

Original Article

Knowledge and Compliance of Hydroxychloroquine Prophylaxis for Severe Acute Respiratory Syndrome Coronavirus 2 Infection among Indian Health-Care Workers

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ABSTRACT

Objective: In the initial days of the coronavirus disease 2019 (COVID-19) pandemic, the Indian Council of Medical Research (ICMR) recommended the use of hydroxychloroquine (HCQ) as chemoprophylaxis for health-care workers (HCWs) involved in the care of COVID-19 patients. The present survey aimed to assess the knowledge and compliance of HCQ prophylaxis as per the ICMR recommendations among Indian HCWs during the first wave of the pandemic. **Methods:** A validated 19-item questionnaire-based survey was distributed to HCWs in our apex tertiary care institute who had completed their duties in the COVID-19 wards to assess the knowledge, attitude, and compliance of all sections of HCWs regarding the ICMR-recommended HCQ prophylaxis. Participation in the survey was voluntary, and anonymity was maintained. Data obtained from the responses were collated and analyzed. **Findings:** Two hundred and fourteen out of 250 HCWs completed the survey (85.6% response rate). Among 214 participants, 87.9% were below the age of 40 years. 83.2% were aware of the use of HCQ for possible prevention of COVID-19 infection, while only 24.6% took HCQ for 7 weeks as was recommended during that period. The main reasons given by 37.3% of the HCWs for not taking HCQ were their knowledge and research on HCQ, where side effects were prominent. Side effects were reported by 35% of the respondents, of which the most notable was nausea/vomiting (14%) followed by gastritis (12%). **Conclusion:** The poor compliance with HCQ prophylaxis by HCWs was influenced by their knowledge and research, lack of strong scientific evidence, and drug-associated adverse effects.

KEYWORDS: Health-care worker, Hydroxychloroquine, pandemic, prophylaxis, severe acute respiratory syndrome coronavirus 2

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) outbreak has triggered an unprecedented health-care crisis by the sheer volume of morbidity and mortality worldwide, including tens of thousands of health-care workers (HCWs). Amid the rapidly

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escalating COVID-19 cases in the initial months of 2020, various scientific organizations and researchers across the globe re-examined the pharmacological properties of already available drugs as prophylactic or therapeutic options. In some countries, including India, the United States, and Russia, hydroxychloroquine (HCQ) was recommended as prophylaxis, mainly for high-risk populations like HCWs, based on *in vitro* studies where HCQ at approved doses demonstrated suppression of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication and ameliorated viral shedding.^[1,2] Furthermore, HCQ has other beneficial properties, such as modulating the expression of Toll-like receptors (TLRs) and TLR-mediated signal transduction, as well as decreasing the production of interleukin-6.

In India, the National Task Force by the Indian Council of Medical Research (ICMR) on May 22, 2020, recommended the use of HCQ as chemoprophylaxis for HCWs involved in the care of suspected or confirmed cases of COVID-19 as an initial loading dose of 400 mg twice on day 1, followed by a maintenance dose of 400 mg once weekly for 7 weeks.^[3] However, the uniform acceptance and adherence to the recommended HCQ chemoprophylaxis guidelines by HCWs of all cadres were contentious. The present survey was thus formulated, and it aimed to assess the knowledge, attitude, and compliance of all the cadres of HCWs toward the use of HCQ chemoprophylaxis against COVID-19 in accordance with the ICMR guidelines in an apex tertiary care institute in North India.

METHODS

The survey involved the cross-sectional analysis of the knowledge, attitude, and compliance of HCWs of all cadres (consultants, residents, technicians, nurses, and sanitation workers) regarding HCQ prophylaxis for COVID-19, based on an anonymous, validated 19-item questionnaire [Supplementary Table 1]. The survey was conducted in July and August 2020 in an apex tertiary-level hospital in northern India, 3 months after the ICMR guidelines were released. The study protocol was approved by the Institute Ethics Committee (2020-122-IP-EXP-18) and was registered in the Clinical Trials Registry of India (CTRI/2020/06/026121). A convenient sampling method was used for data collection, and the study was performed strictly in accordance with the Declaration of Helsinki as revised in 2013.

