCQ prophylaxis under this recommendation.^[6]

Then on 22nd May, 2020 ICMR issued a revised advisory on the use of HCQ as prophylaxis for SARS-CoV-2 infection (in supersession of previous advisory dated 23rd March, 2020).^[7] They recommend use of HCQ in high risk population as summarized in Table 1 along with the recommended dose schedule.

The contraindications for use of HCQ are, children under 15 years of age and persons with known history of retinopathy, G6PD deficiency, hypersensitivity to HCQ or 4-aminoquinoline compounds, pre-existing

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Table 1: HCQ prophylaxis for high-risk groups (National Task Force for COVID-19, GoI)

High-risk group	Dose recommended (to be taken after meals)
All asymptomatic healthcare workers involved in containment and treatment of COVID-19 and asymptomatic healthcare workers working in non-COVID hospitals/non-COVID areas of COVID hospitals/blocks	400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks
Asymptomatic frontline workers, such as surveillance workers deployed in containment zones and paramilitary/police personnel involved in COVID-19 related activities	
Asymptomatic household contacts of laboratory confirmed cases	400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks

cardiomyopathy, and cardiac rhythm disorders. Also, the drug has to be given under strict medical supervision with an informed consent.^[7]

In-vitro studies have shown chloroquine to be effective against several viruses, including SARS-CoV. Doses of 3-6 mg/kg lead to plasma concentrations of 1–3 $\mu\text{mol/L}$ the same concentration range as the half-maximal inhibitory concentration for SARS-CoV inhibition.^[8,9] The dose schedule of chloroquine^[10] found to be effective or being evaluated to prevent or treat confirmed cases of COVID-19 are,

Chloroquine phosphate (500 mg, having 300 mg Chloroquine base):

1. Oral chloroquine phosphate dosage suggested in the EUA: For treatment of hospitalized adults and adolescents weighing 50 kg or more when a clinical trial is not available or participation not feasible, 1 g on day 1, then 500 mg daily for 4-7 days of total treatment based on clinical evaluation
2. Oral chloroquine phosphate: 500 mg twice daily for 10 days
3. Oral chloroquine phosphate: 500 mg twice daily for 7 days (adults 18-65 years weighing >50 kg); 500 mg twice daily on days 1 and 2, then 500 mg once daily on days 3-7 (adults weighing <50 kg)
4. Oral chloroquine phosphate: Initial dose of 600 mg followed by 300 mg 12 hours later on day 1, then 300 mg twice daily on days 2-5

Azithromycin, macrolide group of antibiotic with some *in vitro* activity against viruses (e.g., Influenza A virus subtype H1N1, Zika). It has been used for antibacterial coverage in hospitalized patients with COVID-19 along with hydroxychloroquine. The dose schedule is 500 mg of azithromycin on day 1, then 250 mg daily on days 2-5 in conjunction with 10-day regimen of hydroxychloroquine.^[10,11]

The effectiveness of chloroquine and azithromycin as prophylactic agents against COVID-19 lacks evidence. The WHO is yet to comment on the prophylactic role of HCQ, chloroquine, and azithromycin.

Side effects and drug interactions

The side effects and drug interactions associated with these drugs are a priority concern. FDA recommends initial

evaluation and monitoring when using hydroxychloroquine or chloroquine for the treatment or prevention of COVID-19. Monitoring may include baseline ECG, electrolytes, renal function, and hepatic tests. Also hydroxychloroquine or chloroquine^[12] can cause,

- QT prolongation (increased risk in patients with renal insufficiency/failure), inversion or depression of the T-wave with widening of the QRS complex, hypotension, ventricular arrhythmias and torsade de pointes, cardiomyopathy which may result in cardiac failure
- Hypoglycemia
- Bone marrow failure, aplastic anemia, hemolysis in patients with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency
- Vertigo, tinnitus, nystagmus, nerve deafness, deafness
- Irreversible retinopathy with retinal pigmentation changes (bull's eye appearance), visual field defects (paracentral scotomas), maculopathy, and macular degeneration which may be irreversible
- Headache, dizziness, seizure, ataxia, and extrapyramidal symptoms
- Nausea, vomiting, abdominal pain, diarrhea, hypersensitivity, and photosensitivity.

As the situation is evolving, evidence is being added every day to the knowledge pool. With the likely effective prophylactic measures in hand, it is high time to understand the pattern of side-effects associated with them.^[13] The objective of this study is to assess the issues related to intake of prophylactic medications in view of COVID-19 and the proportion and pattern of side effects.

Methods

This is a descriptive cross-sectional study conducted using pre-designed, pre-tested proforma which includes demographic details, prophylactic medications taken, their dose, side-effects experienced, treatment taken for side-effects, and past history including treatment (To access questionnaire, <https://forms.gle/WP3P4R63GzRPdeyBA>). Having taken any medication (Allopathy) for prophylaxis against COVID-19 was the inclusion criteria and a convenient sample of the same was obtained. The data were collected after clearance from Institutional Ethics Committee of Vinayaka Missions Medical College and Hospital, Karaikal, Puducherry.

The questionnaire was circulated using Google forms to reduce person to person contact and for the ease of data collection among doctors from medical colleges and hospitals in and around Puducherry, India. It was circulated individually and across WhatsApp groups for a period of 1 week between 20th and 27th April, 2020. Completing the form and submitting the same is considered as giving consent for the study. A total of 26 participants completed the proforma. The participants were then contacted individually using contact numbers provided by them in the Google forms. In-depth interviews were conducted among a total of 26 frontline workers who had taken prophylactic medication for COVID-19. Interview was facilitated using an interview guide which was prepared beforehand. The participants were encouraged using open questions to express their knowledge, understanding of the recommendations for COVID-19 prophylaxis and their view of the same. Probes were used among the study participants as a hint to think whenever they were unable to get in depth of the concerned topic. The interview lasted for not more than 20–30 minutes. The interview was recorded after taking consent from the participant and the recordings have been kept confidential.

