A Preventive Study on Hydroxychloroquine Prophylaxis against COVID-19 in Health Care Workers at a Tertiary Care Center in North India

Sudhir Bhandari1, Govind Rankawat2,*, Shivam Priydarshi1, Nachiketa Vyas1, Ajeet Singh1, Raman Sharma1, Vishal Gupta1, Shrikant Sharma1, Nidhi Gupta3, Monisha Singhal3

INTRODUCTION

The year 2020 has witnessed one of the worst pandemics in the history of mankind caused by a novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2). The infection caused is known as Coronavirus disease 2019 (COVID-19). The clinical presentation of COVID-19 is varied, ranging from mild to moderate symptoms like high body temperature, headache, cough and sore throat, difficulty in breathing, body/muscle ache, rhinorrhea, vomiting and diarrhea and complex manifestations like pneumonia, acute respiratory distress syndrome, septic shock and/or multiple organ failure. SARS-CoV-2 emerged from Wuhan, a city of Hubei province of China, has swept across 216 countries infecting 7,941,791 people with 434,796 deaths globally while in India 343,091 people had been infected with 9900 deaths as of 16 June 2020. Until the present scenario there are no such treatments for COVID 19 but the scientific fraternities around the world are working round the clock in order to develop vaccine against the Coronavirus. But the situation at present is very disheartening as despite using personal protective equipment, health care workers have contracted COVID-19.

Hydroxychloroquine (HCQ), an analog of Chloroquine, has been widely used as an anti-malarial drug as it modifies the immune system by increasing the pH levels in the lysosomes, inhibiting the normal functioning of the organelle. The repurposed drug hydroxychloroquine was already been prescribed for treatment of autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis. Since HCQ possess antiviral properties and has shown immune-modulatory action, it has intrigued researchers and clinicians to use this Repurposed drug with COVID-19.
drug in COVID-19 patients. It has been effective against COVID-19 as it suppressed the replication of SARS-CoV-2 and its associated inflammatory process.\textsuperscript{8-11} This drug has been the primary choice against COVID-19 than chloroquine due to a milder adverse reaction profile and lesser drug to drug interactions.\textsuperscript{12} Moreover, HCQ has shown effectiveness against SARS-COV-2 within safe therapeutic range and still achieving 200–700 times higher concentration in the liver, spleen, kidney and lung as compared to the plasma.\textsuperscript{13-14} A recent study published in a reputed journal has forced us to rethink the use of these drugs in serious patients. Even the World Health Organization (WHO) has withdrawn this drug from its solidarity trials for COVID-19 worldwide. This investigation was an attempt to evaluate the effectiveness and safety profile of HCQ prescribed prophylactically among health workers in COVID-19 patients’ management. The present study was undertaken to evaluate the use of hydroxychloroquine (HCQ) in healthcare workers as a prophylactic therapy in combating the COVID-19 infection.

MATERIALS AND METHODS

Study design

Hydroxychloroquine was prescribed as a prophylactic therapy to all the health workers in India engaged in direct management of COVID-19, including the state of Rajasthan as per the advisory of National Taskforce for COVID-19 constituted by the Indian Council for Medical Research (ICMR), India; issued on 23 March 2020.\textsuperscript{15} HCQ prophylaxis was not given to patients who were known cases of hypersensitivity, retinopathy, glucose 6 phosphate dehydrogenase deficiency or had a history of cardiomyopathy and arrhythmias. In this study data of COVID-19 infection in health workers and its clinical manifestations were collected and analyzed. This observational, descriptive study also took into consideration the adverse drug reaction profile of HCQ among healthcare workers engaged in management of COVID-19 patients.

HCQ dosage

Following the protocol of ICMR advisory, all the health workers of SMS Medical College and attached hospitals, Jaipur, India engaged in management of COVID-19 patients were prescribed HCQ in a dose of 400 mg, to be taken twice a day on day 1, followed by 400 mg once weekly for next 7 weeks. Adverse drug reactions were monitored through self-reporting as recommended in pharmaco-vigilance program of India. Approximately 37,000 tablets were distributed among 6,000 health care workers by the hospital administration, unless there was any specific contraindication related to HCQ and information regarding consumption, adverse effects, hospitalization, contacted COVID-19 infection and lab testing for COVID-19 was maintained.