The survey questionnaire consisted of questions on demographics, knowledge, and practices in limited and multiple-choice formats. The preliminary questionnaire version was developed through an extensive literature review in English. A validated Hindi translation of the same

questionnaire was also developed. The respondents were free to answer the questionnaire in any of the languages they were conversant with. The questionnaire content was validated based on relevance, clarity, simplicity, and ambiguity criteria, which were rated by seven experts (two consultants, two residents, one technician, one staff nurse, and one sanitation worker). The percentages of general agreement and free marginal kappa based on the ratings by the seven experts were as follows: 84.35% and 0.79 for relevance, 84.64% and 0.80 for clarity, 92.75% and 0.90 for simplicity, and 88.70% and 0.85 for ambiguity. The questionnaire was then piloted with ten respondents to ensure test-retest reliability, and the Pearson correlation coefficient was 0.92.

This validated and reliability-tested questionnaire was then distributed in a pamphlet form among the targeted HCWs who had completed 7 weeks from the date of their first duty for their COVID postings, and they were requested to complete and return it within 1 week after consenting to do so.

For calculating the sample size, we assumed 50% prior knowledge of HCQ among the HCWs, at a two-sided 95% confidence interval and 15% relative error in the given prevalence. The estimated minimum sample size required came out to be 171. After excluding nonrespondents, this study's minimum sample size was 175. To achieve this, we planned to distribute a questionnaire to 250 targeted health personnel with an expected response from three-fourth. The sample size was estimated using software power analysis and sample size version 16 (PASS-16, NCSS, LLC, USA).

Categorical variables are presented in frequency and percentage. A Chi-square test/Fisher's exact test was used to compare the proportions between the groups. Adjacent, cumulative bar diagrams were used to compare the proportions of doctors, nurse technicians, and other staff. $P < 0.05$ was considered statistically significant. The Statistical Package for Social Sciences, version 23 (SPSS), IBM, Chicago, USA, was used for data analysis.

RESULTS

The present study included responses from 214 HCWs (85.6% response rate). Among the respondents, 44.4% were doctors (9.8% of consultants and 34.6% of residents), 42.5% were paramedical staff (36.9% of nurses and 5.6% of technicians), and 13.1% were other HCWs. 87.9% of the study participants were below the age of 40 years, and 65% of the participants were males. There was no significant difference in age ($P = 0.289$) between the study participants [Table 1].

The respondents' knowledge was assessed, and a comparison of the same between doctors, nurses, technicians, and other HCWs was performed. Most of the study participants (60.6%) were aware of the role of HCQ, with the highest awareness observed among doctors (69.4%), followed by nurses and technicians (60.1%), and finally other HCWs (32.2%). 83.2% of the participants were aware of the use of HCQ for possible prevention of coronavirus infection, with the highest awareness among doctors (96.2%) followed by an equal proportion of awareness seen among nurses and technicians (74.1%) and other HCWs (75%). The awareness regarding possible side effects of HCQ was 77.2%, with the highest degree of awareness in doctors (92.4%). 57.4% of the study participants rated the instructions given by clinicians who prescribed HCQ as good or excellent.

80.4% of the study participants took HCQ with meals. 43.9% of the participants underwent an electrocardiogram (ECG) before taking HCQ, and 23.7% of the participants had started consuming HCQ even before being prescribed. 69.7% of the respondents had begun taking HCQ a day prior, and 18.9% consumed it a day after their COVID ward postings began. A significant association was observed between the type of study participant (doctor, nursing technician, and other staff) with ECG undertaken before HCQ intake, initiating HCQ prophylaxis before it was duly prescribed, timing of the first dose of HCQ, relationship with meals, and the actual number of HCQ doses consumed (each $P < 0.05$) [Table 2].

