Original Article

Efficacy of Hydroxychloroquine in Pre-exposure Severe Acute Respiratory Syndrome Coronavirus 2 Prophylaxis among High-Risk HealthCare Workers: A Multicenter Study

Elahe Nasri[1], Hamed Fakhim[1,2], Mehrdad Salahi[1], Safiyeh Ghafel[1], Samane Pourajam[3], Ali Darakhshandeh[3], Nazila Kassaian[1], Somayeh Sadeghi[3], Behrooz Ataei[2], Shaghayegh Haghjooy Javanmard[4], Afsane Vaezi[5]

[1]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Nosocomial Infection Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Internal Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Applied Physiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Science, Isfahan, Iran, [5]Department of Medical Laboratory Science, School of Allied Medical Sciences, Iran University of Medical Sciences, Tehran, Iran

Abstract

Background: Prophylaxis could be an established strategy to potentially prevent and control infectious diseases and should be considered in the coronavirus disease 2019 (COVID-19) pandemic. The present study aimed to assess the effectiveness of hydroxychloroquine as a prophylaxis treatment strategy in the reduction of the risk of COVID-19 among health professionals.

Materials and Methods: The health professionals were randomly assigned (1:1) to the control group without receiving any hydroxychloroquine as prophylaxis and the hydroxychloroquine group receiving a weekly hydroxychloroquine dose of 400 mg up to 12 weeks.

Results: A total of 146 health professionals were randomly enrolled in this study between August 11 and November 11 in 2020. Among the screened health professionals, 21 (14.6%) were infected with COVID-19 during the 12 weeks, and 14 (66.6%) out of the 21 health professionals were in the control group. Most participants with COVID-19 had mild symptoms (62%). In addition, 9.5% ($n = 2$) of the participants suffered from moderate disease and 28.5% were diagnosed with severe symptoms. In the hydroxychloroquine group, 5 (7.1%) and 2 (2.8%) participants were reported with mild and moderate symptoms of COVID-19, respectively, and 2 participants had moderate, 8 (10.9%) participants had mild symptoms, and 6 (8.2%) participants had severe symptoms in the control group, within 3 months. Severe symptoms of COVID-19 were not observed in the hydroxychloroquine group.

Conclusion: This study addressed the effect and benefit of hydroxychloroquine administration for the prevention of COVID-19 among health professionals. The improved perception of prophylaxis might highlight its important role in future COVID-19 outbreaks to prevent hospital transmission, which is a major route of spread.

Keywords: COVID-19, health-care workers, hydroxychloroquine, prophylaxis

Address for correspondence: Dr. Afsane Vaezi, Department of Medical Laboratory Science, School of Allied Medical Sciences, Iran University of Medical Sciences, Tehran, Iran.
E-mail: vaeziiafsane@gmail.com
Submitted: 04-Feb-2021; **Revised:** 10-Sep-2021; **Accepted:** 04-Oct-2021; **Published:** 27-Jan-2023

Introduction

The novel coronavirus disease 2019 (COVID-19) is a highly contagious infection associated with significant mortality and morbidity among risk groups and a devastating local economic burden around the world.[1,2] During the pandemic,

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_104_21

How to cite this article: Nasri E, Fakhim H, Salahi M, Ghafel S, Pourajam S, Darakhshandeh A, *et al*. Efficacy of hydroxychloroquine in pre-exposure severe acute respiratory syndrome coronavirus 2 prophylaxis among high-risk health care workers: A multicenter study. Adv Biomed Res 2023;12:3.

health professionals are repeatedly exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and asymptomatic health professionals can further spread the virus to the patients and families.[3] The proportion of health professionals with SARS-CoV-2 positivity among all COVID-19 patients was 10.1%. However, the severity and mortality among this population was lower than COVID-19 patients.[4] The implementation of prophylaxis strategies for health professionals can lead to a cost-effective approach, reducing lost working hours, nosocomial transmission, and mortality among hospitalized patients.

