International Journal of Community Medicine and Public Health
Jha A et al. Int J Community Med Public Health. 2021 Dec;8(12):5805-5809
http://www.ijcmph.com
pISSN2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20214569

Original Research Article

Hydroxychloroquine: does prophylaxis work?

Atul Jha*, Manish Bhartiya, Vijay R. Kumar, Vimal Upreti, Parag Deshmukh, Mayank Dudani, Arjun Chandru, Dharambir Singh

151 Base Hospital, Guwahati, Assam, India

Received: 31 August 2021
Accepted: 16 October 2021

***Correspondence:**
Dr. Atul Jha,
E-mail: docatuljha@gmail.com

ABSTRACT

Background: Healthcare workers are front line workers in management of SARS-CoV-2 pandemic. The higher risk of acquiring the infection due to increased contact and exposures has prompted multiple risk mitigation strategies. To assess the role of hydroxychloroquine pre-exposure prophylaxis in prevention of SARS-CoV-2 infection amongst HCWs.
Methods: This retrospective cohort study assessed the effect of HCQS prophylaxis amongst HCWs in a tertiary care hospital in the north-eastern part of India. All HCWs, involved in management of SARS-CoV-2 were enrolled. The subjects were retrospectively divided in two groups on HCQ prophylaxis. Group I (51.8%, n=116) taking HCQ prophylaxis and group II (48.2%, n=108) not taking the prophylaxis. The demographic characteristics, use of PPE, HCQ prophylaxis and side effect profile were noted.
Results: Of the whole cohort, 22.8% (n=51) subjects tested positive. In group I (n=116), 24 subjects (20.7%) tested positive, whereas in Group II (n=108), 27 subjects (25.0%) tested positive. Further analysis of the incidence of SARS-CoV-2 infection amongst the two groups demonstrated that the although the rate of infection was lower (20.7% vs 25%) in Group I as compared to group II [X^2 (1, N=224)=0.371, p=0.5] but it was statistically insignificant.
Conclusions: Our study involving HCWs, does not show a statistically significant reduction in the incidence of infection with pre-exposure prophylaxis. Based on our findings and published literature, a prophylaxis of HCQS against the SARS-CoV-2 infection cannot be recommended.

Keywords: SARS-CoV-2, Hydroxychloroquine, Prophylaxis

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported from China in 2019, is a rapidly emerging virus causing coronavirus disease 2019 (COVID-19) pandemic globally and affecting about 6.8 million people in India and resulting in 100 thousand deaths.[1,2] Healthcare workers (HCW) are the frontline warriors in its management and face the greatest risk of occupational exposure to the deadly virus. The factors responsible for increased risk of contracting the deadly virus include multiple and repetitive exposures to higher inoculum of the virus. A higher than average morbidity and mortality due to COVID-19 has been reported in healthcare workers, prompting endorsements of different strategies to mitigate the risk of infection in this subset of people which include use of appropriate personal protective equipment (PPE), face shields and adequate hand hygiene, frequent disinfection of the workplace and use of negative pressure air filters in the Intensive Care Units (ICUs).[3,4] Though most of these measures are routinely available, accidental exposure to the virus is unavoidable.

Hydroxy chloroquine sulphate (HCQ) an easily available and utilised drug in India which has been shown to reduce in vitro viral load in various studies.[5] Evidence is split

with respect to the usefulness of HCQ in treatment of COVID-19 with some studies showing benefit whereas others show limited gain.[6,7] A role of post-exposure prophylaxis has also been explored but the data which address this question are still emerging.[8] In March 2020, Indian council of medical research (ICMR) recommended the use of HCQ by HCW as a pre-exposure prophylaxis to prevent COVID infection.[9]

METHODS

We conducted a retrospective cohort study to assess the role of HCQ prophylaxis in mitigating the risk of COVID infection in healthcare workers involved in care of sick COVID patients.

Study design

The study was a retrospective observational study carried out at a tertiary care centre involved in active management of COVID-19 patients in North-East India in the months of Jul to Sep 2020.

Subjects and methods

Management of human resources

The hospital has made multiple COVID designated teams which were involved in the care of COVID-19 infected patients. Each team consisted of doctors, nursing and paramedical staff. After two weeks' 'tour of duty' in COVID-19 wards, they were placed in 14 days of quarantine and tested for COVID-19 infection at the end of the quarantine. Any HCW who developed symptoms during the duty was isolated and tested for COVID-19 infection.

