Indian J Med Res 153, January & February 2021, pp 219-226
DOI: 10.4103/ijmr.IJMR_2294_20

Quick Response Code:

Programme

Safety of hydroxychloroquine in healthcare workers for COVID-19 prophylaxis

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Received May 30, 2020

***Background & objectives*: Hydroxychloroquine (HCQ), reported to inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in *in vitro* studies, has been recommended for prophylaxis of COVID-19 in healthcare workers (HCWs). The objective of this study was to assess short-term adverse events (AEs) of HCQ in HCWs.**

***Methods*: This cross-sectional study among consenting HCWs taking prophylaxis and working in hospitals with COVID-19 patients used online forms to collect details of HCWs, comorbidities, prophylactic drugs used and AEs after the first dose of HCQ. Verification of dose and AEs was done by personal contact. Multivariate logistic regression analysis was done to determine the effect of age, gender and dose of HCQ on AE.**

***Results*: Of the 1303 HCWs included, 98.4 per cent (n=1282) took HCQ and 66 per cent (n=861) took 800 mg as first day's dose. Among the 19.9 per cent (n=259) reporting AEs, 1.5 per cent (n=20) took treatment for AE, none were hospitalized and three discontinued HCQ. Gastrointestinal AEs were the most common (172, 13.2%), with less in older [odds ratio (OR) 0.56, 95% confidence interval (CI) 0.35-**

0.89], with more in females (OR 2.46, 95% CI 1.78-3.38) and in those taking a total dose of 800 mg on day one compared to a lower dose. Hypoglycaemia (1.1%, n=14), cardiovascular events (0.7%, n=9) and other AEs were minimal.

***Interpretation & conclusions*: HCQ prophylaxis first dose was well tolerated among HCWs as evidenced by a low discontinuation. For adverse effects, a small number required treatment, and none required hospitalization. The study had limitations of convenience sampling and lack of laboratory and electrocardiography confirmation of AEs.**

Key words Adverse events - chloroquine - coronavirus - COVID-19 - healthcare workers - hydroxychloroquine - prophylaxis - rational

Chloroquine (CQ) and hydroxychloroquine (HCQ) have been shown to inhibit the replication of SARS-CoV-2 *in vitro* and are recommended/being investigated for prophylactic use. Both these drugs have been commonly used in malaria, rheumatoid arthritis (RA) and other immune-mediated diseases for over five decades[1]. Patients on these drugs have reported various early adverse events (AEs) such as abdominal pain, decreased appetite, diarrhoea, nausea, vomiting, prolonged QT interval, ventricular arrhythmia, hypoglycaemia and hypersensitivity. On long-term use, retinopathy and haematologic events have been reported[1].

The evidence on HCQ/CQ use in patients with COVID-19 has been considered futile[2,3], and a randomized trial of HCQ as post-exposure prophylaxis for COVID-19 reported that HCQ did not prevent illness when used as post-exposure prophylaxis within four days after exposure[4]. Yet, to date, there are limited reports from clinical studies on the use of HCQ or CQ prophylaxis in COVID-19. A systematic review of 31 ongoing interventional studies of HCQ prophylaxis in those at high risk of exposures reported wide variation in the dose used (400-1400 mg) and duration (3-24 wk)[5]. The Oxford University Group is currently undertaking a large global trial called COPCOV, evaluating potential for CQ/HCQ to be taken as pre-exposure prophylaxis and safety of these drugs[6,7].

We undertook an observational study to evaluate the safety of HCQ for COVID-19 prophylaxis among HCWs in India to report short-term AEs after its first-day dosing.

Material & Methods

This cross-sectional, observational study was carried out by the Indian Council of Medical Research (ICMR) Rational Use of Medicine Centres (RUMCs), at department of Pharmacology, St. John's Medical College (SJMC), Bengaluru, India, which was one of the coordinating centres, managing data and statistical analyses. The study was conducted during the months of April and May 2020.

Participants consisted of all consenting HCWs (doctors, nurses and ancillary staff such as technicians, laboratory staff, ward attendants, aides, ambulance drivers and security staff) working in RUMCs or neighbouring institutions (henceforth called others) at risk of exposure to COVID-19–suspect or confirmed patients, taking HCQ prophylaxis for COVID-19. There were no exclusion criteria.

