



EFFICACY OF HYDROXYCHLOROQUINE AS PRIMARY PREVENTION IN HEALTHCARE WORKERS WORKING IN COVID-19 HOSPITAL IN NAVI MUMBAI

Medicine

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ABSTRACT

Introduction and Objectives: Hydroxychloroquine is an antimalarial drug being tested as a potential treatment for the novel coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Early data on use of HCQ for COVID treatment suggests anti-viral activity and immunomodulatory properties for reducing inflammation associated with COVID-19. Given the lack of data regarding use of HCQ for COVID-19 prevention in healthy participants in midst of pandemic crisis, this study proposes an expedited feasibility study focusing on safety and early efficacy in high risk population of healthcare workers working in COVID-19 hospitals. The objectives are to demonstrate the efficacy of low-dose hydroxychloroquine as primary prevention in healthcare workers working in COVID-19 hospitals. Additionally, to assess the severity of SARS COV2 disease and side effects in healthcare workers while on primary prophylaxis.

Methods: A prospective observational study of 987 healthcare workers (HCW) working at Dr. D.Y.Patil Hospital, Navi Mumbai (the largest COVID-19 centre in Navi Mumbai) were studied for 12 weeks after initiating the prophylactic course of Hydroxychloroquine as mandated by MoHFW, India. Demographic data, comorbidities were noted along with additional imperative questions and follow ups were maintained over telephonic/personal communication. Weekly monitoring for drug related adverse events and development of COVID-19 infection was done. SARS-CoV-2 assay and biomarker testing was performed for those who developed symptoms of fever, cough, sore throat, breathlessness. Statistical analysis was done in frequencies and percentages. Variables that had biologically plausible association with the outcome and were relevant for planning strategies for the prevention of SARS-CoV-2 infection in HCWs were entered into a standard logistic regression model.

Results: A total of 987 (671 males and 316 females) healthcare workers were studied. 66% were young (18 to 30 years), 28.4% were middle aged (31 to 45 years), 4.5% were aged between 46 to 60 years and 0.09% were elderly (above 60 years). As per guidelines on prophylactic course of Hydroxychloroquine directed by MoHFW, out of 987 participants, 809 (81.9%) HCWs completed the course, 133 (13.4%) HCWs were defaulters and 45 (4.6%) HCWs didn't start the course. 40 (4%) HCWs tested SARS COV2 positive. Out of these 40 HCWs, 62% were males, 92% were aged between 18 to 30 years, 57% were nurses, 42.5% were working in ICU and 17.5% were working in non-COVID areas of the hospital. 95% of the 40 participants who tested SARS COV2 positive belonged to mild category with no mortalities/toxicities reported. 27.5% were HCQ defaulters, 35% didn't start the prophylaxis and 17.5% were midway the course while testing positive for SARS COV2. Overall, 1.85% HCWs on HCQ prophylaxis tested positive suggesting well preventive effects of the drug.

Conclusion: While results of clinical trials for HCQ prophylaxis are awaited, this study provides pivotal information for policymakers to protect HCWs at the forefront of COVID-19 response using HCQ.

KEYWORDS

INTRODUCTION:

In less than 6months, the novel coronavirus disease (COVID-19) pandemic has spread to over 200 countries. The causative agent of this disease- severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was noted to spread efficiently through respiratory droplets and contact routes^{1,2}. While common presenting symptoms are fever, fatigue, dry cough, myalgia and dyspnoea, a few patients have reported having diarrhoea, nausea, vomiting and new-onset anosmia or ageusia. A considerable proportion of the SARS- CoV-2-infected individuals (around 80%) did not have any noticeable symptoms and yet were able to transmit the infection². Such unique transmission potentials of SARS-CoV-2 and lack of definitive antiviral therapy were the reasons behind its wide-scale spread. Evidence indicates that healthcare workers (HCWs) are particularly at risk of acquiring SARS-CoV-2 infection, due to repeated occupational exposure.³ Prophylaxis in the present context refers to the use of a short-term therapy to prevent acquisition of SARS-CoV-2 infection. Currently, there are no approved vaccines against SARS-CoV-2, which makes the alternative of using chemotherapeutic agents an attractive proposition. However, no antiviral medicines proved efficacious during the previous coronavirus outbreaks (SARS 2003; Middle East respiratory syndrome coronavirus 2012) and therefore, did not leave the therapeutic community with any viable options during the present COVID-19 pandemic^{4,5}. Hydroxychloroquine is an antimalarial drug being tested as a potential treatment for the novel coronavirus disease