Statistical analysis

The descriptive data were analyzed using Microsoft Excel and SPSS v23. For qualitative analysis, the transcripts were written from the audio recording of the in-depth interviews and field notes. Manual thematic content analysis based on the prefixed codes and categories was done.

Results

The study included a total of 26 participants who had started with at least one prophylactic regime for COVID-19. The participants included were from 25 to 53 years of age with a mean of 39.4 ± 10.7 years. Majority were males (84.6%). The mean duration between the participants starting prophylaxis (taking the first dose) and the date of survey was 29 ± 5.7 days (Mode = 31 days).

All the participants included in the study took only HCQ as prophylactic medication against COVID-19. It was found that only 15.4% of the participants had a baseline ECG before taking HCQ. The drug was supplied to 61.5% of the participants by the concerned hospital where they work. The dose taken by the participants were not uniform. Only 26.9% of the participants took HCQ based on the recommended Day 1 dose of 800 mg. The other participants (73.1%) took a total of 400 mg on Day 1.

Of the side effects, 23.1% participants reported nausea, 15.4% reported abdominal pain and 7.7% reported loose stools after the first dose of HCQ. None of the participants reported vomiting, hypoglycemia, hypersensitivity, photosensitivity, or cardio vascular effects after the first dose or subsequent doses of HCQ. Only 11.5% reported treatment for side effects and none reported hospitalization.

It was found that 30.8% of the participants were hypertensive and 23.1% were diabetic.

For qualitative data, content analysis was done and themes that emerged from the IDIs are presented in Table 2, supported by participant responses and verbatim.

Discussion

This study aimed to access the issues related to intake of prophylactic medications in view of COVID-19 and the proportion and pattern of side effects. HCQ was the only prophylactic medication used by the HCWs in this study. It was also the only drug recommended by ICMR for prophylaxis against COVID-19. This recommendation is based on evidence from in-vitro studies, drug safety profile and prophylactic efficiency of the drug against SARS-CoV-2.^[7]

This study reports only mild adverse effects such as nausea, abdominal pain, and loose stools. This is similar to an assessment of HCQ prophylaxis among 1323 HCWs indicating mild adverse effects such as nausea (8.9%), abdominal pain (7.3%), vomiting (1.5%), hypoglycemia (1.7%), and cardio-vascular effects (1.9%). However, these results vary from Pharmacovigilance program of India data, where prophylactic HCQ use is associated with 214 reported instances of adverse drug reactions. Of these, 7 were serious individual case safety reports with prolongation of QT interval on ECG in 3 cases.^[7]

This study reported only 15.4% participants having a baseline ECG and only 26.9% of the participants taking HCQ as per recommended guidelines reflecting poor risk communication. Such a situation demands accountability as well. Indian Heart Rhythm Society recommends a mandatory baseline ECG along with estimation of QTc interval in individuals receiving HCQ.^[14] Currently, ICMR also recommends an ECG (with estimation of QT interval) which may be done before prescribing HCQ prophylaxis and in those who are already on HCQ prophylaxis before continuing it beyond 8 weeks. ECG should be done in case any new cardiovascular symptoms occur (e.g., palpitations, chest pain syncope) during the course of prophylaxis or anytime during the course of prophylaxis.^[7] This study because of a small sample size is not representative with regards to adverse effects.

Many HCWs took HCQ prophylaxis out of peer pressure or a feeling of vulnerability. They still felt uncomfortable recommending it to anyone as they understood the lack of evidence to support HCQ use for prophylaxis. Also, the reported adverse events prevented them from endorsing it for wider use in spite of ICMR recommendations. It was reported that less than two third participants were given medication by the concerned hospital they work. HCWs or front liners demanded the concerned hospital to take responsibility of their staff by providing

Table 2: Qualitative data analysis: Content analysis of In-depth interviews

Category	Codes	Responses of the participants
Reason for taking the drug despite uncertain evidence	Reason for taking prophylactic drug	Colleagues suggested (<i>Started taking loading dose when co-workers recommended and took</i>) <i>“Was doing duties in isolation ward, so took it for prophylaxis”</i> Had co-morbidities, felt vulnerable
Do you want to recommend something to others taking prophylaxis for the first time	Recommendation to others	Doing regular clinical practice, since PPE kits were not available or of high cost Since there were no proper guidelines for HCQ as a prophylactic one, we won't recommend it to anyone <i>“Even a doctor cum actor died because of taking HCQ without undergoing baseline ECG”</i> There are reported deaths among few who had consumed Since the intake of drug needs baseline evaluation and routine follow up pertaining to cardiac investigations, we would not like to recommend it because no one will follow it up regularly The hospital should take responsibility of its staff in providing the medications and related baseline investigations
Whether taking the drug increased your efficacy in patient care?	Perception of drug efficacy	<i>“Despite taking HCQ, we don't feel that there is a efficacy, but feel it as a sense of satisfaction that we may not encounter viral attack.”</i>

appropriate medications in appropriate doses along with baseline investigations and further follow up. The hospital providing services solves a multitude of issues ranging from timely medications, baseline investigations, follow-up, and appropriate drug doses. The absence of a safety net and unavailability of monitoring services from their hospital were factors that worried health care workers. These are proven practices to increase job satisfaction, retention, efficiency, and safety of employees at work.^[15]

Conclusions

As the pandemic evolves, so does the evidence. Recommendations based on good quality evidence, effective risk communication, peer education and support, accountability, ease of baseline, and follow-up investigations were the need of the hour to improve intake and adherence to prophylactic regime for COVID-19.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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