Pre-induction briefing

Prior to induction, a lecture-demonstration was held for all members of the COVID team. The main thrust of the lecture-demonstration was the safety of the HCW and dealt with topics like appropriate care while donning and doffing the personal protective equipment (PPE), importance of hand-washing etc. During the same briefing, a lecture was held on HCQ prophylaxis pertaining to the current evidence on HCQ, its dosage (400 mg twice on day 1 and then 400 mg weekly) as recommended in literature and role in pre-exposure prophylaxis and the possible side effects. The decision to take HCQ was entirely with the individual.

Testing for COVID-19 infection

Nasopharyngeal samples using swabs were collected by a trained laboratory technician as per recommended protocol and tested by Real Time Polymerase Chain Reaction (RT-PCR) (qTOWER3 G touch Real-Time PCR Thermal Cycler, Analytik Jena, Germany)

Sample size calculation

It was assumed that at least 50% of the study subjects would be on HCQ prophylaxis and a 1:1 ratio of distribution was planned for the two groups. The disease has been reported to have a high secondary attack rate so an infection incidence of 20 percent was estimated in the cohorts.[11] We postulated that HCQ would substantially decrease the infection (an risk reduction from 20% to 5%).A sample of 154 subjects were required in order to detect a relative risk of 0.25 (80% power and α error of 0.05

Study subjects

All HCWs, who were involved in management of patients of Covid-19 infection from 01 Jun to 30 August 2020, were enrolled for the study. HCWs who had started HCQS on or after the start of the duty were excluded from the study. The demographic characteristics (age, sex, co-morbidities), duty schedule, duration of duty hours, use of PPE, whether taking HCQ prophylaxis and side effect profile (in subjects taking HCQ) were noted. As all subjects had undergone RT-PCR testing at the end of their quarantine, their test result were also noted. Written and informed consent was taken from all the subjects prior to inclusion in the study.The subjects were retrospectively divided in two groups viz Group I (taking HCQ in the dosage of 400 mg twice on Day 1 and then 400 mg weekly) and Group II (not taking HCQS).

Statistical analysis

Statistical analysis was performed using SPSS-22 by AJ, AC and DS. Means were compared using t-test and contingency tables were analysed using Chi Square test, $p<0.05$ was considered to be significant.

RESULTS

We did a retrospective cohort study in a tertiary care centre in North-East India managing COVID-19 patients (Figure 1). A total of 235 HCW were enrolled for the study. HCWs who had started HCQS either on (N=3) or after the first day of the duty (N=3) or in incorrect dosage (N=5) were excluded and 224 HCWs who were involved in the patient care were enrolled for the study. The study participants were grouped into two groups depending upon their HCQ use with group I (51.8%, N=116) taking HCQ prophylaxis and group II (48.2%, N=108) not taking HCQ. The basic demographic profile is shown in (Table 1).

On testing of the both the groups (N=224), 22.8% (N=51) subjects tested positive for COVID-19 infection during the period of active duty and quarantine with symptomatic infection in 5.9% (3/51). In group I (N=116), 24 subjects (20.7%) tested positive for COVID-19 infection, whereas in Group II (n=108), 27subjects (25.0%) tested positive. Further analysis of the incidence

of COVID-19 infection amongst the two groups demonstrated that the although the rate of infection was lower (20.7% vs. 25%) in group I as compared to group II [X^2(1, N=224)=0.371, p=0.5] but it was statistically insignificant (Figure 2). A univariate analysis of both the groups with respect to risk of infection showed a lesser risk of acquiring infection while on HCQ (Relative risk=0.82, 95% CI = 0.51 to 1.34, p=0.44) with relative risk reduction of 17.2% and absolute risk reduction of 4.3% translating into a NNT of 23.2.

Table 1: Basic characteristics.

Characteristics	Total (n=224)	Group I (n=116)	Group II (n=108)	P value
Mean Age (yrs)	33.28±4.7	34.2±3.7	32.3±4.3	0.0005
Females (%)	46 (20.5)	21 (18.1)	25 (23.1)	0.34
Smokers (%)	16 (7.1)	8 (6.9)	8 (7.4)	0.88
Diabetes Mellitus (%)	3 (1.3)	2 (1.7)	1 (0.9)	0.62
Hypertension (%)	3 (1.3)	1 (0.9)	2 (1.8)	0.55
Obstructive airway disease (%)	5 (2.2)	2 (1.7)	3 (2.7)	0.62
Occupation – Doctor (%)	22 (9.8)	12 (10.3)	10 (9.3)	0.83
Occupation – Nurse (%)	46 (20.5)	21 (18.1)	25 (23.1)	0.35
Occupation – Paramedic (%)	87 (38.8)	45 (38.8)	42 (38.9)	0.98
Occupation – Others (%)	69 (30.8)	34 (29.3)	35 (32.4)	0.61

Table 2: Studies on HCQS prophylaxis.

