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Hydroxychloroquine Pre-Exposure Prophylaxis for COVID-19 in Healthcare Workers from India: A Meta-Analysis

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A B S T R A C T

To date, the COVID-19 pandemic has resulted in more than 200 million cases of SARS-CoV-2 infection and more than four million deaths world-wide [1]. Although novel COVID-19 vaccines have become clinically available, the safety and efficacy of these vaccines remains open to question [2]. Alternate approaches to prevention of disease have received little attention, and one medication, hydroxychloroquine (HCQ), has been attacked and dismissed based on flawed studies and political controversy that obscured the value of this treatment as pre-exposure prophylaxis (PrEP) for SARS-CoV-2 infection.

A British study of 120,075 healthcare workers (HCWs) found that these subjects had a 7–8 fold greater risk of developing severe COVID-19 compared to non-HCWs [3]. With this background, the Indian Council of Medical Research (ICMR) National Taskforce for COVID-19 formulated guidelines for weekly HCQ PrEP in high-risk HCWs [4]. We used internet search engines to identify 11 cohort studies of weekly HCQ PrEP in HCWs from India based on the ICMR protocol [5–15]. These case-control studies enrolled a total of 7616 high-risk HCWs who were tested for SARS-CoV-2 infection as an endpoint after varying lengths of time following weekly HCQ PrEP or no treatment.

We have performed a preliminary meta-analysis of these studies, as shown in Table 1. In the 11 studies that included HCWs who used any HCQ PrEP, the infection rate was significantly decreased (RR 0.56, p = 0.0040). In the five studies that included HCWs who took at least six doses of weekly HCQ PrEP, the infection rate was reduced even further (RR 0.25, p < 0.0001). The uniform ICMR treatment protocol used in these studies argues against bias related to variations in dosing of HCQ. There were minimal adverse events reported in the HCQ-treated subjects, consistent with other safety reports for HCQ use in COVID-19 trials [16,17].

Our meta-analysis suggests that weekly HCQ PrEP is safe and effective in preventing COVID-19 in a high-risk group of HCWs. Although severity of disease was not reported for infected subjects in most of the studies, prevention of infection implies a lower risk of severe illness in treated HCWs. It is important to recognize that these studies exclusively analyzed HCQ PrEP and excluded HCQ post-exposure prophylaxis (PEP) or treatment of SARS-CoV-2-infected individuals. Lumping of these groups in prior studies has resulted in flawed analysis and inaccurate conclusions about the safety and efficacy of HCQ PrEP [18]. Although the cohort studies have limitations in terms of retrospective design and subject homogeneity, they suggest that HCQ PrEP could serve as a stop-gap approach to COVID-19 prevention until universal vaccination is achieved. Further randomized trials of HCQ PrEP should be conducted to evaluate this promising method of prevention for COVID-19 and future pandemics.