2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)⁶. Although the efficacy of hydroxychloroquine for COVID-19 remains uncertain, it may serve as a potential prophylactic agent especially in those at high risk, such as healthcare workers, household contacts of infected patients, and the immunocompromised⁷. Early data on use of HCQ for COVID treatment suggests anti-viral activity and immunomodulatory properties for reducing inflammation associated with COVID-19^{8,9}. Given the lack of data regarding use of HCQ for COVID-19 prevention in healthy participants in midst of pandemic crisis, this study proposes an expedited feasibility study focusing on safety and early efficacy in high risk population of healthcare workers working in COVID-19 hospitals.

AIMS & OBJECTIVES:

1. To demonstrate the efficacy of low-dose hydroxychloroquine as primary prevention in healthcare workers working in COVID-19 hospitals.
2. To assess disease burden, side effects in healthcare workers while on primary prophylaxis.

MATERIALS AND METHODS:

Study Design: This was a prospective observational study based on implementation of ICMR and MOHFW, India Guidelines to administer Tab. Hydroxychloroquine(HCQ) to healthcare

workers(HCW) of Covid-19 Hospitals at the dose of 400mg twice a day on Day 1 followed by 400mg once a week for 7 weeks¹⁰. The study was conducted after securing Institutional Ethics Committee (IEC) approval on 987 participants after excluding the ones not eligible over 12 weeks between March 30th to June 20th 2020 to at Dr. D.Y.Patil Hospital, Nerul, Navi Mumbai. Participants demographic data, comorbidities were studied using a questionnaire. During the 12 week study period, participants were weekly monitored for drug related adverse events and assessed for development of COVID-19. SARS-CoV-2 assay and biomarker testing was performed for those who developed symptoms of fever, cough, sore throat, breathlessness. Safety outcomes were assessed by the number of adverse events (AEs) and their severity; and early efficacy as the number of participants who tested positive at the end of the 7-week period.

STATISTICAL ANALYSIS:

The questionnaire and telephonic/personal interview was computerized. The association of key risk factors with SARS-CoV-2 infection was examined by comparing distributions of cases and controls across different exposures. Categorical variables are shown as frequencies and percentages. Variables that had biologically plausible association with the outcome and were relevant for planning strategies for the prevention of SARS-CoV-2 infection in HCWs were entered into a standard logistic regression model. Comparisons were made using unpaired t-test and Chi-Square test. A p value of less than 0.05 was considered significant.

INCLUSION CRITERIA:

- Adults aged 18 years and above,
- Able to sign own informed consent form,
- Considered high-risk healthcare care providers in a hospital setting with active exposure to COVID-19 infection.

High-risk HCW's are defined as those working during the study duration in the Emergency Department, Fever OPD, Isolation Ward, Positive Ward and in Intensive Care Setting, for the purpose of this study.

EXCLUSION CRITERIA:

- Inability to tolerate an oral medication or known allergy or contraindication to chloroquine or hydroxychloroquine
- Pregnancy or breast-feeding
- Immunocompromised status
- Confirmed COVID-19 infection prior to participating in the study

RESULTS:

A total of 987 (671 males and 316 females) healthcare workers working at various COVID areas of the hospital were considered for the study. It was noted that majority of the hospital working population were below the age of 45 years. 66% (n= 652) of healthcare workers were young (18 to 30 years), 28.4% (n= 281) were middle aged (31 to 45 years), 4.5% (n=45) were aged between 46 to 60 years and 0.09% (n=9) were elderly (above 60 years).

