Original Article

Hydroxychloroquine pre-exposure prophylaxis for COVID-19 among healthcare workers: Initial experience from India

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Abstract

Background: Hydroxychloroquine (HCQ) had generated considerable interest for coronavirus disease 2019 (COVID-19) prophylaxis. We conducted a prospective observational study at a tertiary care hospital in India, with dedicated COVID-19 care facilities. **Objectives:** Primary objective was incidence of adverse effects, secondary objective being efficacy in preventing COVID-19. **Methods:** Healthcare workers were recruited and grouped based on voluntary HCQ prophylaxis as per national guidelines. Side effects in HCQ group were graded in accordance with national cancer institute-common terminology criteria for adverse events (NCI-CTCAE) version 5.0. At 3–7-week follow-up, groups were compared for COVID-19 exposure, symptoms development and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR results. **Results:** Among 358 participants recruited, 216 (60.3%) were males and mean age was 31.2 ± 6.6 years. Chemoprophylaxis was initiated by 258 (72%) participants. After loading dose, 7 (2.7%) reported grade 2 and 1 (0.4%) grade 3 adverse effects. Discontinuation of HCQ due to side effects was reported in 11 (4.3%) participants. Electrocardiogram was done by 50 (19.4%) participants on HCQ; no abnormalities were noted. A total of 106 (41%) among those taking and 63 (63%) among those not taking HCQ were tested for SARS-CoV-2 due to influenza-like illness or significant exposure. Among all participants, 25 (6.9%, 95% confidence interval [CI] 4.3–9.6) developed COVID-19 during the study period. In the group taking HCQ, 10 (3.9%) tested positive compared to 15 (15%) in the group not taking HCQ ($P < 0.001$). Odds ratio with HCQ intake was 0.34 (95% CI 0.13–0.83, $P = 0.01$) and the number needed to treat was 12. **Conclusion:** HCQ is safe at the recommended dose for pre-exposure prophylaxis of COVID-19.

Keywords: COVID-19, healthcare workers, hydroxychloroquine, pre-exposure prophylaxis, SARS-CoV-2

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been wreaking havoc across the world since the initial outbreak in Wuhan, China, in December 2019. Healthcare workers (HCWs) have been shown to be at an increased risk of contracting the disease. Reports from various countries suggest that between

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3.5% and 20% of HCWs have acquired the disease in the early days of the pandemic.[1-4]

Attempts were made to repurpose existing drugs as effective therapeutic or prophylactic options for COVID-19. Hydroxychloroquine (HCQ) was used widely for treatment in the early part of the pandemic; however, later it was removed from treatment protocols after results from trials did not demonstrate any efficacy.[5] HCQ, a safer derivative of chloroquine, has been postulated to have numerous mechanisms of action as an antiviral agent in various studies.[6] These include inhibition of viral attachment, entry into the host cell, new viral particle maturation and spread.[7-9] Pre-treatment of Vero cells with HCQ versus chloroquine showed that the anti-viral and prophylactic activity of HCQ was better than chloroquine.[10] Due to favourable pharmacokinetics including long half-life, high concentration in the lung tissue and favourable safety profile, HCQ was being studied as a chemoprophylactic agent for COVID-19 in early days of the pandemic.[7,8,11] On 22 March 2020, Indian health authorities recommended the use of HCQ pre-exposure prophylaxis in selected high-risk groups including HCWs at a dose of 800-mg loading followed by 400 mg weekly for a total of 8 weeks.[12] This advisory has been the subject of much debate and controversy.[13,14]

We conducted a prospective observational study to evaluate the incidence of adverse effects as primary objective and efficacy as the secondary objective of HCQ pre-exposure prophylaxis for COVID-19 among HCWs at a tertiary care hospital with dedicated COVID-19 wards and intensive care units.

Materials and Methods

This prospective observational study was conducted between 23 April and 11 June 2020 among HCWs (doctors and nursing staff) at a tertiary care hospital in New Delhi, India. More than 2500 confirmed COVID-19 cases were managed at this facility during the study period. Ethical clearance was obtained from the Institute Ethics Committee.

All HCWs were eligible to participate in the study. We approached and invited the HCWs working at the institute to be a part of this study irrespective of their voluntary choice of HCQ chemoprophylaxis for COVID-19. They were enrolled in this study and segregated into two groups based on HCQ intake. HCW symptomatic at the time of starting HCQ was exclusion criteria. After taking informed consent, baseline demographic details, comorbidities and details of other ongoing medications of the participants were documented. Additionally, adverse effects with the loading dose of HCQ and history of any exposure to COVID-19-positive cases were also noted. There was no pre-decided sample size.