Hydroxychloroquine is a low-cost and well-known drug widely used as an antimalarial, immunomodulatory, and anti-inflammatory agent.[5,6] It has also been proven with antiviral effects *in vitro*[7,8] and is suggested to decrease SARS-CoV-2 load in some studies.[7,9] The use of hydroxychloroquine might reduce or even eliminate the risk of secondary household transmission.[10,11] Although the effectiveness of hydroxychloroquine has been shown,[7,12,13] some studies have suggested no beneficial effect of hydroxychloroquine for postexposure prophylaxis or treatment of COVID-19 in hospitalized patients.[11,14] Therefore, randomized controlled trials on hydroxychloroquine in patients with COVID-19 are needed. A study reported that 3300 Chinese health-care workers have been infected with SARS-CoV-2 with a mortality rate of 0.4%.[15] In Italy, 3654 health-care workers have been infected with SARS-CoV-2 up to March 2020, representing 9% of the total cases, and 17 health-care workers expired.[16] A large number ($n = 69$) of mortalities among Iranian health-care workers have been also reported due to COVID-19 up to March 2020.[12] Protection and plan for additional arrangements against SARS-CoV-2 among health professionals are critical.

In the planning and implementation of strategies to increase the rate of health safety among health professionals, it is necessary and important to consider beneficial prophylaxis and vaccine. Therefore, the present multicenter, randomized, and open-label study was performed to investigate the effectiveness of hydroxychloroquine as a prophylactic strategy in the reduction of the risk of COVID-19 among health professionals.

Materials and Methods

This multicenter, randomized, and open-label study was conducted between August 11 and November 11 in 2020. The study population consisted of nurses and physicians who were working in three referral COVID-19 hospitals, namely 166-bed Omid hospital, 224-bed Amin hospital, and 114-bed Isabn-e-Maryam hospital in Isfahan, Iran. All the health professionals with 18 years of age or older working at least 3 days a week in the hospitals with a negative nucleic acid tests were eligible for inclusion, and written informed consent was obtained from all the participants. Previous use of chloroquine, hydroxychloroquine, azithromycin, or any other macrolide for more than 24 h before enrolment, pregnancy, breastfeeding, and ongoing antiretroviral and corticosteroid therapies were the exclusion criteria of the present study.

A total of 146 health professionals (including 13 physicians and 133 nurses) participated in the present study. The health professionals were randomly assigned to the control group without receiving any hydroxychloroquine as prophylaxis and the hydroxychloroquine group receiving weekly a hydroxychloroquine dose of 400 mg up to 12 weeks. The data were daily collected based on randomization up to the 90th day in electronic case report forms. The participant with episodes of symptomatic respiratory illness was suspected as COVID-19 patient and confirmed positive for SARS-CoV-2 infection by real-time reverse transcription-polymerase chain reaction.[17]

Statistical analysis

All data were summarized using descriptive statistics including means, standard deviations (SD), minima and maxima, frequencies, and percentages. Clean data were extracted into STATA (StataCorp. 2017. Stata Statistical Software: Release 15. StataCorp LLC, College Station, TX, USA) for statistical analysis.

Ethical statement

The present study was approved by the Research and Ethics Committee (IR. MUI. MED. REC.1399.017) of Isfahan University of Medical Sciences, Isfahan, Iran, and registered in the Trial Protocol Iranian Registry of Clinical Trials (registry number: IRCT20200414047076N1).

Results

In total, out of 146 health professionals, 70 and 73 subjects were randomly divided into the hydroxychloroquine and control (without receiving any hydroxychloroquine as prophylaxis) groups, respectively. Three patients in the hydroxychloroquine group were excluded after randomization (two subjects withdrew after randomization and one case had severe nausea). A 90-day follow-up was performed for the remaining 143 health professionals. The mean age (SD) of the participants was 29.7 (10.5) years, and 89.7% were female. Among the 143 screened health professionals, 21 (14.6%) cases were infected with COVID-19 between August 11 and November 11 in 2020.

Participants with COVID-19 were categorized into three groups, including mild, moderate, and severe, according to the symptoms.[18] Patients with fever, headache, chills, and muscle aches were classified as the mild group. The health professionals with moderate symptoms had fever, headache, chills, muscle aches, and cough. In patients with severe symptoms, SaO_2 <94 was also added. Most (n = 13, 62%) participants with COVID-19 had mild symptoms, and 2 (9.5%) suffered from moderate disease. In addition, 28.5% of the cases were diagnosed with severe symptoms.