As per guidelines on prophylactic course of Hydroxychloroquine directed by MoHFW, out of 987 participants, 809 (81.9%) HCWs completed the course, 133 (13.4%) HCWs were defaulters and 45 (4.6%) HCWs didn't start the course.

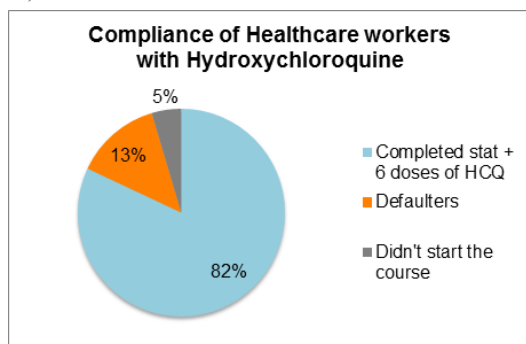


Figure 1. Healthcare workers compliance with Hydroxychloroquine

The reasons for defaulting were: calls not answered, wrong numbers, negligence, side effects such as gastritis, nausea, vomiting, diarrhea. Out of 987 participants, a very minor population of 40 (4%) HCWs

developed symptoms and were tested SARS COV2 positive. In these 40 HCWs, males were at a higher risk as 62% (n=25) was males and 37% (n=15) were females. A higher incidence of 92% (n= 37) was seen in young adults aged between 18 to 30 years, 5% (n=2) between the age of 31 to 45 years and 2.5% (n=1) in the age of 46 to 60 years. No significant correlation of BMI to the rate of infectivity was noted.

Table 1. Occupation of HCW tested SARS COV-2 positive

Healthcare workers	SARS COV2 positive (out of 40)	%
Doctors	6	15%
Nurses	23	57.50%
Housekeeping staff	7	17.50%
Administration	4	10%

A significantly higher risk of infection was noted in 57.5% (n=23) nurses. The highest risk of infection was observed in HCWs working in COVID ICUs as 42.5% (n=17) tested positive. 5% (n=2) HCWs working in Emergency Room (ER), 2.5 (n=1) HCWs working in Fever OPD, 15% (n=6) HCWs working in COVID suspect ward, 12.5% (n=5) HCWs working in COVID positive ward, 17.5% (n=7) working in various non- COVID areas and 5% (n=2) in Screening area were diagnosed with SARS COV2 infection.

Table 2. Association of Hospital area of work with Healthcare workers testing SARS COV2 positive

Area of Work	SARS COV2 positive (out of 40)	%
Intensive Care Unit (ICU)	17	42.50%
Emergency Room (ER)	2	5%
Fever OPD	1	2.50%
COVID-19 Suspect Ward	6	15%
COVID-19 Positive Ward	5	12.50%
Non-COVID Hospital Area	7	17.50%
Screening Area	2	2%

The disease mainly manifested as mild category with 95% (n=38) and 5% (n=2) as moderate category and none in severe category. No mortalities were seen at the end of the treatment.

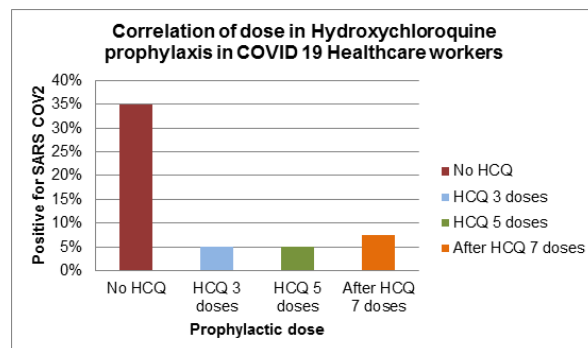


Figure 2. Correlation of Prophylactic dose of Hydroxychloroquine in COVID-19 positive Healthcare workers.