A convenience sampling method was followed as it was not known as to how many HCWs had started taking HCQ. Administrative approval and Ethics Committee approval for conducting the study were obtained by each centre. Eligible participants were approached by the RUMC investigator teams.

A questionnaire was developed for data collection which included questions on medicines used for prophylaxis; total dose of medicines taken on day one; whether prior ECG was taken; presence of co-morbidities and exposure to COVID-19 patients. Participant information sheet and informed consent form were part of the form. The link to the questionnaire form was sent by e-mail or instant messaging application to all eligible personnel. After the participants ticked their consent, they were allowed to fill data on the questionnaire form online. For HCWs with challenge in filling the online form, a printed copy was provided which was then transcribed to the online form. To verify total dose on day one of HCQ (if other than 800 mg) and reports of AEs by personally contacting the participants, their contact details were shared by the coordinating centre with RUMCs and others, after confidentiality and data privacy agreement were signed by them.

Statistical analysis: Data were extracted into MS Excel for verification as well as sending queries to sites. Clean data were extracted into STATA (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) for statistical analysis.

Age was categorized into three groups as less than and equal to 30, 31-45 and more than 45 yr. Association of AEs by age, gender and HCQ dose was determined by univariate logistic regression with a $P<0.05$ set for significance and multivariate logistic regression analysis reporting the odds ratio (OR) and its 95 per cent confidence intervals (CIs).

Results

Between April 2, and May 13, 2020, 1303 participants taking HCQ and other medications for COVID-19 prophylaxis were recruited. The mean age of the participants was 35 yr; 42 per cent (n=547) were less than or equal to 30 yr, 36.5 per cent (n=476) were 31-45 yr and 21.5 per cent (n=280) over 45 yr; males comprised 56.2 per cent; doctors 43.5 per cent (n=567), ancillary staff 32.5 per cent (n=424) and nurses 23.9 per cent (n=312). A low proportion of participants had comorbidities such as diabetes (4.3%, n=56), hypertension (6.3%, n=82), cardiovascular (CV) disease (0.6%, n=8) and recurrent respiratory disease (1.5%, n=19). A total of 208 (16%) participants reported exposure to COVID-19 suspect and 10.5 per cent (n=137) reported exposure to confirmed patients.

Medicines taken for prophylaxis: Participants took one drug, either HCQ (98.4%, n=1282) or CQ (0.5%, n=5). A few (<1%) reported taking other drugs [HCQ+azithromycin 11 (0.8%) and HCQ+ivermectin 2 (0.2%); 1021 (78.4%) of the participants got their medication from the hospital. The most common total dose of HCQ taken on day one was 800 mg (66.1%, n=861), 28.1 per cent (n=366) reported taking 400 mg and 4.6 per cent (n=60) reported taking 200 mg.

Adverse events and discontinuation of prophylaxis: AEs reported and their management are presented in Table I. 19.9 per cent (n=259) reported one AE and 1.5 per cent (n=20) reported taking treatment for the AE. None were serious enough to require hospitalization. Three participants discontinued prophylactic treatment due to AE (palpitation and gastritis in one; migraine flare-up in another and gastritis, headache, body ache and sleeplessness in the third). The focus was on AEs that were commonly reported and those likely to be serious and affecting compliance, *e.g.* gastrointestinal (GI) events, hypoglycaemia and CV events. Rest of the AEs were grouped as other.

Table I. Frequency, types and management of adverse events reported

Characteristic	n=1303, n (%)
Any one or more adverse effects	259 (19.9)
Number of adverse effects	
0	1044 (80.1)
1	166 (12.7)
2	72 (5.5)
≥3	21 (1.6)
Type of adverse events	
Nausea	114 (8.7)
Vomiting	18 (1.4)
Abdominal pain	91 (7.0)
Hypoglycaemia	14 (1.1)
Hypersensitivity	12 (0.9)
Photosensitivity	7 (0.5)
Cardiovascular effects	9 (0.7)
Others	115 (8.8)
Any treatment taken	20 (1.5)
Hospitalization	0

Among the AEs, 13.2 per cent (n=172) were GI system related such as nausea (8.7%, n=114), abdominal pain (7%, n=91) and vomiting (1.4%, n=18). Symptoms suggestive of hypoglycaemia were reported by 1.1 per cent (n=14) of participants as they experienced hunger or fatigue that was relieved with food or chocolate. It was not confirmed with blood glucose testing. Those with diabetes did not report significantly higher rate of hypoglycaemia compared to those without diabetes (3.5 vs. 1%, $P=0.064$). Participants reported experiencing CV AEs (0.7%, n=9), symptoms of palpitation and tightness of the chest. No ECG was taken.