All participants were followed up between 3 and 7 weeks after enrolment. Participants in the HCQ group were assessed for compliance, details of any adverse events associated with weekly doses and reasons for discontinuation if applicable. History of exposure to COVID-19 patients, adequacy of personal protective equipment (PPE) during exposure and development of symptoms after exposure were assessed in all the participants. Risk stratification of the contacts was done according to the standard operating procedure (SOP) prepared by institutional hospital infection control committee. Accordingly, high-risk contacts were defined as direct contacts of confirmed cases who performed aerosol-generating procedure without any of the following – N95 mask, eye/face protection and gloves; or if the patients respiratory secretions or saliva come in contact with non-intact skin; or anyone in close proximity (<1 m) of the confirmed case without mask for a duration of more than 15 min; or household contacts of a known positive case. All other contacts were defined as low-risk contacts. Study participants, who fulfilled the criteria as laid down by national guidelines at the time of the study, were tested for COVID-19 by reverse transcriptase-polymerase chain reaction (RT-PCR) of combined nasal and oropharyngeal swab specimens. These criteria recommended testing of any HCW who developed symptoms of influenza-like illness (ILI) or who was exposed to a known COVID-19-positive patient without adequate PPE (between day 5 and 10 after contact).[15,16] Standard PPE in COVID-19 caring facilities included coverall, N95 mask, goggles, long shoe covers, double gloves and face shield to use during aerosol-generating procedures; PPE for non-COVID-19 caring facilities included gown, goggles, N-95 mask and gloves. Electrocardiogram (ECG) was not mandatory as per the initial advisory on the use of HCQ as prophylaxis. Details of ECG done voluntarily by participants were recorded. Participants not willing for follow-up interview were considered as drop-outs.

The primary outcome was the occurrence of adverse events with HCQ. Adverse events were categorized as mild, moderate, severe and life-threatening according to the National Cancer Institute's Common Terminology Criteria for Adverse Events NCI-CTCAE version 5.0.[17] The efficacy of HCQ in preventing COVID-19 was assessed as a secondary outcome at follow-up.

Data were analysed using STATA 15.0, categorical variables were represented as frequency and percentages, and continuous variables as mean (±SD) and median (range). Statistical significance of categorical variables was calculated using Chi-square test, while *t*-test was used for continuous variables. Association of HCQ with outcome was determined by OR (95% confidence interval [CI]) with potential confounders adjusted in multivariable logistic regression analysis to compute adjusted odds ratio. *P* value <0·05 was considered as statistically significant.

Results

Among 358 participants recruited for the study, HCQ pre-exposure prophylaxis had been voluntarily initiated by 258 (72%) HCWs as shown in [Figure 1].

Among the recruited cohort, 216 (60.3%) were males; 222 (62%) were doctors and 136 (38%) nursing staff. Mean age of participants was 31.2 ± 6.6 years. At least one comorbidity including hypertension, hypothyroidism, diabetes mellitus,

bronchial asthma and others were reported by 54 (15%) participants. The various characteristics of the two groups are compared in Table 1. Doctors, those working in COVID-19 care facilities and those with no comorbidities were more likely to have initiated HCQ pre-exposure prophylaxis.

Among the 258 HCWs on HCQ, 69 (26.7%) reported grade 1 (mild transient) and 7 (2.7%) reported grade 2 (moderate) adverse events [Table 2]. One (0.4%) participant reported mild facial puffiness after taking the first 400 mg of the loading dose and subsequently after 3 h of the second 400 mg dose-reported symptoms suggestive of angioedema (in the form of facial puffiness and mucosal oedema) requiring emergency visit (grade 3 adverse events). None of the participants had grade 4 or 5 adverse event. No significant differences were noted between the groups reporting and not reporting any adverse events. Neurological and gastrointestinal symptoms were the most common adverse events reported. Out of the five (2%) participants in the HCQ group who had reported palpitations, two underwent ECG, both of which were normal. ECG performed in 28 (10.8%) of participants taking HCQ at baseline were normal with corrected QT (QTc) interval ranging between 360 and 430 ms.