Out of the 40 HCWs who were diagnosed with SARS COV-2, 11 (27.5%) were defaulters, 14 (35%) didn't start prophylaxis, 7 (17.5%) were midway in the course of prophylaxis and 8 (20%) had completed the course. It has been observed that HCWs who have taken or are in the course of prophylactic dose of HCQ developed mainly mild SARS COV-2 as compared to the ones who have defaulted or not initiated the course at all. It is noteworthy that only 1.85% (n=15) out of 809 healthcare workers who completed or were in the course of completion of prophylactic dose of HCQ developed SARS COV-2.

DISCUSSION:

There are several studies and ongoing trials on the use of hydroxychloroquine not only in hospitalized patients of Covid-19 but also as a post-exposure prophylactic drug^{11,12}. However, there is lack of data on its potential benefit for prevention of Covid-19 among healthcare workers (HCWs). Based on the invitro results, Yao et al first put forward the optimal dosing regimen of hydroxychloroquine and also demonstrated that hydroxychloroquine was more potent than chloroquine in inhibiting SARS-CoV-2 infection¹³. Based on available evidence, the National Task force for Covid-19 reviewed the use of hydroxychloroquine and Indian council of medical research (ICMR)

approved its use as a prophylactic agent in asymptomatic HCWs treating suspected or confirmed cases. There is limited published literature available on prophylactic use of HCQ among healthcare workers. Few HCQ chemoprophylaxis trials are underway in the US (NCT04318444) and Mexico (NCT04318015).

Our study comprised a large sample size of 987 healthcare-workers of which 68% were males and 32% were female participants. The noteworthy finding of our study was lesser incidence of HCWs getting infected with SARS COV2 virus and better outcomes of those on the prophylaxis. 81.9% completed the course. 4% of the participants turned out to be positive for SARS-CoV-2 infection. Of those who were positive, higher incidence was noted in: male HCWs (62%), nursing staff (57%&, house-keeping staff (17.5%), working in Intensive care units (ICU) (42.5%), non-covid hospital area (17.5%). In addition, they suffered from either mild disease (95%) or moderate illness (5%). There was no severe/critical case. No Hydroxychloroquine toxicities were noted. Those who tested positive were mainly the ones who did not start the prophylaxis (35%) or were defaulters (27%). It is also significant that the chances of developing SARS COV2 infection when not taking HCQ prophylaxis are significantly higher than during or on completion of the course.

A retrospective, cross-sectional study conducted using web-based questionnaire among healthcare workers involved in COVID-19-related services in various hospitals across India demonstrated that out of 166 responses considered, who were mostly doctors, a predominant male distribution (n=122; 73.5%) was noted with most participants belonging to the age group of 26–30 years (n=72; 43.4%). This was comparable to our study. However, 79.5% of them were not tested for COVID-19, while 34 (20.5%) participants tested negative¹⁴.

A cohort study by Bhattacharya et al among healthcare workers at a tertiary health care center had enrolled 106 participants, of whom 54 had taken HCQ and 52 had not taken HCQ. It was found that 7.4% of those taking HCQ developed Covid-19. On comparative analysis of incidence of Covid-19 infection between the two groups, it was seen that pre-exposure HCQ usage was associated with lesser likelihood of developing SARS-CoV-2 infection, compared to those who were not on it. This was found to be statistically significant¹⁵.