A comparison of the reasons for avoiding HCQ prophylaxis among doctors, nurses, technicians, and other HCWs was made. 3.3% avoided HCQ due to pre-existing diseases, 4.7% experienced side effects, and 37.3% declined to use it based on their knowledge and research where side effects appeared more or for some other reason, whereas 4.2% had no particular reason for declining HCQ prophylaxis [Figure 1].

Regarding side effects, 35% of the participants did not experience any side effects. The most common side effects were nausea and vomiting (14%), followed by gastritis (12%) and skin and eye irritation (5%) [Figure 2].

DISCUSSION

In our study, most of the respondents were males, graduates aged between 31 and 40 years old, and working as nurses. This is consistent with the structure of health-care facilities and the findings of previous studies that examined the patterns of HCWs performing HCQ prophylaxis.^[4,5] When asked about possible contraindications or hypersensitivities, 4.52% of the participants replied in the affirmative. Furthermore, 11.21% of the respondents had preexisting illnesses. Among them, hypertension and diabetes were the most common, which is in concordance with the HyPE study's findings.^[6] The risk of adverse drug interaction with HCQ exists with drugs for seizures (phenytoin and carbamazepine), tuberculosis (rifampicin), and arrhythmias (amiodarone and digoxin). However, none of our study participants were receiving them.^[7] In our study, 3.1% of the respondents consumed regular

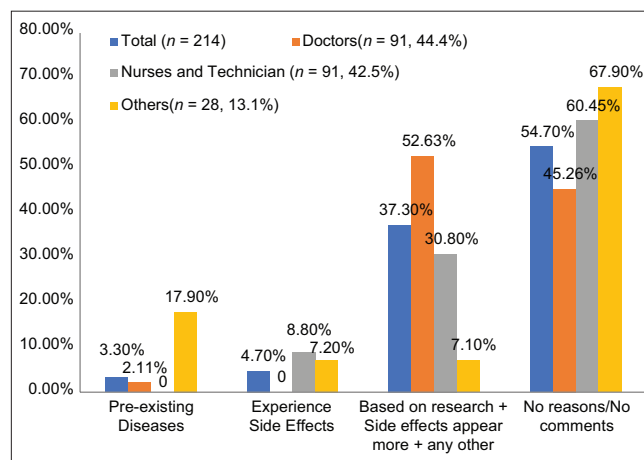


Figure 1: Reasons for noncompliance to National Task Force recommendations for Hydroxychloroquine prophylaxis (n = 214).

Table 1: Demographic and clinical characteristics of the participating health-care workers (n=214)

Variables	Total (n=214)	Doctors (n=95; 44.4%)	Nurses and technician (n=91; 42.5%)	Others (n=28; 13.1%)	P
Age (<40 years)	188 (87.9)	87 (91.6)	78 (85.7)	23 (82.1)	0.289
Sex (male)	139 (65)	69 (72.6)	49 (53.8)	21 (75)	0.013
Staying with family members	161 (75.23)	67 (70.53)	71 (78.02)	23 (82.14)	0.327
Education (graduation and above)	180 (84.1) (n=213)	95 (100)	80 (87.9)	23 (85.2) (n=27)	0.006
Any known medical illness present (yes)	24 (11.21) (n=203)	5 (5.5) (n=90)	8 (9.3) (n=86)	1 (3.7) (n=27)	0.482
Taking any regular medication (yes)	6 (3.1) (n=195)	2 (2.38) (n=84)	3 (3.57) (n=84)	1 (3.70) (n=27)	0.887
Previous allergy/contraindication for HCQ (yes)	9/199 (4.52)	1 (1.16) (n=86)	5 (5.9) (n=85)	3 (10.71)	0.078

The number of participants varied in some questions mentioned with parenthesis, otherwise actual numbers are applicable. Data presented in frequency (%), compared by Chi-square test/Fisher's exact test. HCQ: Hydroxychloroquine

