Original Article

Hydroxychloroquine/Chloroquine Prophylaxis among Health-care Workers: Was it Really Preventive? – Evidence from a Multicentric Cross-sectional Study

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Abstract

Background: Despite the low level of clinical evidence in hydroxychloroquine (HCQ) favor, it was prescribed for pre- and post-exposure prophylaxis in India and worldwide. In absence of a large randomized control trial, the evidence needs to be generated through observation study, hence the study was conducted to find the evidence for prophylaxis of HCQ. **Materials and Methods:** A multi-centric cross-sectional study involving government hospitals was chosen for serosurvey conducted from August 21, 2020, to November 20, 2020. Questionnaire was adopted from WHO. Data about chloroquine (CQ) use among health-care workers (HCWs) were added and the duration of CQ intake was also noted. **Results:** A total of 2,224 HCWs were recruited. The mean duration of time of taking HCQ was 7.1 weeks (standard deviation ± 6.1 weeks, median = 4 weeks with IQR, 3–10 weeks). Training on personal protective equipment (PPE), knowledge of handwashing, direct care to the patient, availability of alcohol hand rub, close contact with the patient, duration of contact, and usage of PPE were associated with HCQ intake. The antibody formation in group taking HCQ was 16.9% compared to 19.8% not taking it ($P = 0.08$). The Chi-square for linear trend for weeks of HCQ intake and antibody formation. However, the same was not statistically significant (Chi-square = 3.61, $P = 0.06$). **Conclusion:** Our study did not find a statistically significant association in the large multicentric study. The absolute difference of 2.9% in the two groups may not be sufficient to warrant its widespread use for prophylaxis.

Keywords: Chemo-prophylaxis, COVID-19, hydroxychloroquine

Hydroxychloroquine (HCQ), the widely used drug for rheumatologic conditions, attracted widespread interest for the prevention of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Despite a low level of clinical evidence in its favor, the necessity of coronavirus disease (COVID-19) pandemic, saw it being officially prescribed for pre- and post-exposure prophylaxis in India as well as worldwide. The *in-vitro*, as well as observational studies, provided scant evidence regarding the effectiveness of HCQ in the prophylaxis of SARS-CoV-2 infection.[1,2] An observational study in South Korea at the beginning of the pandemic, using postexposure prophylaxis with HCQ after a large COVID-19 exposure event in a hospital, showed all follow-up PCR tests as negative.[3]

The Indian National Task Force for COVID-19 on March 22, 2020, recommended HCQ on the basis of *in vitro* and preclinical data for prophylaxis of health-care workers (HCWs) and household contacts with caution and strict advisory for extensive reporting of adverse reactions.[4,5]

A systematic review showed the prophylactic effects of chloroquine (CQ) and HCQ against SARS-CoV-2.[6] Although preclinical results were promising, to date there is a dearth of evidence to support the efficacy of CQ or HCQ in preventing COVID-19. Considering potential safety issues and the likelihood of imparting a false sense of security it was

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thought that prophylaxis with CQ or HCQ against COVID-19 needs to be thoroughly evaluated in observational studies or high-quality randomized controlled studies. However, once the use of HCQ was started as per recommendations, majority HCWs considered the existing evidence as satisfactory and were willing for HCQ prophylaxis for self and family members. Many HCWs considered a randomized control trial (RCT) necessary but were not willing to participate.[7] Moreover, few RCTs which could have provided quality evidence were terminated early and suffered from various biases.[8-10] Later, due to its widespread use by May/June, an RCT could not have been done as it is.

A case–control study among HCWs randomly drawn from the countrywide COVID-19 testing data portal maintained by the Indian Council of Medical Research showed that consumption of four or more maintenance doses of HCQ was associated with a significant decline in the odds of getting infected and a dose-response relationship existed between frequency of exposure to HCQ and such reductions.[11] Few other hospital-based studies amongst HCWs in India provided evidence of HCQ prophylaxis being effective for the prevention of SARS-CoV-2 infection.[12,13]

Thus, in the absence of well-designed and conducted RCTs, the onus was on observational studies to generate evidence on this vexatious issue, which saw polarization on extreme ends not based solely on scientific evidence but majorly due to political and unscientific reasons. In view of the ongoing need, the objective of assessing the effectiveness of HCQ prophylaxis amongst HCWs was included in the main study of sero-surveillance of the HCWs with the aim to generate evidence for use of HCQ among HCWs.