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| Study | HCQ (n) | No HCQ (n) | RR (95% CI) | P-value*
|-------|---------|------------|-------------|---------
| 1. Chatterjee et al., 2020 | 365 | 386 | 0.90 (0.60–1.35) | 0.62 |
| HCQ any dose infection | 172 | 193 | 0.04 (0.01–0.16) | <0.0001 |
| HCQ > 6 doses infection | 12/68 | | |
| 2. Bhattacharya et al., 2020 | 54 | 52 | 0.19 (0.07–0.53) | 0.0013 |
| HCQ any dose infection | 4 | 20 | | |
| HCQ ≥ 6 doses infection | NA | | |
| 3. Khurana et al., 2021 | 90 | 91 | 1.36 (1.02–1.82) | 0.013 |
| HCQ any dose infection | 54 | 40 | 0.62 (0.30–1.28) | 0.19 |
| HCQ > 6 doses infection | 6/22 | | |
| 4. Goenka et al., 2020 | 237 | 885 | 0.62 (0.39–0.98) | 0.041 |
| HCQ any dose infection | 19 | 115 | 0.10 (0.01–0.71) | 0.021 |
| HCQ > 6 doses infection | 1/77 | | |
| 5. Yadav et al., 2021 | 178 | 221 | 0.78 (0.44–1.39) | 0.40 |
| HCQ any dose infection | 17 | 27 | 0.39 (0.17–0.93) | 0.033 |
| HCQ > 6 doses infection | 6/125 | | |
| 6. Kadur et al., 2020 | 248 | 86 | 0.14 (0.03–0.70) | 0.017 |
| HCQ any dose infection | 2 | 5 | | |
| HCQ > 6 doses infection | NA | | |
| 7. Dev et al., 2021 | 260 | 499 | 0.74 (0.61–0.90) | 0.0024 |
| HCQ any dose infection | 155 | 351 | | |
| HCQ > 6 doses infection | NA | | |
| 8. Mathai et al., 2020 | 491 | 113 | 0.10 (0.05–0.21) | <0.0001 |
| HCQ any dose infection | 10 | 22 | | |
| HCQ > 6 doses infection | NA | | |
| 9. Datta et al., 2020 | 146 | 135 | 0.78 (0.42–1.45) | 0.43 |
| HCQ any dose infection | 16 | 19 | | |
| HCQ > 6 doses infection | NA | | |
| 10. Behera et al., 2021 | 186 | 186 | 0.56 (0.19–1.63) | 0.29 |
| HCQ any dose infection | 7 | 12 | | |
| HCQ > 6 doses infection | NA | | |
| 11. Badyal et al., 2021 | 1,234 | 1,473 | 0.81 (0.73–0.90) | <0.0001 |
| HCQ any dose infection | 415 | 611 | 0.28 (0.21–0.37) | <0.0001 |
| HCQ > 6 doses infection | 247/981 | | |
| Total | 3,489 | 4,127 | | |
| Infection | 871 (25%) | 1,428 (35%) | 0.56 (0.37–0.83) | 0.0040 |
| HCQ > 6 doses | 1,273 | | |
| Infection | 272 (21%) | 0.25 (0.13–0.50) | <0.0001 |

HCQ, hydroxychloroquine; PrEP, pre-exposure prophylaxis; NA, not available; RR, adjusted risk ratio; CI, confidence interval.

* Treated subjects versus untreated controls.

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Competing interests

None declared.

Ethical approval

Not required.