References	Total		On HCQS Prophylaxis		Not on HCQS prophylaxis		ARR	RRR	NNT
	Total	Infected	Total	Infected	Total	Infected			
Boulware et al	821	107	414	49	407	58	2.4	16.9	41
Abella et al	125	8	64	4	61	4	0.3	4.6	325
Vijay et al	224	51	116	24	108	27	2.4	16.1	40
Total	1170	166	594	77	576	89	2.4	16.1	40

ARR (Absolute risk reduction), RRR (Relative risk reduction), NNT (Number needed to treat)

Table 3: Cumulative data on HCQS prophylaxis.

Parameters	RT-PCR Positive for SARS-CoV-2 (%)	RT-PCR Negative for SARS-CoV-2 (%)
On HCQS prophylaxis (N=594)	77 (12.9)	517 (87.1)
Not on HCQS prophylaxis (N=576)	89 (15.5)	487 (84.5)

X^2(1, N=1170)=1.290, p=0.25

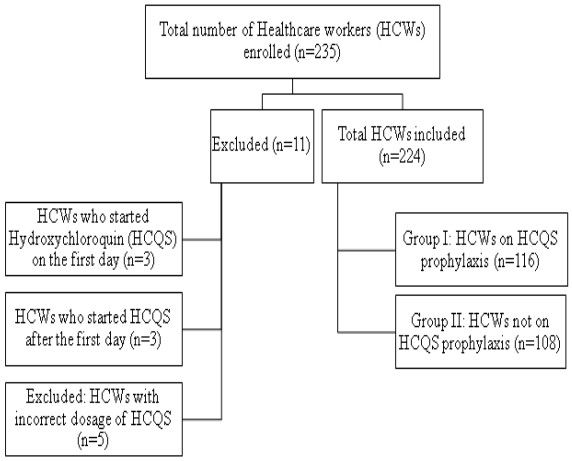

Figure 1: Study protocol and enrolment.

Side effects were reported in 07subjects (6.1 %) in group I, which were mild in nature. The most common adverse effects were diarrhoea (N=4, 3.4%), headache (N =2, 1.7%), fatigue (N =3, 2.6%), diaphoresis (N =3, 2.6%) and skin rash (N =01, 0.8%).

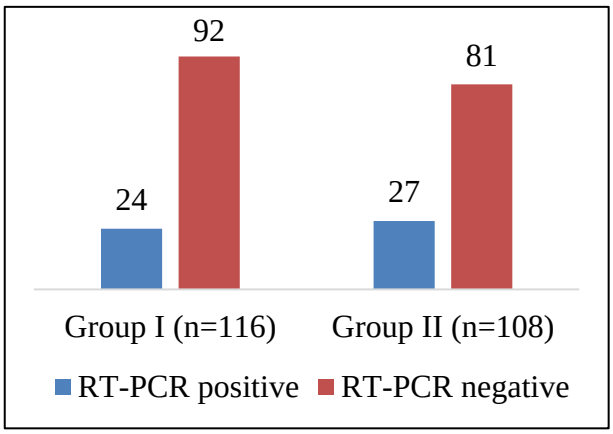

Figure 2: RT-PCR for SARS-Cov-2 positivity amongst the two groups [X^2(1, N=224)= 0.371, p=0.5).

No subject had to stop HCQ due to the side effects. No participants in the study reported grade 2, 3 or 4 adverse events on the common toxicity criteria for adverse event scale.[12] All positive cases were either asymptomatic or had a mild disease after which they fully recovered.

DISCUSSION

We studied retrospectively the role of HCQS as a pre-exposure prophylaxis for prevention of SARS-CoV-2 amongst HCWs who were actively involved in management of patients of SARS-CoV-2 infection. We analysed the data of 224 HCWs involved in management of SARS-Cov-2 infected patients with 51.8% subjects on HCQS prophylaxis. HCQS did not prevent illness compatible with SARS-Cov-2 infection as compared to no prophylaxis. There have been only two trials published which have evaluated the role of HCQS with one trial assessing the role of post exposure prophylaxis [8] and the other recently published assessing the role the drug as a pre-exposure prophylaxis.[13] Our findings are similar to both the trials as both the strategies have not been able to prevent the infection in HCW as compared to no prophylaxis or placebo.