Materials and Methods

The detailed methodology of the serosurvey has been given elsewhere.[14] Briefly, eight government-designated COVID-19 hospitals were chosen for the serosurvey, which was carried out from August 21, 2020, to November 20, 2020, based on geographical location and local epidemiology of COVID-19. A questionnaire duly pilot tested and checked for content validity by experts was adapted from the WHO questionnaire on serosurvey.[15] Questions about CQ use among HCWs were added and the duration of CQ intake was also noted.

Within the hospital chosen, stratified sampling strategy was followed. List of all eligible participants was prepared as per various categories (Doctors, Nurses, Nursing Assistants, Ambulance Assistants, etc.), which were further compressed into three groups namely doctors, nurses and ancillary workers, during the analysis. Study participants were selected by random sampling from each category, proportional to their size in each category. It was decided *a priori* that any center with <5% participants on HCQ would be dropped from the analysis. This was done because the inclusion of these centers may bias the results. The sample size was estimated for the original research on estimating the prevalence of antibodies. However, assuming the effect size of 0.05 with 80% power and 5% alpha error and two side test, the calculated sample size for this study was 780 HCWs in CQ intake and non-CQ intake groups.

Requisite ethical clearance was obtained from the institutional ethical committee at the institute level/centrally and from each participating center. Throughout the survey, patient confidentiality was maintained by censoring personal identifiers, and the final report was presented in aggregate numbers only.

All categorical variables were described as numbers and percentages and quantitative variables as mean and standard deviation (SD). Contingency tables were prepared for the association between seropositivity and other studied variables. Multiple Logistic Regression was done to adjust for confounders, estimation of the strength of association, and check for interactions. All variables having $P < 0.05$ were included in the model. Data were analyzed using StataCorp. 2019, Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC and *P* value of 0.05 was taken as statistically significant.

Results

Data from 2224 HCWs of four centers were analyzed as data from other four centers showed the HCQ intake of <5%. The mean age of the participant was 34.1 (SD ± 8.6). The socio-demographic, Infection prevention and control training, personal protective equipment (PPE), and other variables regarding HCQ intake have been depicted in Table 1. The mean duration of time of taking HCQ was 7.1 weeks (SD ± 6.1 weeks, median = 4 weeks with IQR, 3–10 weeks).

Training on PPE, knowledge of handwashing, direct care to the patient, availability of alcohol hand rub, close contact with the patient, duration of contact, and usage of PPE were associated with HCQ intake. The antibody formation in the group taking HCQ was 16.9% compared to 19.8% not taking it ($P = 0.08$). We did the multiple logistic regression to adjust for sex, training of PPE, and occupation and the adjusted odds ratio (AOR) for antibody formation was 0.8 (95% confidence interval [CI]: 08–1.9) [Table 2].

The data were also collected for the number of weeks of HCQ intake. Figure 1 shows the dose-response curve of the HCQ intake and antibody formation. The Chi-square for linear trend is statistically not significant (Chi-square = 3.61, $P = 0.06$).

Discussion

We did not find any statistically significant difference between CQ and antibody formation. The mean age of participants in our study was similar to the initial study in India was conducted as a case-control study among 378 cases and 373 controls. The study concluded that CQ consumption was associated with a significant decline in the odds of getting infected (AOR: 0.44; 95% CI 0.22–0.88). The study also found the

Table 1: Characteristic of health care workers with reference to chloroquine intake (N=2224)