At follow-up interview, out of 258 participants on HCQ, 59 (22.8%) discontinued the drug within first 3 weeks, most common reasons being missed weekly doses in 20 (7.7%) participants, perceived lack of adequate evidence favouring HCQ in 21 (8.1%), adverse events in 11 (4.3%) (mostly grade 1) and other reasons in 7 (2.7%). Persistence of adverse effects was reported in 21 (8.1%) of those continuing HCQ, all of which were classified as grade 1 adverse events. ECG was done in 50 (19.4%) participants after initiation of HCQ, none revealed prolonged QTc intervals calculated using Bazzet's formula. During the study period, 62 (24%) in the HCQ group

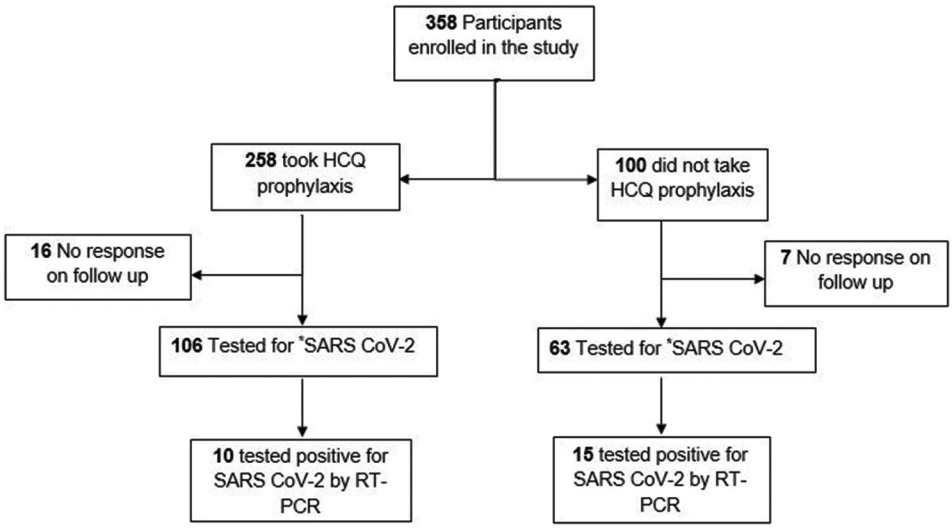

Figure 1: Flowchart of participants in the study (*n* = 358). Legend: *Based on symptoms of influenza like illness or high-risk exposure to a confirmed COVID-19 patient without adequate PPE

Table 1: Baseline demographic, follow-up exposure and disease characteristics of healthcare workers (*n*=358)

Parameter	Hydroxychloroquine group (258)	No hydroxychloroquine group (100)	*P*
Age in years*	30.5±6.0	33.2±7.8	<0.001
Gender, female	93 (36%)	49 (49%)	0.02
Comorbidities	30 (11.6%)	24 (24%)	0.003
Profession			<0.001
Doctors	175 (67.8%)	47 (47%)	
Nursing officer	83 (32.2%)	53 (53%)	
Working area			<0.001
COVID-19 care facilities	133 (51.5%)	19 (19%)	
Non-COVID-19 care facilities	125 (48.5%)	81 (81%)	
Symptoms of ILI	62 (24%)	40 (40%)	0.002
Accidental exposure requiring quarantine	49 (19%)	40 (40%)	<0.001
Tested positive for COVID-19†			<0.001
SARS-CoV-2 positive	10 (3.9%)	15 (15%)	
SARS-CoV-2 negative/not required testing as per national guidelines	248 (96.1%)	85 (85%)	

ILI: Influenza-like illness. All figures in *n* (%) except *mean±standard deviation. †This value has been calculated from 358 participants as we confirmed from institute database that those who did not fill the follow-up questionnaire either tests were not done/did not test positive

and 40 (40%) in the non-HCQ group reported ILI symptoms. A significantly greater proportion of participants in the non HCQ group were quarantined ($P < 0.001$) [Table 1].

A total of 106 (41%) participants on HCQ and 63 (63%) not taking HCQ were tested for SARS-CoV-2 during the study period as per the national guidelines (ILI symptoms or accidental exposure with a laboratory-confirmed COVID-19 patient without adequate PPE). Among all participants, 25 (6.9%, 95% CI 4.3–9.6) developed COVID-19 disease during the study period. In the group taking HCQ, 10 (3.9%) tested positive compared to 15 (15%) in the group not taking HCQ ($P < 0.001$). Majority of the COVID-19-positive cases (n = 20, 80%) among the participants were working in non-COVID-19 facilities of the hospital [Table 3].