Informed Consent

Approval for this study from Institutional ethics’ committee was obtained and a duly informed consent was also taken from all subjects for their participation. The nasopharyngeal and oropharyngeal swabs of the suspected health workers was tested at Laboratory of Microbiology of the Institute using reverse–transcriptase polymerase chain reaction (RT – PCR) techniques following ICMR guidelines.

Outcomes of the study

Out of 6,000 healthcare workers who were provided HCQ tablets, record of 4,239 workers that consumed the tablets was available. 139 subjects did not consume HCQ tablets as prescribed (summarized in Figure 1). As of 29\textsuperscript{th} May 2020, a total of 93 health workers at S.M.S. Medical College and Attached Hospitals, Jaipur, that were either doctors, nursing or paramedical personnel, contracted the COVID-19 infection, confirmed with RT-PCR test for SARS-CoV-2.

Among infected 93 patients, majority of patients (n=70) were infected with COVID-19 in first week of initiation of HCQ prophylactic therapy. Therefore, it can be inferred that these cases might be infected prior to onset of therapy. The remaining 15 patients were shown positive RT-PCR confirmatory test in second week of the preventive therapy, 6 patients in third week and only 2 patients were infected in the fourth week. Most of infected patients (n=85) asymptomatic while only a few (n=8) developed mild symptoms, although symptomatic manifestation seen in early phase of initiation of HCQ prophylactic therapy especially five patients in first week and three patients in second week (Figure 2).

The mean age of the health workers who got infected was 35.70 ± 10.26 years. Gender based analysis showed that more males (n=57, 61%) were infected than females (n=36, 39%). The most common adverse effects were related to gastrointestinal system, with 20 subjects reporting either gastritis (n=12), diarrhoea (n=3), nausea (n=2), vomiting (n=2) or mouth ulcers (n=1) due to HCQ consumption. Headache was another common side effect (n=10) with other uncommon effects like sweating, palpitation, tremors, vertigo and breathing difficulty. Palpitation,
mouth ulcer and breathing problems were reported in one subject each (Table 1 and Figure 3). The significance among the asymptomatic and symptomatic subjects was seen using paired t-test. The p value of 0.2535 was obtained which clearly suggested the association between the variables.

**DISCUSSION**

The pandemic of COVID-19 has created a huge burden on global health care system with no effective drug/vaccine available yet in market, for its management. The current situation has led to a search for novel approaches in treatment of COVID-19, which might help in suppression of viral load somehow. The available literature indicated that chloroquine and hydroxychloroquine possess antiviral properties that might be effective in combat against COVID-19.\(^1\) There is paucity of data regarding antiviral effects of chloroquine and hydroxychloroquine due to lack of large sample studies on use of these drugs in COVID-19 patients.

The present study demonstrated that prophylactic HCQ therapy deaccelerated infectivity and prevented severe infection, in healthcare workers who closely participated in management of COVID-19 patients. Although a few health workers were reported positive for COVID-19 infection but mostly in initial two weeks of administering the prescribed dose of HCQ. This suggested that those patients as were actively involved in management of COVID-19 patients might have been exposed prior to onset of HCQ prophylactic therapy. Therefore, prophylactic HCQ therapy has been proven protective for healthcare workers who were closely associated with management of COVID-19 infections. The most important observation was that no mortality related to COVID-19 was reported among healthcare workers who consumed HCQ. Milder adverse drug reaction profile might have been due to antiviral, immunomodulatory and anti-inflammatory properties of HCQ.\(^17\)

The rapid progression of COVID-19 patients with subsequent poor outcome has been linked to the associated cytokine storm.\(^19\) HCQ might prevent this storm by attenuation of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) in addition to its antioxidant activities, that has been observed in autoimmune diseases.\(^19,17\) For this, IL-6 antibody blocker, transfusion of convalescent plasma and other therapies have been applied to counteract the cytokine storm.\(^20,21\) The protective effect of HCQ prophylaxis against COVID-19 is also evident by ability of HCQ in a version of new infection in South Korea’s long-term care facility, after a large exposure.\(^22\)

