Research Article

Prophylactic Use of Hydroxychloroquine and Subsequent SARS-CoV-2 Infection among Healthcare Workers - A Matched Case-control Study

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DOI: https://doi.org/10.24321/2455.7048.202201

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A B S T R A C T

Introduction: Healthcare Workers (HCWs) are at a higher risk of contracting SARS-CoV-2 infection as they have greater exposure to confirmed COVID-19 patients. It is essential to implement prophylactic measures to reduce the incidence of COVID-19 among them. The Indian guidelines recommend the use of hydroxychloroquine (HCQ) as prophylaxis for HCWs.

Objective: To investigate the role of HCQ as prophylaxis against SARS-CoV-2 infection among HCWs.

Method: The cases and controls were matched at an individual level on occupation (doctor, nurse, technical staff, attending/ cleaning staff, administrative staff), area of posting (whether designated COVID care area or non-COVID area), use of personal protective equipment (PPE), and risk category of exposure.

Results: In matched-pair analysis, no statistically significant difference was found in the incidence of COVID-19 infection with the use of HCQ for prophylaxis (OR 0.73, 95% CI: 0.40-1.36).

Conclusion: Prophylactic use of HCQ does not have any effect on the prevention of COVID-19 infection.

Keywords: Healthcare Workers, COVID-19, Prophylaxis, Hydroxychloroquine, Case-control Study

Introduction

Healthcare Workers (HCWs) are at a higher risk of contracting SARS-CoV-2 infection as they are more exposed to confirmed COVID-19 patients. It is, therefore, essential to implement prophylactic measures to reduce the incidence of COVID-19 among them. The Indian guidelines recommend the use of hydroxychloroquine (HCQ) as prophylaxis for HCWs. This advisory was based on a few observational studies.[1-3] In addition, few in-vitro studies had reported that both HCQ and chloroquine have antiviral properties against novel coronavirus (COVID-19).[4,5] Many studies from India also

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reported that prophylactic use of HCQs was associated with a significant reduction in the risk of SARS CoV-2 infection.[2,3,6] It was noticed that these Indian studies had some methodological issues. However, other studies reported that prophylactic use of HCQ did not reduce the risk of SARS-CoV-2 infection.[7] The World Health Organization suspended the HCQ arm in the SOLIDARITY trial, and later, in the RECOVERY trial and concluded that HCQs did not have a beneficial effect in SARS-CoV-2 infection.[8] The Indian Council of Medical Research issued a revised advisory in May 2020, and still recommended the prophylactic use of HCQs among HCWs.[9] We undertook this study to investigate the role of HCQ as prophylaxis against SARS-CoV-2 infection among HCWs while overcoming the methodological deficiencies noted in previous studies.

Subjects and Method

The study was conducted at the All India Institute of Medical Sciences, New Delhi from 16 April 2020 to 19 June 2020. The study site was a tertiary health care facility. This is a hospital-based matched case-control study.

All HCWs of the institution who tested positive for COVID-19 were included as case, while those that were negative were included as control. HCWs who were already taking HCQ due to some other condition and those with previous history of adverse reaction or allergy to HCQ were excluded from the study. The potential participants were identified from the list prepared by the contact tracing team of the institute. A detailed description of contact tracing is provided in a previous article.[10]

Sample Size: We assumed HCQ prophylaxis among controls to be 40%. Considering 80% power, 5% alpha, 1:1 ratio of cases to controls, the sample size was estimated to be 85 pairs i.e. 170 individuals.

The cases and controls were matched at an individual level on occupation (doctor, nurse, technical staff, attending/cleaning staff, administrative staff), area of posting (whether designated COVID care area or non-COVID area), use of personal protective equipment (PPE), and risk category of exposure.

Operational Definitions

Case: A person who tested positive for SARS-CoV-2 by qualitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) test, conducted at the virology laboratory of the institution, or at any other laboratory approved by the Indian Council of Medical Research (ICMR).

Control: A HCW who

- Came in contact with a COVID-19 confirmed case
- Tested negative after the 5th day of exposure to a COVID-19 confirmed patient

Level of Exposure

High-risk Exposure: This included any one of the following:

- Performed a respiratory Aerosol Generating Procedure (AGP) without any one of these - N95 mask, eye/ face protection or gloves
- If the patient's respiratory tract secretions or saliva came in contact with the mucous membranes of the eyes/ nose/ mouth
- Anyone who was in close proximity (within 1 meter) of a confirmed case without a mask (both case and contact) for a duration of more than 15 minutes
- Household contact of a known positive case

Low-risk Exposure: All exposures to COVID-19 patients except the high-risk exposure.