In the hydroxychloroquine group, 5 (7.1%) participants with mild symptoms of COVID-19 and 2 (2.8%) with moderate

versus 8 (10.9%) participants with mild symptoms and 6 (8.2%) with severe symptoms of COVID-19 in the control group were reported within 3 months. Among the participants infected with COVID-19, 14 (66.6%) were in the control group. Severe symptoms of COVID-19 were not observed in the hydroxychloroquine group and the frequency of mild symptoms was lower in this group than that reported for the control group. In the hydroxychloroquine group, six participants showed mild and reversible side effects, including nausea, anorexia, abdominal pain, vomiting, dizziness, and headache.

Local protocol for COVID-19 was activated. The patients with mild disease were treated with hydroxychloroquine sulfate (oral doses of 400 mg BID for 24 h and then 200 mg BID). In addition, the participants with severe COVID-19 received remdesivir (intravenous doses of 200 mg on the 1st day and then 100 mg for 4 days) and after 2 days, methylprednisolone (a dose of 1 mg/kg daily for 5 days). None of the cases developed severe pneumonia, and none of them died. A total of 21 patients had the virus cleared after 2 weeks of follow-up (two continuous negatives of nucleic acid tests).

Discussion

The development and screening of new vaccines and antivirals are time-consuming and expensive; however, priority attention should be given to the use of available drugs against COVID-19. Up to November 29 in 2020, the COVID-19 pandemic due to SARS-CoV-2 has killed over 47,874 and infected over 948,749 individuals in Iran.[19] Despite advances in supportive care and treatment, the mortality rate remains high, and prophylaxis could be an established strategy to potentially prevent and control infectious diseases and should be considered in the COVID-19 pandemic.[20] Health professionals are at the frontline against COVID-19 and are particularly exposed to this infection.

The results of the present study showed that the frequency (n = 7; 33.3%) of COVID-19 was lower in the health-care professionals assigned to the hydroxychloroquine group than that (n = 14; 66.6%) in the control group. This study addressed the effect and benefit of hydroxychloroquine administration for the prevention of infection among health professionals. However, available evidence does not support the use of this drug for the prevention or treatment of COVID-19.[11,20] The obtained results of this study are inconsistent with those of two randomized clinical trials carried out on hydroxychloroquine for preexposure prophylaxis against COVID-19 in health-care workers.[21,22] The reasons for the difference in the effect and benefit of hydroxychloroquine use for the prevention of COVID-19 between studies remain unknown. The study design and its suitability to study aims, definitions of exposure and outcome measures, and control group selection should be considered more as the main reasons associated with these differences. Awareness of all of these elements is vital for adequate epidemiological interpretation of studies examining the effect of hydroxychloroquine use as prophylaxis for COVID-19.

Hydroxychloroquine is a safe and successful anti-inflammatory agent that has been used for the treatment of autoimmune diseases and can significantly decrease the production of cytokines (as anticytokine storm drugs) and pro-inflammatory factors in COVID-19 patients.[23] Although the macular toxicity of hydroxychloroquine could be a concern in long-term treatment, short-term prophylactic use is not a relevant concern.[24,25] Further studies are needed to determine the efficacy of hydroxychloroquine, optimal dosage, and balance between the benefits and risks for the prevention of transmission in health professionals.

The present study had some limitations. Firstly, the rate of participation in this study was relatively low. Secondly, the study was conducted in only one region. Thirdly, this study was carried out only on physicians and nurses; therefore, the results cannot be assumed to represent all health-care workers. In summary, the present study identified a consistent benefit for the use of hydroxychloroquine prophylaxis over 12 weeks for the prevention of COVID-19 in health professionals. The improved perception of prophylaxis might highlight its important role in future COVID-19 outbreaks to prevent hospital transmission, which is a major route of spread.

Ethical conduct of research

This study was approved by the Research and Ethics Committee (IR. MUI. MED. REC.1399.017) of Isfahan University of Medical Sciences, Isfahan, Iran.