Characteristics	*n* (%)	Chloroquine		*P*
		No, *n* (%)	Yes, *n* (%)	
Centre				
Pune	321 (14.4)	84 (26.2)	237 (73.8)	<0.001
Kolkata	623 (28)	479 (76.9)	144 (23.1)	
Delhi	655 (29.5)	281 (42.9)	374 (57.1)	
Mumbai	625 (28.1)	125 (20)	500 (80)	
Sex				
Female	542 (24.4)	241 (44.4)	301 (55.6)	0.6
Male	1682 (75.6)	728 (43.3)	954 (56.7)	
HCWs category				
Ancillary workers	1494 (67.2)	633 (42.4)	861 (57.6)	0.1
Doctors	358 (16.1)	173 (48.3)	185 (51.7)	
Nurses	372 (16.7)	163 (43.8)	209 (56.2)	
Previous molecular test positive				
No	1984 (89.2)	878 (44.3)	1106 (55.7)	0.06
Yes	240 (10.8)	91 (37.9)	149 (62.1)	
Training on IPC				
No	572 (25.7)	259 (45.3)	313 (54.7)	0.3
Yes	1652 (74.3)	710 (43)	942 (57)	
Training on PPE				
No	280 (12.6)	162 (57.9)	118 (42.1)	<0.001
Yes	1944 (87.4)	807 (41.5)	1137 (58.5)	
Hand washing technique				
Don't know	20 (0.9)	17 (85)	3 (15)	0.003
Each time	1214 (54.6)	528 (43.5)	686 (56.5)	
Selective	966 (43.4)	413 (42.8)	553 (57.2)	
Don't have time	24 (1.1)	11 (45.8)	13 (54.2)	
Direct care to a COVID-19 case				
No	919 (41.3)	457 (49.7)	462 (50.3)	<0.001
Yes	1305 (58.7)	512 (39.2)	793 (60.8)	
Availability of alcohol based hand rub				
No	147 (6.6)	92 (62.6)	55 (37.4)	<0.001
Yes	2077 (93.4)	877 (42.2)	1200 (57.8)	
Close contact (within 1 meter) with a confirmed COVID-19 patient				
No	919 (41.3)	468 (50.9)	451 (49.1)	<0.001
Yes	1305 (58.7)	501 (38.4)	804 (61.6)	
PPE used				
No	244 (11)	187 (76.6)	57 (23.4)	<0.001
Yes	1980 (89)	782 (39.5)	1198 (60.5)	
Smoking				
No	2113 (95)	912 (43.2)	1201 (56.8)	0.09
Yes	111 (5)	57 (51.4)	54 (48.6)	
Symptoms in the last 30 days				
No	2017 (90.7)	859 (42.6)	1158 (57.4)	0.004
Yes	207 (9.3)	110 (53.1)	97 (46.9)	
Risk factors				
No	2054 (92.4)	878 (42.7)	1176 (57.3)	0.006
Yes	170 (7.6)	91 (53.5)	79 (46.5)	
Duration of contact (in case of multiple contacts) (min)				
<15	455 (33.4)	147 (32.3)	308 (67.7)	0.001
>15	908 (66.6)	375 (41.3)	533 (58.7)	
Antibody (final result)				
No	1820 (81.8)	777 (42.7)	1043 (57.3)	0.08
Yes	404 (18.2)	192 (47.5)	212 (42.5)	

HCWs: Health-care workers, IPC: Infection prevention and control, PPE: Personal protective equipment, COVID-19: Coronavirus disease-2019

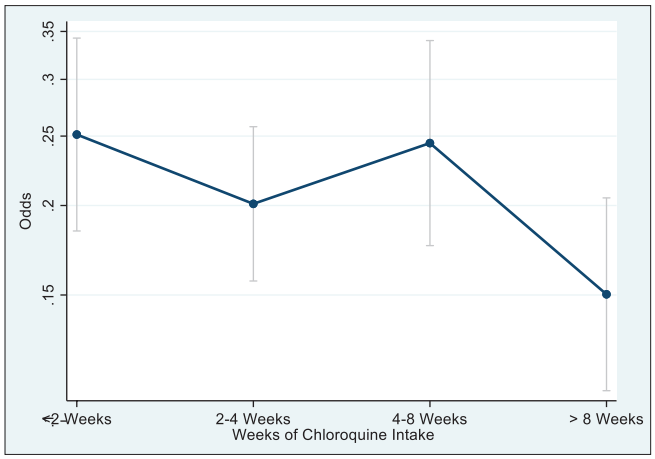

Figure 1: Dose-response curve for chloroquine. Chi-square for linear trend = 0.06