On multivariable logistic regression analysis, the odds ratio for HCQ was 0.34 (95% CI 0.13–0.83, P = 0.01) indicating that odds of developing COVID-19 among those receiving HCQ are 0.34 times as compared to those not taking HCQ. It is protective against developing COVID-19 disease among HCWs [Table 4]. In other words, after taking HCQ, the risk of developing COVID-19 is reduced by 66%. Number needed to treat was 12 to prevent 1 case of COVID-19.

Table 2: Adverse event profile of participants after loading dose of HCQ (n=258)

Adverse event	No. of participants (n=258)
Gastrointestinal (36)*	
Nausea	23 (8.9%)
Diarrhoea	9 (3.48%)
Gastritis	9 (3.4%)
Other gastrointestinal	5 (1.9)
Neurological (47)*	
Headache	30 (12.1%)
Dizziness	21 (8.5%)
Irritability	9 (3.6%)
Other neurological	5 (2%)
Palpitation	5 (2%)
Allergic reaction	
Rash and itching	3 (1.2%)
Swelling of lip and face	1 (0.4%)
Others	4 (1.6%)

Number of participants reported more than one adverse event, so numbers do not add-up. *Composite side effects (gastrointestinal side effect: 36, neurological side effect: 47, both gastrointestinal and neurological side effect: 15)

Discussion

This prospective observational study was conducted during the early phase of COVID-19 pandemic when several trials on pre- and post-exposure prophylaxis were initiated. The findings in the study suggested safety of HCQ at the recommended doses with 2.7% reporting grade 2 and 0.4% reporting grade 3 adverse events after the loading dose and 4.2% discontinuing the drug due to adverse events. Initial acceptability of the recommendation was good in our cohort with 72% initiating pre-exposure prophylaxis; however, 22.8% discontinued HCQ by the third week of prophylaxis. There was a decreased incidence of COVID-19 among those on pre-exposure prophylaxis with an odds ratio of 0.34 (95% CI 0.13–0.83, P = 0.01).

HCQ has been regarded as a safe drug with long experience of use in autoimmune diseases.[18,19] The incidence of adverse events and discontinuation reported are consistent with that reported in rheumatological conditions like systemic lupus erythematosus;[18] however, the reports usually are on long-term use of this drug. It has been regarded as a safe drug when used in appropriate dosages for short durations such as in malaria.[19] Majority of the participants observed neurological and gastrointestinal side effects similar to the literature.[19,20] QTc prolongation has received attention recently when used for COVID-19 treatment.[21] ECG was not done by the majority of participants; however, among 50 (19.4%) on HCQ who did get an ECG done, QTc intervals were within normal limits. Also, among two out of five participants who reported palpitations, ECG findings were normal.

Table 3: Characteristics compared between those testing positive and negative for SARS-CoV-2

	SARS-CoV-2 positive (n=25)	SARS-CoV-2 negative (n=333)	P
Age*	35.6±8.9	30.9±6.3	<0.001
Gender (female)	14 (56)	128 (38.4)	0.08
Comorbidities	4 (16)	50 (15)	0.89
Profession (doctors)	8 (32)	214 (64.3)	0.001
Working area (COVID-19 care facility)	5 (20)	147 (44.1)	0.01
On HCQ	10 (40)	248 (74.5)	<0.001
ILI symptoms	20 (80)	80 (24)	<0.001

All figures in percentages n (%), except *in mean±standard deviation

Table 4: Univariate and multivariable logistic regression analyses to determine role of HCQ as pre-exposure prophylaxis for COVID-19

Exposure	COVID-19 25 (7%)	No COVID-19 333 (93%)	P	OR (95% CI)	P
HCQ intake	10 (40%)	248 (74.5%)	<0.001	0.34 (0.13, 0.83)	0.01
Not taking HCQ	15 (60%)	85 (25.5%)		1.0	-

OR: Odds ratio, CI: confidence interval, HCQ: hydroxychloroquine. Logistic regression analysis, adjusted for gender, working area, profession

HCWs working in COVID-19 care facilities of the hospital and those without comorbidities were more likely to initiate pre-exposure prophylaxis. This may be due to perceived fear of side effects related to drug interactions. A significant proportion (22.8%) discontinued the drug within 3 weeks of initiation, the most common cause being lack of evidence of efficacy. A significant proportion of participants (7.7%) discontinued HCQ as they forgot to take their weekly doses, while 4.3% discontinued due to adverse events. The former may be due to international caution advisories sensitizing the minds of medical professionals.