A recent large sample study has demonstrated the protective effects of HCQ against COVID-19 in four or more maintenance doses while six or more prophylactic doses of HCQ significantly reduced the odds of SARS-CoV-2 infection in healthcare worker.\(^23\) This finding supports the observation of the present study. Due to beneficial effects of HCQ prophylaxis against SARS-CoV-2 a revised advisory from National Task Force of ICMR, India issued in supersession of the previous one has also included other frontline workers at risk of COVID-19 infection such as surveillance workers, paramilitary and police personnel.\(^24\)

Serious adverse effects of chloroquine and HCQ, especially cardiac, ophthalmological and hematological manifestations have hindered its therapeutic use in COVID-19.\(^25\) The chances of HCQ causing cardiovascular toxicity of electrical instability due to hERG potassium channel blockade clinically characterized by QTc elongation and torsades de pontes are rare but co-prescription of other drugs like azithromycin or other co-morbid condition have the potential to amplify the risk.\(^26\) However, it would be pertinent to add that rheumatologists have been using HCQ for millions of patients globally for years and hardly have they ever come across this complication, though long term use of HCQ has been documented to cause eye toxicity. In this aspect it would be relevant to add that cardiac toxicity of short-term use of HCQ is least likely, though HCQ needs to be used with caution in COVID-19 positive patients with co-existing co-morbid cardiac complications as it could very well add fuel to already flagrant fire, especially because of relatively high loading dose used in COVID-19.

On the basis of the findings of the present study together with the available literature on HCQ, it can be concluded that HCQ prophylaxis is safe and effective in standard dosage against COVID-19 infection due to its antiviral and anti-inflammatory actions. National Task force (NTF) for COVID-19 constituted by ICMR, India reviewed the use of HCQ for prophylaxis of SARS-CoV-2 infection for high risk population especially health worker engaged in management of COVID-19. The NTF reviewed the data on *in vitro* and *in vivo* testing of HCQ for antiviral efficacy against SARS-CoV-2 and concluded that prophylactic HCQ had been found to reduce viral load in high risk group and prompt to hampered complications of COVID-19 infection.\(^24\) Our study also proved that prophylactic HCQ therapy prevented severe and

**Table 1: Adverse effects of HCQ reported and its frequency.**

| Name of Department | Adverse effects       | Frequency |
|--------------------|-----------------------|-----------|
| Microbiology       | Diarrhoea             | 3         |
|                    | Headache              | 1         |
|                    | Palpitation           | 1         |
|                    | Sweating              | 2         |
|                    | Nausea                | 2         |
|                    | Gastritis             | 8         |
| ENT                | Gastritis             | 4         |
|                    | Headache              | 1         |
| Nursing            | Headache and vomiting | 2         |
|                    | Headache and vertigo  | 1         |
|                    | Headache, tremors and vertigo | 1 |
|                    | Mouth ulcers and headache | 1 |
|                    | Headache, diarrhoea   | 1         |
|                    | Headache and body ache| 1         |
|                    | Headache and tremor   | 1         |
|                    | Breathing difficulty (h/o CABG) | 1 |
| Chest and TB       | Headache              | 1         |

**Figure 3:** Adverse drug reaction profile of health care workers on HCQ prophylaxis at S.M.S. Medical College and Attached hospitals, Jaipur.
complicated COVID-19 infection. For validity of HCQ as prophylaxis and safety profile the treatment of severe COVID-19 disease and in patients with known cases of cardiovascular disease need further validation.

Ethical approval
This study proved by ethical and research committee of SMS Medical College and Hospital, Jaipur, India.

Author contributions
S. Bhandari, S. Priyadarshi and N. Vyas formulated the research questions, designed the study and developed the preliminary search strategy. G. Rankawat, S. Priyadarshi and N. Vyas collected and analyzed data and drafted the manuscript. S. Bhandari, A. Singh, R. Sharma, V. Gupta, S. Sharma, N. Gupta and M. Singh conducted the quality assessment and review the manuscript. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

ACKNOWLEDGEMENT
I would like to thanks to my professionals Dr. Abhishek Agrawal, Dr. C. L. Nawal, Dr. S. Banerjee, Dr. Prakash Keswani, Dr. Sunil Mahavar, Dr. R S Chejara, Dr. Vidyadhar Singh, Dr. Kapil, Dr. Shivanikan, Dr. Dileep Wadhawan and team of Department of General Medicine SMS Medical college and attached group of Hospital, Jaipur for their valuable support and Department of Radiodiagnosis for providing radiological information of COVID-19 patients.