Table 2: Multiple logistic regression with antibody detection as outcome

Characteristic	UOR (95% CI)	AOR (95%CI)	*P* for AOR
Chloroquine			
No	Reference	Reference	0.1
Yes	0.8 (0.7-1)	0.8 (0.7-1)	
Sex			
Female	Reference	Reference	0.4
Male	2 (1.5-2.6)	1.2 (0.8-1.9)	
Training of PPE			
No	Reference	Reference	0.001
Yes	0.5 (0.4-0.7)	0.6 (0.4-0.8)	
Occupation			
Ancilliary worker	Reference	Reference	
Doctors	0.4 (0.2-0.5)	0.4 (0.2-0.5)	<0.001
Nurses	0.4 (0.3-0.6)	0.5 (0.3-0.8)	0.007

PPE: Personal protective equipment, OR: Odds ratio, UOR: Unadjusted OR, AOR: Adjusted OR

dose-response relationship.[11] However, in this study to adequate sample size could not be met and sensitivity analysis were not done.[16] In our study, there are some indications of the dose-response relationship, however the same was not statistically significant. The dose-response relationship would have strengthened the evidence for chemoprophylaxis use of HCQ. Another study from a tertiary care center at Kolkata, recently posted on a preprint server, reported that among 106 HCWs, HCQ consumption as preexposure prophylaxis was associated with a significant reduction in risk of SARS-CoV-2 infection.[12] A systematic review on the subject till March 30, 2020, said there is a dearth of data for clinical evidence of HCQ.[6] A Cochrane review published concludes that drug is less likely to be effective in the prevention of infection although this cannot be excluded entirely.[17]

Our study results of an absolute difference of minus 2.9% (statistically not significant) in antibody prevalence between those consuming HCQ and those not doing so is similar to a postexposure HCQ prophylaxis trial among HCWs across the USA and parts of Canada, which found that the incidence of new illness compatible with COVID-19 did not differ significantly between participants receiving HCQ (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]) with an absolute difference of minus 2.4%.[10] An ongoing exposure trial amongst HCWs in the USA and Manitoba, Canada showed that once or twice weekly HCQ intake did not significantly reduce laboratory-confirmed COVID-19 cases.[8] RCT among HCWs caring for patients with COVID-19 showed no significant difference in infection rates in participants randomized to receive HCQ compared with placebo (4 of 64 [6.3%] vs. 4 of 61 [6.6%]; $P > 0.99$). Of the 8 participants with positive results for SARS-CoV-2 (6.4%), 6 developed viral symptoms; none required hospitalization, and all clinically recovered. However, the trial was terminated early and was statistically not powered enough to assess a meaningful difference.[9]

In our study, the intake of CQ was associated with centers. It was also noticed that the centers with the highest antibody formation also had the highest intake of the HCQ. Those who were trained in PPE and were using PPE, involved in direct care, close contact with the confirmed COVID-19 patient were more likely to use HCQ. This gives an indication that those taking HCQ were also taking most of the precautions. In multivariate analysis, training of PPE was associated with decrease in risk in those centers, however even though the CQ was protective in bivariate and multivariate analysis, the same was not statistically significant. Hospital policies and the local epidemiological situation at the time of the survey may have an influence over CQ use among HCWs.

The question of HCQ for COVID-19 prevention has got somewhat out of hand due to interference from politicians and nonscientists via social media and nonscientific journals. However, as Kim *et al*. stated, "it is our responsibility as clinicians, researchers, and patient partners to promote proper and rigorous interpretation of results, particularly in our interactions with the nonscientific community. We must consider the societal implications of published work in these unprecedented times."[18] The role of prophylactic HCQ in SARS-CoV-2 and the definition of the optimal dosage are two important issues requiring attention.

While early in the course of the pandemic, due to limited knowledge and many unanswered questions, an empiric use of HCQ for prophylaxis may be justified as a *prudent* approach, since it is a cheap, readily available, and relatively safe drug with a favorable pharmacokinetic profile (prolonged half-life, high concentration within lung tissue). However, experience with other viral infections and evidence generated in recent months has generated considerable doubts and concerns over the widespread use of HCQ.