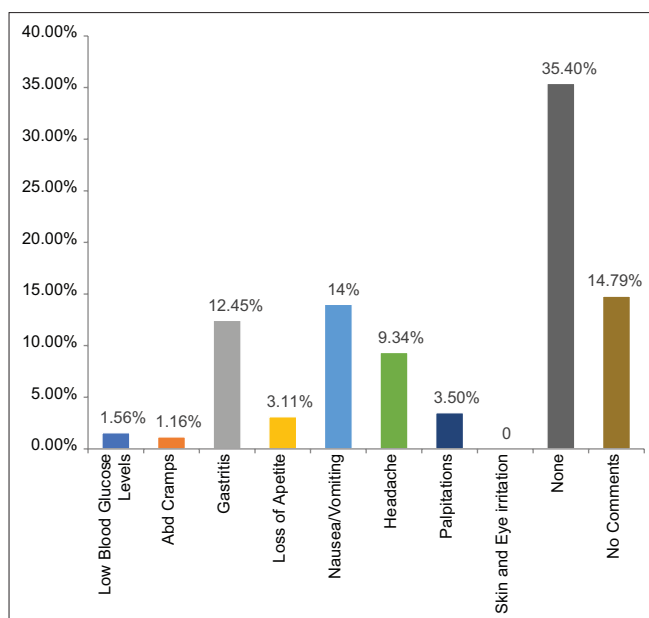


Figure 2: Frequency of side effects (from total number of side effects) among study participants where multiple responses were also recorded

medications, mostly antihypertensive and oral hypoglycemic agents.

Assessment of knowledge concerning HCQ revealed that most HCWs were aware of its possible prophylactic benefits. Considering the global hype that was created regarding the off-label use of HCQ for its prophylactic as well as therapeutic applications during the pandemic, it is expected that HCWs would be well aware of its usage. Certain conditions eliminate the scope of using HCQ. These include retinopathy, hypersensitivity, G6PD deficiency, concurrent azithromycin usage, preexisting cardiomyopathy, and cardiac rhythm disorders.^[8-10] 77.2% of the HCWs were aware of the side effects of HCQ. Similarly, Mohakuda *et al.* reported that 43.9% of their respondents were apprehensive of the side effects of HCQ, of whom the majority were nurses and doctors, while the paramedical staff was least concerned. They attributed lower levels of awareness about the possible adverse effects of HCQ among paramedical staff as the reason behind this statistically significant difference.^[5]

About one-fourth of participants (49 [23.7%]) commenced HCQ prophylaxis themselves before being formally prescribed. Due to the nature of their jobs, HCWs are well aware of the health advisories and have better access to pharmacological agents, which might have prompted them to begin the prophylaxis on their own despite the limited data on its efficacy. The fear created in the psyche of the masses during the initial months of the pandemic would have also initiated the tendency of self-prescribing the drug, overlooking