Both cases and controls were interviewed either face-to-face or telephonically. Information regarding demographic details, area of work, symptom status, personal protective measures and use of hydroxychloroquine (HCQ), multi-vitamins or other drugs for prophylaxis against COVID-19 were collected. If HCQ was used, the details like dose, frequency, and duration of intake were asked. All the participants were followed up for a period of 14 days from the date of last exposure. The information regarding the result of qRTPCR was obtained from the participants.

Statistical Analysis

Data were entered in MS Excel 2016. Statistical analysis was done by the use of STATA 12.0 (Stata Corp LLC 4905, Texas, USA). We did both unmatched and matched-pair analysis. The categorical and continuous variables were shown by proportion and mean (standard deviation) respectively. To find the statistical difference between cases and controls across the variables, chi-square or Fisher exact test was applied for categorical variables and unpaired t-test was applied for continuous variables. To find the strength of association between HCQ intake and risk of COVID-19, bi-variable logistic regression analysis was done for unmatched analysis and conditional logistic regression analysis for matched-pair analysis. The level of significance was taken as 0.05 and 95% confidence interval was estimated.

Ethical Consideration

The Institute Ethics Committee of All India Institute of Medical Sciences, New Delhi approved the study. The participants gave informed verbal consent on the phone. The information obtained from the participants was kept confidential and personal identifiers were removed before the analysis was begun.

Results

A total of 172 participants were enrolled in the study, which included 86 cases and 86 controls. Of the total study

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participants, 112 (65.1%) were male. The mean (SD) age of cases was 33.8 (8.4) years and among the controls, it was 33.7 (9.0) years. Ten (5.8%) of the participants were working in designated COVID care areas. Nurses constituted 30.8% of the study group, while 28.4% were housekeeping staff, and 11% were security personnel. Nearly 10% of the participants were doctors and 7% were laboratory staff. Nearly 32% (n = 51) of the participants reported appropriate and consistent use of PPE (Personal Protective Equipment). Majority (94.4%) of the participants reported exposure to COVID-19 patients in the hospital setting, while 5.6% reported exposure to a household contact (Table 1).

Nearly one-third of the participants [n = 54 (31.4%)] had used HCQ for prophylaxis. Of these, 25 (46.3%) were cases and 29 (53.7%) were controls. Nearly 10% of the cases and controls had taken the loading dose of HCQ i.e. 400 mg of HCQ twice on day one (p = 0.938). The mean (SD) number of hydroxychloroquine tablets taken by the cases and controls were 6.3 (4.6) and 4.8 (2.8) respectively (p = 0.155).

In matched-pair analysis (Table 2), there was no statistically significant difference in the incidence of COVID-19 infection with the use of HCQ for prophylaxis (OR 0.73, 95% CI: 0.40 - 1.36), use of HCQ along with azithromycin (OR 0.71, 95% CI: 0.10 - 5.21), and use of HCQ with multivitamin (OR 2.0, 95% CI: 0.18 - 22.6).

In the multivariate conditional logistic regression model, HCQ prophylaxis had no statistically significant difference in the incidence of COVID-19 infection among HCWs after adjusting for gender, risk category of exposure, and setting of exposure (Table 3).

Table 1. Distribution of Cases and Controls by Baseline Characteristics

Characteristics	Cases (n = 86) N (%)	Controls (n = 86) N (%)	Total (n = 172) N (%)	p value
Gender				
Male	54 (62.7)	58 (67.4)	112 (65.1)	0.52
Female	32 (37.3)	28 (32.6)	60 (34.9)	
Age (years)				
Mean (SD)	33.8 (8.4)	33.7 (9.0)	0.07	
Occupation				
Doctors	8 (9.3)	9 (10.6)	17 (9.9)	0.369
Nurses	26 (30.3)	27 (31.7)	53 (30.8)	
Housekeeping staff	23 (26.7)	26 (30.6)	49 (28.5)	
Security personnel	9 (10.5)	10 (11.8)	19 (11.0)	
Laboratory and technical staff	5 (5.8)	7 (8.1)	12 (7.0)	
Administration personnel	12 (13.9)	5 (5.8)	17 (9.9)	
^Others	3 (3.5)	2 (2.3)	5 (2.9)	
Area of work				
COVID area	3 (3.5)	7 (8.2)	10 (5.8)	0.19
Non-COVID area	83 (96.5)	79 (91.8)	162 (94.2)	
Risk category of exposure				
High risk	28 (32.5)	25 (29.1)	53 (30.8)	0.64
Low risk	58 (67.5)	61 (70.9)	119 (69.2)	
Symptom status				
Asymptomatic	23 (25.6)	55 (64.7)	78 (45.3)	< 0.001
Symptomatic	63 (74.4)	31 (35.3)	94 (54.7)	
***PPE use**	**n = 83**	**n = 79**	**n = 162**	0.92
No use	11 (15.7)	10 (12.7)	21 (13.0)	
Inconsistent use	47 (59.3)	43 (54.4)	90 (55.6)	