CONFLICT OF INTEREST
All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential.

ABBREVIATIONS
HCQ: Hydroxychloroquine; ICMR: Indian Council for Medical Research; WHO: World Health Organization; IL: Interleukin; TNF: Tumor necrosis.

REFERENCES
1. Centers for Disease Control and Prevention (CDC) Coronavirus Disease (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical Features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
3. World Health Organization (WHO) Coronavirus Disease (COVID-19) Dashboard. 2020. https://covid19.who.int/
4. Ministry of Health and Family Welfare. 2020. https://www.mohfw.gov.in/
5. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Seminars in Arthritis and Rheumatism. 1993;22(2):82-91. doi:10.1016/s0049-0172(10)80012-5
6. Biot C, Daher W, Chavain N, Fandeur T, Khalfie J, Dive D. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. J Med Chem. 2006;49(9):2845-9.
7. Principi N, Esposito S. Chloroquine or hydroxychloroquine for prophylaxis of COVID-19. Lancet Infect Dis. 2020. published online April 17. https://doi.org/10.1016/S1473-3099(20)30296-6.
8. Perricone C, Triggianni P, Bartoloni E, et al. The anti-viral facet of anti-rheumatic drugs: lessons from COVID-19. J Autoimmun. 2020. published online April 17. DOI:10.1016/j.jaut.2020.102488.
9. 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):1-4.
10. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: What to expect for COVID-19? Int J Antimicrob Agents. 2020. published online March 12. DOI:10.1016/j.ijantimicag.2020.105938.
11. Hashem AM, Alghamdi AS, Alsaiai AA, Alshehri FS, Bukhari A, AlQaheh MA, et al. Therapeutic use of chloroquine and hydroxychloroquine in COVID-19 and other viral infections: A narrative review. Travel Med Infect Dis. 2020;101735. doi:10.1016/j.tmaid.2020.101735.
12. Al-Bari MAA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. Pharmacol Res. 2020;101:2947-52.
13. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu R, et al. 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). Clinical Infectious Diseases. 2020.
14. Popert AJ. Chloroquine: A review. Rheumatology. 1976;15:235-8.
15. National Taskforce for COVID-19. Advisory on the use of hydroxy-chloroquine as prophylaxis for SARS-CoV-2 infection. Dated 23rd 2020.
16. Biot C, Daher W, Chavain N, Fandeur T, Khalfie J, Dive D. Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. J Med Chem. 2006;49(9):2845-9.
17. Al-Bari MA. Chloroquine analogues in drug discovery: New directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. J Antimicrob Chemother. 2015;70(6):1680-21. DOI:10.1093/jac/dkv018.
18. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. MedRxiv. 2020. 02. 16.20023671. DOI: https://doi.org/10.1101/2020.02.16.20023671.
19. Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and pharmacological properties of hydroxychloroquine and chloroquine in treatment of systemic lupus erythematosus, rheumatoid arthritis and related diseases. Inflammopharmacology. 2015;23(5):231-69. DOI:10.1007/s10787-015-0239-y.
20. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): Anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020;34(2):1. doi:10.23812/CONTI-E.
21. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: What to expect for COVID-19? Int J Antimicrob Agents. 2020. published online March 12. DOI:10.1016/j.ijantimicag.2020.105938.
22. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;30(9):103-9. [published online ahead of print, 2020 Mar 14] DOI:10.1016/j.infectdis.2020.02.17 48194.
23. 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):1-4.
24. Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for COVID-19 infection. 2020. https://www.mohfw.gov.in/pdf/COVID-19/2020031419.pdf.
25. Me Garbane B. Chloroquine and hydroxychloroquine to treat COVID-19: between hope and caution. Cln Toxicol. 2020;1-2. Available at: https://doi.org/10.1080/15563650.2020.1748194.
26. Traebert M, Dumotier B, Meister L, Hoffmann P, Dominguez-Estevez M, Suter W. Inhibition of hERG K+ currents by antimalarial drugs in stably transfected HEK293 cells. Eur J Pharmacol. 2004;484(1):41-8.