the assessment of its possible risks and benefits. The availability of HCQ for self-medication by the public without medical advice and driven by media and social forces became a greater concern. To prevent its unauthorized use, the availability of HCQ had to be tightly regulated.^[11] As 108 (57.4%) participants rated the quality of instructions provided during the drug prescription as excellent or good, we can assume that directions for the drug consumption and the resolution of the related queries were appropriate. As emphasized previously, the high prevalence of HCQ prophylaxis was often dependent upon institutional policies (where prophylaxis was suggested or made mandatory) as previously proving that appropriate institutional impetus was necessary to ensure high compliance.^[5] A few of the HCWs were prescribed other medications along with the HCQ prophylaxis, which included Vitamin C and zinc supplements. Vitamin C has an established role in both innate and adaptive immunities through modulation of cellular functions, which also aids in reducing the susceptibility to various viral infections and thus has been suggested as a prophylactic against COVID infection.^[12-14] The ICMR guidelines recommended an initial loading dose of 400 mg twice on day 1, followed by a maintenance dose of 400 mg once weekly. A similar dosage was followed by 78.04% of the participants in our study. A maximum (69.7%) of the HCWs started consuming their first doses before reporting for their duties, and 18.9% started consuming after their COVID duties. Some alterations in the dosing guidelines (especially loading doses) have been suggested by some authors based on the pharmacokinetic properties of the drug to achieve a steady-state plasma concentration early and to maintain the target concentration.^[15-17] HCQ has been advised to be taken along with food to reduce gastrointestinal side effects.^[18] In our survey, 80.4% of the participants similarly consumed the drugs. Only 42.52% of the participants consumed none or <2 tablets after the loading dose. A study by Chatterjee *et al.* showed that the number of maintenance doses taken after the intake of a loading dose influenced the protective dose–response relationship. Consuming four or more maintenance doses was associated with a lower risk of SARS-CoV-2 infection, while six doses had a remarkable (>80%) protective effect.^[19] Cardiac safety of HCQ is questionable, and conduction disorders have been associated with leading to QT prolongation, arrhythmias, and myocardial arrest.^[20] As a result, cautious use in conjunction with other pro-arrhythmic drugs such as azithromycin^[21] and routine ECG before starting HCQ therapy is advised. Our survey showed that only 43.9% of the HCWs underwent ECG before

Table 2: Knowledge, attitude, and compliance of Hydroxychloroquine prophylaxis as per National Task Force recommendations among Indian health-care workers

Survey questions and their response	Total (n=214)	Doctors (n=95; 44.4%)	Nurses and technician (n=91; 42.5%)	Others (n=28; 13.1%)	P
Prior awareness regarding the role of HCQ in the prevention of coronavirus infection					
Yes	126 (60.6)	66 (69.4)	51 (60.1)	9 (32.2)	0.001
No	31 (14.9)	5 (5.3)	19 (22.3)	7 (25)	0.002
Unsure	51 (24.5)	24 (25.3)	15 (17.6)	21 (75)	<0.001
n	208	95	85	28	
Reason for HCQ prescription					
To boost immunity	23 (12.04)	3 (3.8)	13 (15.3)	7 (25)	0.001
Treatment of corona infection	9 (4.71)	0	9 (10.6)	0	0.001
Possible prevention of Corona infection	159 (83.2)	75 (96.2)	63 (74.1)	21 (75)	0.315
n	191	78	85	28	
Awareness regarding possible side effects of HCQ					
Yes	160 (77.2)	86 (92.4)	61 (70.9)	13 (46.4)	<0.001
n	207	93	86		
Any other medications prescribed in addition to HCQ					
Yes	10 (5.1)	8 (9.6)	2 (2.3)	0	0.060
n	169	83	86		
Rating for instructions given by clinician who prescribed HCQ					
Good to excellent	108 (57.4)	52 (65)	44 (55)	12 (42.8)	0.105
Fair or poor	80 (42.5)	28 (35)	36 (45)	16 (57.1)	
n	188	80	80	28	
ECG done before HCQ started					
Yes	69 (43.9)	23 (40.4)	43 (58.10)	3 (11.5)	0.002
n	157	57	74	26	
Started HCQ intake before it was prescribed					
Yes	49 (23.7)	13 (13.8)	21 (24.7)	15 (53.5)	<0.001
n	207	94	85	28	
The first dose of HCQ taken					
Never taken	20 (11.4)	10 (14.7)	10 (12.7)	0	0.108
Before starting COVID duties	122 (69.7)	52 (76.5)	58 (73.4)	12 (42.9)	0.003
After starting COVID duties	33 (18.9)	6 (8.8)	11 (13.9)	16 (57.1)	<0.001
n	175	68	79	28	
Relation of HCQ intake with a meal					
With meal	164 (80.4)	59 (66.3)	79 (90.8)	26 (92.9)	<0.001
Empty stomach	3 (1.5)	3 (3.4)	0	0	0.362
Don't know	37 (18.1)	27 (30.3)	8 (9.2)	2 (7.1)	0.003
n	204	89	87	28	
The actual number of HCQ doses consumed for prophylaxis (tab)					
≤2	56 (31.3)	33 (44.6)	20 (25.4)	4 (14.8)	0.004
3-8	79 (44.1)	28 (37.8)	31 (39.2)	20 (74.1)	0.005
≥9	44 (24.6)	13 (17.6)	28 (35.4)	3 (11.1)	0.006
n	179	74	79	27	