Acknowledgments

This study was supported by grants from the emergency special program for COVID-19 of Isfahan University of Medical Sciences, Isfahan, Iran project (no. 199004).

Financial support and sponsorship

This study was supported by grants from the emergency special program for COVID-19 of Isfahan University of Medical Sciences, Isfahan, Iran project (no. 199004).

Conflicts of interest

There are no conflicts of interest.

References

1. Chang MC, Park YK, Kim BO, Park D. Risk factors for disease progression in COVID-19 patients. BMC Infect Dis 2020;20:445.
2. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: A narrative review to highlight clinical and research needs in the acute phase and the long return to normality. Child Adolesc Psychiatry Ment Health 2020;14:20.
3. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, *et al.* Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci 2020;63:706-11.
4. Sahu AK, Amrithanand VT, Mathew R, Aggarwal P, Nayer J, Bhoi S. COVID-19 in health care workers – A systematic review and meta-analysis. Am J Emerg Med 2020;38:1727-31.
5. Winzeler EA. Malaria research in the post-genomic era. Nature 2008;455:751-6.

6. Parhizgar AR, Tahghighi A. Introducing new antimalarial analogues of chloroquine and amodiaquine: A narrative review. Iran J Med Sci 2017;42:115-28.
7. 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;6:16.
8. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res 2020;30:269-71.
9. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56:105949.
10. Lee SH, Son H, Peck KR. Can post-exposure prophylaxis for COVID-19 be considered as one of outbreak response strategies in long-term care hospitals? Int J Antimicrob Agents 2020;55:105988.
11. 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;383:517-25.
12. Guitti P, Parnaz P, Parichehr P, Fariba G. Prophylactic recommendation for healthcare workers in COVID-19 pandemic. Adv J Emerg Med 2020;4.
13. Pereira BB. Challenges and cares to promote rational use of chloroquine and hydroxychloroquine in the management of coronavirus disease 2019 (COVID-19) pandemic: A timely review. J Toxicol Environ Health B Crit Rev 2020;23:177-81.
14. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, *et al.* Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. JAMA 2020;323:2493-502.
15. Keshavan M. Hospital Workers Across the U.S. Present Sharply Different Pictures of their Preparedness for the Coronavirus. STAT. Available from: https://www.statnews.com/2020/03/. [Last accessed on 2020 Mar 14].
16. Tahiri Joutei Hassani R, Bennis A. Hydroxychloroquine as antiviral prophylaxis for exposed caregivers to Covid-19: An urgent appraisal is needed. J Infect Public Health 2020;13:865-7.
17. World Health Organization. Diagnostic Detection of 2019-nCoV by Real-Time RT-PCR. Available from: https://www.who.int/docs/default-source/coronaviruse/protocol-v2-1.pdf?sfvrsn=a9ef618c_2. [Last accessed 2020 Dec 10].
18. Cheng SH, Taiwan HCQ Study Group. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19). PLoS One 2020;15:e0242763.
19. Mohammadi F, Pourzamani H, Karimi H, Mohammadi M, Mohammadi M, Ardalan N, *et al.* Artificial neural network and logistic regression modelling to characterize COVID-19 infected patients in local areas of Iran. Biomed J 2021;44:304-16.
20. Jorge A. Hydroxychloroquine in the prevention of COVID-19 mortality. Lancet Rheumatol 2021;3:e2-3.
21. Abella BS, Jolkovsky EL, Biney BT, Uspal JE, Hyman MC, Frank I, *et al.* 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 2021;181:195-202.
22. Rajasingham R, Bangdiwala AS, Nicol MR, Skipper CP, Pastick KA, Axelrod ML, *et al.* Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: A randomized trial. medRxiv 2020; 2020.09.18.20197327.
23. 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;395:497-506.
24. Marmor MF, Carr RE, Easterbrook M, Farjo AA, Mieler WF, American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy: A report by the American Academy of Ophthalmology. Ophthalmology 2002;109:1377-82.
25. Chang R, Sun WZ. Repositioning chloroquine as ideal antiviral prophylactic against COVID-19-time is now. Drug Discov Today 2020;25:1786-92.