Adverse events by age: AEs related to the GI system were reported differently across age groups. Older individuals (>45 yr) reported less GI symptoms as compared to the younger individuals (≤ 30 yr) (OR 0.56, 95% CI 0.35-0.89). Hypoglycaemia was reported more in older individuals (>45 yr) compared to younger ones, but this was not significant (OR 2.78, 95% CI 0.87-8.84). The other specified AEs, namely hypersensitivity and photosensitivity, were not significantly different in the three age groups (Table II).

Table II. Univariate analysis of adverse events by age, gender and dose of hydroxychloroquine on day one

Adverse events	Risk factor	Adverse events		OR	95% CI		*P*
		Present, n (%)	Absent, n (%)		Lower	Upper	
Any gastrointestinal symptoms	Age (yr)						
	≤30	82 (14.99)	465 (85.01)	Reference			
	31-45	65 (13.66)	411 (86.34)	0.90	0.63	1.27	0.544
	>45	25 (8.93)	255 (91.07)	0.56	0.35	0.89	0.015
	Gender						
	Male	67 (9.15)	665 (90.85)	Reference			
	Female	105 (18.39)	466 (81.61)	2.24	1.61	3.11	<0.001
	Dose of HCQ# (mg)						
	≤400	42 (9.9)	384 (90.1)	Reference			
	800	127 (14.8)	734 (85.2)	1.58	1.09	2.29	0.015
Hypoglycaemia	Age (yr)						
	≤30	5 (0.91)	542 (99.09)	Reference			
	31-45	2 (0.42)	474 (99.58)	0.46	0.89	2.37	0.351
	>45	7 (2.5)	273 (97.50)	2.78	0.87	8.84	0.083
	Gender						
	Male	3 (0.41)	729 (99.59)	Reference			
	Female	11 (1.93)	560 (98.07)	4.77	1.33	17.19	0.017
	Dose of HCQ# (mg)						
	≤400	5 (1.2)	421 (98.8)	Reference			
	800	9 (1)	852 (99)	0.89	0.30	2.67	0.835
Hypersensitivity	Age (yr)						
	≤30	5 (0.91)	542 (99.09)	Reference			
	31-45	6 (1.26)	470 (98.74)	1.38	0.42	4.56	0.594
	>45	1 (0.36)	279 (99.64)	0.39	0.05	3.34	0.389
	Gender						
	Male	2 (0.27)	730 (99.73)	Reference			
	Female	10 (1.75)	561 (98.25)	6.51	1.42	29.81	0.016
	Dose of HCQ# (mg)						
	≤400	5 (1.2)	421 (98.8)	Reference			
	800	7 (0.8)	854 (99.2)	0.69	0.22	2.19	0.529
Photosensitivity	Age (yr)						
	≤30	2 (0.37)	545 (99.63)	Reference			
	31-45	5 (1.05)	471 (98.95)	2.89	0.56	14.98	0.206
	>45	0	280 (100)	1.0	-	-	-
	Gender						
	Male	4 (0.55)	728 (99.45)	Reference			
	Female	3 (0.53)	568 (99.47)	0.96	0.21	4.31	0.959
	Dose of HCQ# (mg)						
	≤400	1 (0.2)	425 (99.8)	Reference			
	800	6 (0.7)	855 (99.3)	2.98	0.36	24.85	0.312

Contd...