Data presented in frequency (%), compared by Chi-square test/Fisher's exact test. HCQ: Hydroxychloroquine, ECG: Electrocardiogram

HCQ therapy, which is less than what was observed in a previous survey (67.8%).^[19] This raises serious apprehensions regarding the uniform prescription of HCQ for all HCWs, many of whom may have underlying cardiac disorders, which can lead to serious consequences. Thus, in practice, mandatory

ECG should be considered before beginning chemoprophylaxis with HCQ. Furthermore, experts had taken cognizance of this aspect and recommended HCQ's use beyond 8 weeks in conjunction with strict monitoring of clinical and ECG parameters in their revised advisory.

For 37.3% of the HCWs, the reason for not adhering to the HCQ prophylaxis regimen was their individual research and the fact that the side effects outweighed the benefits. Robust evidence and sufficient investigations regarding the possible role of HCQ prophylaxis were still lacking, which explained the skepticism of using it among the HCWs.^[22] Preliminary studies on the efficacy of HCQ against COVID-19 have shown contradictory results, and a few of them have been discredited due to a lack of adequate evidence.^[10,23-25] Data from international multicenter, randomized, open clinical trials such as Discovery^[26] and Solidarity^[27] to assess the efficacy of HCQ in the treatment of COVID-19 remained awaited. This was reiterated by a minority (2.34%) of the respondents that conclusive evidence about the effectiveness of HCQ was lacking.

Although HCQ has a relatively safe tolerability profile and most of our participants did not experience any serious adverse effects, 71 of them experienced gastrointestinal side effects such as cramps, nausea, gastritis, and so on, which is consistent with other studies.^[6,20]

In sum, in the absence of an effective vaccine or proven pharmacological prophylaxis during the initial months of the COVID-19 pandemic, HCQ, by virtue of its cost-effectiveness and easy availability, emerged as a forerunner in chemoprophylaxis for high-risk HCWs. However, our study highlighted that lack of adequate evidence, its side effects, and the tendency to instill a false sense of security were the main reasons for poor compliance with the recommended HCQ prophylaxis against COVID-19 among HCWs.

Certain limitations are inevitable, and they are present in our study too. First, the survey involved only HCWs; thus, its findings cannot be extrapolated to the general population. Second, participation being voluntary could have introduced selection bias. Third, as the data collected were based on self-reporting, recall bias may have occurred, and errors might have crept in a while entering the data.

Although the knowledge regarding HCQ chemoprophylaxis was fairly high among HCWs, the compliance and adherence to the ICMR guidelines were inadequate and highly variable. Even though HCWs, by virtue of the nature of their job, have greater access to information and the drug, their consumption of the same is influenced by their personal research, lack of strong scientific evidence, and drug-associated side effects. Health regulatory bodies might alter their recommendations in the near future due to vaccine availability as well as emerging evidence from ongoing

studies (like the COPCOV study [NCT04303507] and the PATCH study [NCT04329923]).

AUTHORS' CONTRIBUTION

R. Haldar and M. Gurjar conceptualized the study; R. Haldar, M. Gurjar, P. Mishra, and V. Agarwal prepared the study protocol; R. Haldar, O. P. Sanjeev, V. D. Upadhyaya, A. Bhatnagar, and D. Bhaduria completed the data acquisition; R. Haldar and P. Mishra analyzed the data; R. Haldar, O. P. Sanjeev, V. D. Upadhyaya, A. Bhatnagar, and D. Bhaduria prepared the manuscript; M. Gurjar edited the manuscript. All authors approved the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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