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Appropriate use	25 (25.0)	26 (32.9)	51 (31.4)	
#Setting of exposure	**n = 86**	**n = 76**	**n = 162**	0.69
Health care setting	82 (95.3)	71 (93.4)	153 (94.4)	
Household exposure	4 (4.7)	5 (7.6)	9 (5.6)	

^ Others - students, cook, food bearer
*Data for 3 cases and 7 controls not available
Data of 10 controls not available

Table 2.Matched-pair Analysis of Prophylaxis taken against COVID-19

Strata	OR 95% CI	p value
HCQ taken (n = 86)		
No	Reference group	0.329
Yes	0.73 (0.40 to 1.36)	
HCQ loading dose only (n = 82)		
No	Reference group	0.386
Yes	0.74 (0.37 to 1.47)	
HCQ + azithromycin (n = 59)		
No	Reference group	0.764
Yes	0.71 (0.10 to 5.21)	
HCQ + multivitamin (n = 58)		
No	Reference group	0.571
Yes	2.0 (0.18 to 22.06)	
HCQ + any other remedy (ayurvedic/ alternate system and household remedies) (n = 58)		
No	Reference group	0.775
Yes	1.42 (0.13 to 16.1)	
HCQ tablet count (taking cut off of 4 tablets as per the recommendations) (excluding those taking HCQ < 4 tablets) (n = 29)		
No	Reference group	0.835
≥ 4 tablets	1.1 (0.48 to 2.47)	

Table 3.Effect of HCQ on Risk of COVID-19 Infection in Matched-pair Analysis using Conditional Logistic Regression Analysis

(N = 172)

Variable		Cases (n = 86)	Controls (n = 86)	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
HCQ taken	No	61	57	Reference	0.413	Reference	0.292
	Yes	25	29	0.76 (0.39 to 1.46)		1.2 (0.26 to 1.49)	
Gender	Female	32	28	Reference	0.339	Reference	0.618
	Male	54	58	0.68(0.32 to 1.48)		0.78 (0.28 to 2.13)	
Risk category of exposure	Low	58	61	Reference	0.403	Reference	0.933
	High	28	25	1.35 (0.66 to 2.77)		0.96 (0.34 to 2.70)	

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Setting of exposure (n = 66)	Hospital	62	61	Reference	0.215	Reference	0.329
	Household	4	5	0.25 (0.02 to 2.20)		0.2 (0.02 to 1.91)	

Discussion

In our study, we did not find any significant difference in the risk of SARS-CoV-2 infection among HCWs who used HCQ for prophylaxis, compared to those who did not use it. The results of our study are consistent with two randomised controlled trials conducted by Abella et al.[11] and Rajasingham et al.,[6] where HCWs were randomly assigned to take HCQ for 8 or 12 weeks. In both these trials, no difference was found in the risk of SARS-CoV-2 infection between the intervention and control arm of the study.

In another study, Rentsch et al. followed up 30,569 patients with SLE or rheumatoid arthritis who were already taking HCQ and found no evidence to support the use of HCQ for the prevention of COVID-19 mortality.[12]

A few studies in India reported that HCQ was an effective prophylaxis against COVID-19 among HCWs. Chatterjee et al. conducted a case-control study among participants drawn randomly from a country-wide COVID-19 testing data portal, and reported that consumption of four or more doses of HCQ was associated with a significant decline in the odds of getting SARS-CoV-2 infection.[2] The authors had included only the symptomatic HCWs who tested positive or negative (as cases and controls). A large number of individuals with SARS-CoV-2 infection remain asymptomatic. The exclusion of asymptomatic HCWs compromises the representativeness of all HCWs. We included both asymptomatic and symptomatic HCWs in our study. Bhattacharya et al. also reported the beneficial effect of HCQ in preventing SARS-CoV-2 infection in a retrospective cohort study among HCWs in Kolkata.[6] Although the authors compared the baseline characteristics of the participants in the two groups, however, they did not consider the category of exposure at the workplace, use of PPE, and household contacts. In our study, we overcame this deficiency and included these factors while assessing the effect of HCQs on SARS-CoV-2 infection. Robust prospective data generated as a part of the ongoing contact tracing programme, follow-up for 14 days, collection of data on selected variables within 24 hours of exposure, and matched case-control study design are some of the strengths of our study.

Acknowledgement

Conclusion

Prophylactic use of HCQ does not prevent SARS-CoV-2 infection among HCWs.

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