Adverse events	Risk factor	Adverse events		OR	95% CI		*P*
		Present, n (%)	Absent, n (%)		Lower	Upper	
Cardiovascular effects	Age (yr)						
	≤30	3 (0.55)	544 (99.45)	Reference			
	31-45	2 (0.42)	474 (99.58)	0.77	0.13	4.60	0.770
	>45	4 (1.43)	276 (98.57)	2.63	0.58	11.82	0.208
	Gender						
	Male	2 (0.27)	730 (99.73)	Reference			
	Female	7 (1.23)	564 (98.77)	4.53	0.94	21.89	0.060
	Dose of HCQ[#] (mg)						
	≤400	2 (0.5)	424 (99.5)	Reference			
	800	7 (0.8)	854 (99.2)	1.74	0.36	8.40	0.492
Any specified[*] adverse events	Age (yr)						
	≤30	89 (16.3)	458 (83.7)	Reference			
	31-45	71 (14.9)	405 (85.1)	0.90	0.64	1.27	0.552
	>45	32 (11.4)	248 (88.6)	0.66	0.43	1.02	0.064
	Gender						
	Male	72 (9.8)	660 (90.2)	Reference			
	Female	120 (21)	451 (79)	2.44	1.78	3.34	<0.001
	Dose of HCQ[#] (mg)						
	≤400	50 (11.7)	376 (88.3)	Reference			
	800	139 (16.1)	722 (83.9)	1.45	1.02	2.05	0.036

[*]Any gastrointestinal symptoms (nausea, vomiting, abdominal pain), hypoglycaemia, hypersensitivity, photosensitivity and cardiovascular effects; [#]Dose of HCQ available for only 1287 patients. HCQ, hydroxychloroquine; OR, odds ratio; CI, confidence interval

Adverse events by gender: In the univariate analysis, compared to males, females reported over twice the number of GI symptoms (OR 2.24, 95% CI 1.61-3.11). Similarly, compared to males, females reported significantly more hypoglycaemia (OR 4.77, 95% CI 1.33-17.19) and hypersensitivity (OR 6.51, 95% CI 1.42-29.81). Other AEs such as photosensitivity and CV AEs were not different by gender. Overall, occurrence of any of the specified AEs was higher in females than in males (OR 2.44, 95% CI 1.78-3.34) (Table II).

In the multivariate logistic regression analysis, GI AEs were more in females (OR 2.19, 95% CI 1.57-3.08) and in the younger age group compared to those in the older groups but was not significant. Female gender was an independent predictor for specified AEs (OR 2.46, 95% CI 1.78-3.38) (Table III).

Adverse events by dose of HCQ: Participants who took a total dose on day one of 800 mg of HCQ compared to lower doses did not report increased rates of AEs such as hypoglycaemia, hypersensitivity, photosensitivity or CV AEs but reported higher GI AEs (OR 1.45, 95% CI 1.02-2.05) (Table II). In the multivariate analysis, only GI AEs was significantly higher in the group taking total dose of 800 mg (OR 1.56, 95% CI 1.07-2.26) (Table III).

Discussion

In this cross-sectional study among HCWs in hospitals with COVID-19 patients, the population was predominantly young with a mean age of 35 yr. Chronic comorbidities such as diabetes, hypertension or any CV disease were low (9.2%), as expected in this type of population distribution.

Overall, 20 per cent reported one AE and the most common was related to the GI system (13.2%), more in the younger age group, among females, and in those getting total dose of 800 mg of HCQ on day one. Some patients needed treatment (1.5%) for AEs, but none of them were serious enough to require hospitalization. For indications such as lupus nephritis, RA, systemic lupus erythematosus (SLE) and others, HCQ has been reported to cause GI AEs such as nausea, vomiting, cramps or diarrhoea on the first few days of treatment.

Table III. Multivariate analysis of adverse events by age, gender and dose of hydroxychloroquine on day one

Adverse events	Risk factor	OR	95% CI		*P*
			Lower	Upper	
Any gastrointestinal	Age (yr)				
	≤30	Reference			
	31-45	1.01	0.70	1.44	0.976
	>45	0.62	0.38	1.00	0.051
	Gender				
	Male	Reference			
	Female	2.19	1.57	3.08	<0.001
	Dose (mg)				
	≤400	Reference			
	800	1.56	1.07	2.26	0.021
Any specified* adverse events	Gender				
	Male	Reference			
	Female	2.46	1.78	3.38	<0.001
	Dose				
	≤400	Reference			
	800	1.41	1.00	2.01	0.053

*Any gastrointestinal symptoms (nausea, vomiting, abdominal pain), hypoglycaemia, hypersensitivity, photosensitivity and cardiovascular effects

Most events are self-limiting, dose dependent and occur with a loading dose of 800 mg[8].