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References

[1] Stricker RB, Fesler MC. Flattening the risk: pre-exposure prophylaxis for COVID-19. Infect Drug Resist 2020;13(October):3689–94.
[2] Haynes BF, Corey L, Fernandes P, Gilbert PB, Hotez PJ, Rao S, et al. Prospects for a safe COVID-19 vaccine. Sci Transl Med 2020;12(November (568)):eaee0948, http://dx.doi.org/10.1126/scitranslmed.aee0948.
[3] Mutambudzi M, Niedzwiedz C, Macdonald EB, Leyland A, Mair F, Anderson J, et al. Occupation and risk of severe COVID-19: prospective cohort study of 120,075 UK biobank participants. Occup Environ Med 2020;(November), http://dx.doi.org/10.1136/oemed-2020-106731. Available at:.
[4] [Indian Council of Medical Research National Taskforce for COVID-19, March 22. Available at: https://www.mohfw.gov.in/pdf/AdvisoryontheuseofHydroxychloroquinasprophylaxisforSARS-CoV2andlepticoinfection..pdf] Advisory on the use of Hydroxychloroquine as prophylaxis for SARS CoV-2 infection; 2020.
[5] Chatterjee P, Anand T, Singh KJ, Rasaily R, Singh R, Das S, et al. Healthcare workers and SARS-CoV-2 infection in India: a case-control investigation in the time of COVID-19. Indian J Med Res 2020;151(5):459–67, http://dx.doi.org/10.4103/imr.IMR_2234_20.
[6] Bhattacharya R, Chowdhury S, Nandi A, Mukherjee R, Kulshrestha M, Ghosh R, et al. Pre-exposure hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers. Internat J Res Med Sci 2020;9:89–96, http://dx.doi.org/10.18203/2320-6012.ijrms20205444.
[7] Khurana A, Kaushal GP, Gupta R, Verma V, Sharma K, Kohli M. Prevalence and clinical correlates of COVID-19 outbreak among health care workers in a tertiary level hospital in Delhi. Am J Infect Dis 2021;17:107–19, http://dx.doi.org/10.3844/ajidsp.2021.107.119.
[8] Goenka MK, Afzalpurkar S, Goenka U, Das SS, Mukherjee M, Jadodia S, et al. Seroprevalence of COVID-19 amongst health care workers in a tertiary hospital care of a metropolitan city from India. J Assoc Physicians India 2020;68:14–9, Available at: https://pubmed.ncbi.nlm.nih.gov/33187030/.
[9] Yadav RM, Pate A, Shankarkumar A, Shreyasi A, Shinde S, Bargir UA, et al. Sero-survey for health-care workers provides corroborative evidence for the effectiveness of hydroxychloroquine prophylaxis against COVID-19 infection. J Epidemiol Global Health 2021 (in press). Available at: https://www.atlantispress.com/journals/jegh/129596914/view.
[10] Kadur HB, Aggarwal A, Sonjha M, Singh K, George N, Nischal N, et al. Hydroxychloroquine pre-exposure prophylaxis for COVID-19 among health-care workers: initial experience from India. Lancet Preprints 2020, http://dx.doi.org/10.1016/smr.3623250. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3623250.
[11] Dev N, Meena RC, Gupta DK, Gupta N, Sanark J. Risk factors and frequency of COVID-19 among healthcare workers at a tertiary care centre in India: a case-control study. Trans Royal Soc Trop Med Hyg 2021:trab047, http://dx.doi.org/10.1093/trstmh/trab047.
[12] Mathai SS, Behera V, Hande V. Hydroxychloroquine as pre-exposure prophylaxis against COVID-19 in health-care workers: a single-center experience.
Datta D, Ghosal S, Sinha B, Datta S, Chakraborty T, Gangopadhyay KK, et al. No role of HCQ in COVID-19 prophylaxis: a survey amongst Indian doctors. J Vaccines Vaccin 2020;S6:002.

Behera P, Patro BK, Singh AK, Chandanshive PD, SR R, Pradhan SK, et al. Role of ivermectin in the prevention of SARS-CoV-2 infection among healthcare workers in India: a matched case-control study. PLoS One 2021;16(2):e0247163, http://dx.doi.org/10.1371/journal.pone.0247163.

Badyal D, Chandy SJ, Chugh PK, Faruqui A, Gupta YK, Hazra A, et al. Hydroxychloroquine for SARS CoV2 prophylaxis in healthcare workers – a multicentric cohort study assessing effectiveness and safety. J Assoc Physicians India 2021;69(6):17–23 . https://www.japi.org/issue/2021/69/6/hydroxychloroquine-for-sars-cov2-prophylaxis-in-healthcare-workers-a-multicentric-cohort-study-assessing-effectiveness-and-safety.

Lofgren SM, Nicol MR, Bangdiwala AS, Pasticak KA, Okafor EC, Skipper CP, et al. Safety of hydroxychloroquine among outpatient clinical trial participants for COVID-19. Open Forum Infect Dis 2020;7:ofaa500. Available at: https://academic.oup.com/ofid/article/7/11/ofaa500/5930834.

Sogut O, Can MM, Guven R, Kaplan O, Ergenc H, Umit TB, et al. Safety and efficacy of hydroxychloroquine in 152 outpatients with confirmed COVID-19: a pilot observational study. Am J Emerg Med 2020;40(December):41–6.

Stricker RB. Response to: A living WHO guideline on drugs to prevent COVID-19. BMJ 2021;372:n526. Available at: https://www.bmj.com/content/372/bmj.n526/rapid-responses.