Conclusion

Our study did not find statistically significant association in the large multicentric study. The authors also feel that absolute

difference of 2.9% in two groups may not be sufficient to warrant its widespread use. The take-home message of our research is that a correct methodological approach is a key to understanding whether prophylactic HCQ can really represent an effective strategy in preventing COVID-19. Thus, a systematic review of the results of the ongoing RCTs and inclusion of studies by other designs would serve to lend weight to their results and may be able to provide evidence regarding the large-scale use of prophylactic HCQ. At present, there is a lack of evidence for the prophylactic use of HCQs in COVID-19.

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Conflicts of interest

There are no conflicts of interest.

References

1. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, *et al.* Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection *in vitro*. Cell Discov 2020;6:1-4.
2. Meo SA, Klonoff DC, Akram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. Eur Rev Med Pharmacol Sci 2020;24:4539-47.
3. Lee SH, Son H, Peck KR. Can post-exposure prophylaxis for COVID-19 be considered as an outbreak response strategy in long-term care hospitals? Int J Antimicrob Agents 2020;55:105988.
4. Available from: https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARSCoV2infection.pdf. [Last accessed on 2021 Feb 26].
5. Available from: https://www.icmr.gov.in/pdf/covid/techdoc/V5_Revised_advisory_on_the_use_of_HCQ_SARS_CoV2_infection.pdf [Last accessed on 2021 Feb 26].
6. Shah S, Das S, Jain A, Misra DP, Negi VS. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). Int J Rheum Dis 2020;23:613-9.
7. Baicus C, Pinte L, Stoichitoiu LE, Badea C. Hydroxychloroquine for prophylaxis of COVID-19 physicians survey: Despite lack of evidence, many would take or give to dear ones, and despite the perceived necessity of an RCT, few would participate. J Eval Clin Pract 2020;26:1579-82.
8. Rajasingham R, Bangdiwala AS, Nicol MR, Skipper CP, Pastick KA, Axelrod ML, *et al*. Hydroxychloroquine as Pre-exposure Prophylaxis for Coronavirus Disease 2019 (COVID-19) in Healthcare Workers: A Randomized Trial. Clin Infect Dis. 2021;72:e835-e843. doi: 10.1093/cid/ciaa1571. PMID: 33068425; PMCID: PMC7665393.
9. Abella BS, Jolkovsky EL, Biney BT, Uspal JE, Hyman MC, Frank I, *et al.* Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: A randomized clinical trial. JAMA Intern Med 2021;181:195-202.
10. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, *et al.* A Randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. N Engl J Med 2020;383:517-25.
11. Chatterjee P, Anand T, Singh KJ, Rasaily R, Singh R, Das S, *et al.* Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. Indian J Med Res 2020;151:459.
12. Bhattacharya R, Chowdhury S, Mukherjee R, Kulshrestha M, Ghosh R, Saha S, *et al.* Pre exposure hydroxychloroquine prophylaxis for COVID-19 in healthcare workers: A retrospective cohort. medRxiv 2020.06.09.20116806; doi: https://doi.org/10.1101/2020.06.09.20116806.
13. Nagaraja BS, Ramesh KN, Dhar D, Mondal MS, Dey T, Saha S, *et al*. HyPE study: Hydroxychloroquine prophylaxis-related adverse events' analysis among healthcare workers during COVID-19 pandemic: A rising public health concern. J Public Health Oxf Engl 2020;42:493-503.
14. Sero-Surveillance of SARS-CoV2 Infection among Health-Care Workers: A Protocol; 2021. Available from: https://www.mjdrdypv.org/preprintarticle.asp?id=308621;type=0. [Last accessed on 2021 Feb 26].
15. Available from: https://apps.who.int/iris/bitstream/handle/10665/331656/WHO-2019-nCoV-Seroepidemiology-2020.1-eng.pdf?sequence=1&isAllowed=y. [Last accessed on 2020 Jul 15].
16. Kunte R, Yadav AK, Faujdar DS, Sahu R, Basannar D, Patrikar S, *et al.* Prophylactic use of hydroxychloroquine among healthcare workers in a case-control study. Indian J Med Res 2020;152:127-8.
17. Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database Syst Rev 2021;2:CD013587.
18. Kim AH, Sparks JA, Liew JW, Putman MS, Berenbaum F, Duarte-García A, *et al.* A rush to judgment? Rapid reporting and dissemination of results and its consequences regarding the use of hydroxychloroquine for COVID-19. Ann Intern Med 2020;172:819-21.