A small number of participants (1.1%) reported the possibility of hypoglycaemia based on symptoms such as weakness, fatigue, hunger and feeling better after taking sugar, food or chocolate. The symptoms were not severe or serious enough to discontinue HCQ. Hypoglycaemia is reported in diabetic patients with short-term use of HCQ[9]. In our study, participants with diabetes did not report significantly higher rates of symptoms suggestive of hypoglycaemia compared to those without diabetes (3.5 vs. 1.0%, $P = 0.064$).

CV AEs such as palpitation and chest tightness were reported in 0.7 per cent. None were severe or serious to discontinue treatment. ECG was not taken. Among our participants, 0.6 per cent reported known CV disease and 6.3 per cent had hypertension. Baseline ECG was done by 12 per cent. A combination of HCQ and azithromycin was taken by 0.8 per cent. However, the patients taking azithromycin (0.84%) did not have a history of CV disease nor did they report any CV events. Those with CV disease or hypertension did not report higher incidence of CV AE.

It is known that HCQ causes QTc prolongation and risk is exacerbated by the use of other QTc prolonging medications. There are studies with CQ in healthy volunteers, but most studies with HCQ are limited to case reports of chronic use[10,11]. The risk of CV events has also been addressed in a meta-analysis[12]. The use of HCQ in patients with lupus nephritis, RA and SLE was associated with significant protection against occurrence of CV disease in patients with rheumatic disorder (OR 0.041, 95% CI 0.26-0.69)[12].

Dermatologic AEs involving skin, hair or nails have been reported in the literature though the majority occurred after treating auto-immune conditions with cumulative dosages. While photosensitivity is a less commonly seen reaction with HCQ, it is reported at a lower mean cumulative dose of 150 g as compared to more commonly seen drug rash, seen with nearly three times the dose (mean dose of 530 gm)[13]. In our study, 12 (0.9%) and four (0.5%) participants reported hypersensitivity and photosensitivity, respectively. None were severe enough to discontinue HCQ. Furthermore, those taking a total dose of 800 mg compared to 400 mg on day one did not report higher rates of AEs such as hypoglycaemia, CV events,

photosensitivity or hypersensitivity, except for higher rates of GI symptoms (nausea, vomiting or abdominal pain) (OR 1.58, 95% CI 1.09-2.29).

There is considerable experience with the use of HCQ for different indications. Dosage for HCQ varies as per the treatment indication; for uncomplicated malaria, it is 800 mg followed by 400 mg at 6, 24 and 48 h (total dose 2000 mg); for SLE, it is 200-400 mg single or divided dose daily; for RA, it is 400-600 mg and the usual maintenance dose is 200-400 mg[14].

The study had some limitations. The participants did not represent all HCWs taking prophylaxis for COVID-19, since convenience sampling was the method used. However, the ICMR RUMCs are located in different regions of country and include both government and private institutions. All HCWs including doctors, nurses and ancillary staff were approached to participate in the study, thus attempting to include a broad representation. Another limitation was that participants filled the form by recalling symptoms. Since the form was filled during a short time span. The description of AEs was not asked to the participant. Hypoglycaemia and CV AEs were not investigated with blood sugar estimation or ECG. Participants were contacted telephonically after they filled the forms to verify the reported AEs. Some AEs such as headache and sleeplessness were grouped as others.

In this study, among HCWs working in hospitals with COVID-19 patients, it was found that majority of the participants took HCQ for prophylaxis of COVID-19. Overall rates of AE reported by these HCWs were low; none were serious; were mainly related to the GI system; were seen more commonly in the younger population and among females.

***Acknowledgment*:** Authors acknowledge Prof. (Dr) Balram Bhargava, Secretary, Department of Health Research, Ministry of Health and Family Welfare Government of India, and Director-General, Indian Council of Medical Research (ICMR), New Delhi, for his support. Dr Vijay Kumar, Head of BMS Division; TAG members – Dr V.P. Kamboj (Chairperson), Drs Y.K. Gupta and Subir Maullick for their valuable suggestions and guidance and Ms Priyanka Tadkase, Ms Aishwarya Bhoir for secretarial assistance.

***Financial support & sponsorship*:** This study was conducted by ICMR RUMCs which have been established in 2019 with a grant from the ICMR. No additional financial support was provided to the centres.

***Conflicts of Interest*:** None.

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