Another Case-Control study by Chatterjee et al in collaboration with ICMR Covid-19 research team where telephonic interview of HCWs (378 cases i.e. Covid-19 PCR positive and 373 controls i.e. Covid-19 PCR negative) was done. In their study too, most participants were males (58% in case and about 50% in control group). Majority individuals in both the groups were in the age range of 26-33 years and were mostly nurses. Univariate analysis conducted on distribution of cases and controls across exposures indicated the association of risk (P=0.087) of SARS-CoV-2 infection with the lack of HCQ prophylaxis. It was also noted that just the initiation of HCQ prophylaxis did not decrease the odds of acquiring SARS-CoV-2 infection among HCWs. However, the protective effect was evident after intake of four or more maintenance doses of HCQ. A significant reduction (>80%) in the odds of SARS-CoV-2 infection among HCWs was observed by multivariate analysis¹⁶.

Keeping in mind that newer therapies are still being tried and tested in treatment of SARS-CoV-2 infection and that vaccines are still in developing stages, our study aims to highlight the use of HCQ as an alternative, cost-friendly option for prophylaxis. Considering the higher risk healthcare workers possess of contracting the infection, HCQ can be recommended with due monitoring of any adverse effect. Further, more trials are warranted for definite clinical evidence.

REFERENCES:

1. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. *Lancet* 2020; 395 : 514-23
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020; 382 : 1199-207.
3. Nguyen LH, Drew DA, Joshi AD, Guo C-G, Ma W, Mehta RS, et al. Risk of COVID-19 among frontline healthcare workers and the general community: A prospective cohort study. *medRxiv* 2020. doi: <https://doi.org/10.1101/2020.04.29.20084111>.
4. Zhong NS, Zheng BJ, Li YM, Xie ZH, Chan KH, Li PH, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet* 2003; 362 : 1353-8.
5. Ramadan N, Shaib H. Middle East respiratory syndrome coronavirus (MERS-CoV): A review. *Germs* 2019; 9 : 35-42.
6. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020.
7. Al-Kofahi M, Jacobson P, Boulware DR, et al. Finding the dose for hydroxychloroquine prophylaxis for COVID-19; the desperate search for effectiveness [published online ahead of print, 2020 Apr 28]. *Clin Pharmacol Ther.* 2020;10.1002/cpt.1874. doi:10.1002/cpt.1874
8. Al-Kofahi M, Jacobson P, Boulware DR, et al. Finding the dose for hydroxychloroquine prophylaxis for COVID-19; the desperate search for effectiveness [published online ahead of print, 2020 Apr 28]. *Clin Pharmacol Ther.* 2020;10.1002/cpt.1874. doi:10.1002/cpt.1874
9. Shukla AM, Archibald LK, Wagle Shukla A, Mehta HJ, Cherabuddi K. Chloroquine and hydroxychloroquine in the context of COVID-19. *Drugs Context.* 2020;9:2020-4-5. Published 2020 Apr 28. doi:10.7573/dic.2020-4-5
10. National Task Force for COVID-19 in India. Recommendation for empiric use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection; 2020. Available from: <https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquineforSARSCoV2infection.pdf>, accessed on May 25, 2020.
11. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med.* 2020;382 (25):2411-18.
12. 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(6):517-25.
13. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. 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 Infect Dis.* 2020;71(15):732-739.
14. Nagaraja BS, Ramesh KN, Dhar D, Mondal MS, Dey T, Saha S, Khan MA, Rutul SD, Pratik K, Manjula J, Sangeeth TA, Singh V. HyPE study: hydroxychloroquine prophylaxis-related adverse events' analysis among healthcare workers during COVID-19 pandemic: a rising public health concern. *J Public Health (Oxf).* 2020 Jun 3:fdaa074. doi: 10.1093/pubmed/fdaa074.
15. Raja Bhattacharya, Sampurna Chowdhury, Rishav Mukherjee, Anita Nandi, Manish Kulshrestha, Rohini Ghosh, Souvik Saha. Pre exposure Hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers - a Retrospective cohort. *medRxiv* 2020.06.09.20116806
16. Chatterjee P, Anand T, Singh KJ, Rasaily R, Singh R, Das S, Singh H, Praharaj I, Gangakhedkar RR, Bhargava B, Panda S. Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19. *Indian J Med Res* 2020;151:459-67