Boulware et al were the first to study the role of HCQS as a post exposure prophylaxis in self-identified significant exposure in participants.[8] The self-reporting and subsequent initiation of HCQS (upto 4 days as per therapeutic protocol) resulted in most prophylaxis being initiated on the third or fourth day. A limitation of the study was the delay in starting the therapy and was postulated to be a reason of failure of the prophylaxis. Abella et al (and our study group) formulated the study protocol using a pre-exposure prophylaxis.[13] Where Abella et al used a randomised control trial, we analysed the data retrospectively amongst participants assuming prophylaxis being taken by 50% of participants. It was expected before the commencement of the study that a pre-exposure prophylaxis would bypass the limitation of the study by Boulware as the drug availability would be optimal at the time of exposure. Two situations that would have led to a sub-optimal plasma drug levels at the time of exposure were; a different dosage than recommended (400 mg twice on Day 1 and then 400 mg weekly) and starting the prophylaxis on or after the first day of duty. Hence all patients who had a different dosage or had been ‘late’ in the initiation of prophylaxis were excluded.

The results confounded us because, when seen along with the studies by Abella et al and Boulware et al as shown in (Table 2), all the three studies show a very limited application of HCQS as a prophylaxis against COVID-19 with either a pre or post exposure strategy.[13] However, individually it also is clear that in all three studies the rate of infection was lesser, albeit insignificantly, in the treatment arm. Even when a cumulative analysis is done for all three studies, the results, although statistically insignificant, do indicate a lesser rate of infection (Table 3). Probably a larger study may give us a better clue.

Limitations

Our study is limited by an observational and retrospective nature and thus all confounding factors may not have been excluded. Another limitation of our study may be a higher rate of HCWs infection which may be due to a multitude of reasons including a higher exposure of patients or poor compliance to PPE. As the exposure was same in both groups, it just goes on to corroborate the fact that HCQS did not help in avoiding the infection.

CONCLUSION

Current study involving healthcare workers, who have been exposed to SARS-CoV-2, pre-exposure prophylaxis does not show a statistically significant reduction in the incidence of infection. When reviewed with the published literature, this finding is corroborated. Based on our findings and published literature, a prophylaxis of HCQS against the SARS-CoV-2 infection cannot be recommended as this would lead to a false sense of security amongst health care workers.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Zhu H, Wei L, Niu P. The novel coronavirus outbreak in Wuhan, China. Global Health Res Policy. 2020; 5(6):1-3.
2. COVID-19 information. Available at: https://www.mohfw.gov.in. Accessed on 10 October 2020.
3. Nguyen LH, Drew DA, Graham MS. Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. Lancet. 2020;5:e475-83.
4. Mehta Y, Chaudhry D, Abraham OC. Critical Care for COVID-19 Affected Patients: Position Statement of the Indian Society of Critical Care Medicine. Indian J Crit Care Med. 2020;24 (4):222-41.
5. Yao X, Ye F, Zhang M. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Inf Dis. 2020;71:732-9.
6. Gautret P, Lagier JC, Parola P. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56:01-06.
7. Sarma P, Kaur H, Kumar H, Mahendru D, Avti P, Bhattacharyya A. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: A systematic review and meta-analysis. J Med Virol. 2020;1-10.

8. Boulware DR, Pullen MF, Bangdiwala AS et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med. 2020;383(6):517-25.
9. Recommendation on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. Available at:https://icmr.nic.in/sites/default/files/upload_documents/HCQ_Recommendation_22March_final_MM_V2.pdf. Accessed on 22 May 2020.
10. Interim guidelines for collecting, handling, and testing clinical specimens from persons for coronavirus disease 2019 (COVID-19). Available at: https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html. Accessed on 15 June 2020
11. Rocklöv J, Sjödin H, Wilder-Smith A. COVID-19 outbreak on the Diamond Princess cruise ship: estimating the epidemic potential and effectiveness of public health countermeasures. J Travel Med. 2020; 27(3):1-7.
12. Common Toxicity criteria. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed on 15 Jun 2020.
13. Abella B, Jolkovsky EL, Biney BT. 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. 2020;24:45-9.

Cite this article as: Jha A, Bhartiya M, Kumar VR, Upreti V, Deshmukh P, Dudani M, et al. Hydroxychloroquine: does prophylaxis work?. Int J Community Med Public Health 2021;8:5805-9.