There was a higher known exposure among HCWs in non-COVID-19 facilities of the hospital which mandated quarantine as per the hospital policy. These were related to accidental exposure to pre-symptomatic and unusual presentation of cases in the non-COVID-19 wards. Also, the level of PPE provided in non-COVID-19 care facility was not the same as that in COVID-19 care facilities. RT-PCR for severe acute respiratory syndrome coronavirus 2 was performed for 47.2% of participants as per the national guidelines and incidence of COVID-19 was found to be 6.9% (95% CI 4.3–9.6). Even though this incidence is similar to that reported from other countries where 3.5–20% of HCWs have been affected with COVID-19, it might be an overestimate in our hospital as HCWs with high-risk exposure may have been more eager to participate in the study.[1-4]

The group not on HCQ had higher known exposure because they were likely to be working in non-COVID-19 care facilities and accidental exposure without adequate PPE skewed the exposure in this group. However, it is interesting to note that out of 25 patients, only 4 had known exposure to the laboratory-confirmed case. Majority of them had unknown exposure, reflecting possible transmission from pre-symptomatic and asymptomatic individuals. This fact became well known as the pandemic progressed. Further, the occurrence of COVID-19 among HCWs in non-COVID-19 care facilities due to known/unknown exposure and few cases among HCWs in the COVID-19 care facilities suggest that the adequate PPE is the most important factor in preventing infection transmission.

In this observational study, HCQ was shown to have protective effect. In a study from Korea evaluating HCQ as post-exposure chemoprophylaxis, none of the participants among 189 patients and 22 HCWs developed COVID-19 even after significant exposure.[22] In another observational study from Spain, no benefits were seen.[23] In the first published randomized trial, comparing HCQ with placebo for post-exposure prophylaxis among 821 COVID-19-exposed participants, no statistically significant difference was found in the number of participants developing COVID-19 within 14 days of exposure. This study had some important limitations. Syndromic diagnosis without subsequent microbiological confirmation was a nonspecific measure of primary outcome overestimating the event rate. It is noteworthy that ~57% of participants were enrolled on days 3 and 4 of exposure, which would be too late to prevent the subsequent infection. A large proportion did not complete the 14-day survey and were lost to follow-up. It was an underpowered study to detect small but clinically meaningful differences, as RT-PCR confirmed cases were only a few.[24] The issue was addressed in subsequent randomized controlled trials, wherein HCQ did not demonstrate any efficacy as prophylaxis for COVID-19.[25-27]

Limitations

The study has several important limitations. It was conducted as a prospective observational after the drug was approved by Indian health authorities for pre-exposure prophylaxis among high-risk groups. Further, participation bias might have also crept in probably because more HCWs taking HCQ may have consented for the study, in addition to an overall small sample size. Baseline and follow-up ECG was not performed for all the participants (it was voluntary); however, 50 of the participants on HCQ who had an ECG on follow-up had a normal QTc interval. Hypoglycaemia is an uncommon side effect of HCQ as noted in many case reports. Blood sugar monitoring would have been an objective measure of monitoring it. Another major limitation of our study was that only those symptomatic or with high-risk exposure were tested for SARS-CoV-2 with RT-PCR as per national guidelines. Owing to the non-availability of reliable and validated antibody test kits during the study period, we could not estimate the proportion of asymptomatic infections in the cohort at baseline or follow-up. Finally, the pharmacokinetic parameters related to HCQ absorption or the serum drug levels were not available at this time in the cohort.

Conclusion

HCQ was found to be safe at the recommended dose for pre-exposure prophylaxis of COVID-19 and a small proportion discontinued the drug due to adverse events. We observed reduced incidence of COVID-19 among HCW taking HCQ prophylaxis; however, the same has not been validated by RCT.

Key points

1. Hydroxychloroquine for pre-exposure prophylaxis against COVID-19 is safe.
2. In observational study, we found HCQ decreased incidence of COVID-19 with odds of 0.34 among HCWs receiving HCQ; however, no efficacy has been seen in multiple RCT.
3. Given the probability of post-vaccination breakthrough infections, the search for an effective post-exposure chemoprophylaxis should continue.

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Conflicts of interest

There are no conflicts of interest.

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