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Can Hydroxychloroquine Prophylaxis be Useful among Health Care Workers in Prevention of COVID-19?

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ABSTRACT

Introduction: *This study aims to evaluate the pre-exposure and post-exposure efficacy of hydroxychloroquine prophylaxis among Healthcare Workers (HCW) to prevent COVID-19 infection.* ***Materials and Methods:*** *This was a retrospective cohort study. Pre-exposure prophylaxis was given to the HCW in the pre-exposure group according to their willingness. Post-exposure prophylaxis was initiated to HCW after exposure in the hospital or social area within 96 hours. The main outcome was symptomatic or asymptomatic COVID-19 infection confirmed by PCR during the study period for the pre-exposure prophylaxis group and symptomatic or asymptomatic COVID-19 infection confirmed by PCR within 5 to 14 days from exposure for the post-exposure prophylaxis group. An online structured survey was sent to HCW participating in the study. The data were also validated by the available medical records of the hospital and analyzed with R, an open-source statistical package.* ***Results:*** *A total of 492 HCW who worked between March 20 and June 20 of 2020 in our hospital were recruited for the study. A total of 40 (8.1%), 152 (31%), 266 (54%), and 34 (6.9%) HCWs had received pre-exposure prophylaxis, post-exposure prophylaxis, no-prophylaxis, or both pre and post-exposure prophylaxis, respectively. Eventually, 47 HCWs obtained a diagnosis of COVID-19 confirmed with the PCR test. The rate of COVID-19 was 9.6% among the HCW who participated in the study. PCR-confirmation rates of COVID-19 were 18%, 4.6%, 12%, and 2.9% in those receiving pre-exposure prophylaxis, post-exposure prophylaxis, no prophylaxis, and both pre-exposure and post-exposure prophylaxis, respectively. The final logistic model revealed a negative association between post-exposure prophylaxis and PCR confirmation COVID-19 disease (effect estimate: -1.179; 95% limits: -1.969-0.390).* ***Conclusions:*** *This study implies that pre-exposure prophylaxis is not protective. Post-exposure prophylaxis with hydroxychloroquine may decrease the acquisition of COVID-19 disease.*

Keywords: Hydroxychloroquine, Prophylaxis, COVID-19

INTRODUCTION

Health Care Workers (HCW) are at significant risk for disease transmission while fighting COVID-19. A considerable number of HCW have been infected with SARS COV-2 worldwide, and some had, unfortunately, lost their lives. In the

People's Republic of China, as of February 24, 2020, 3387 of 77.262 patients infected with COVID-19 were reported to be HCW involved in the management of COVID-19 patients [1]. In Italy, in March 2020, 20% of HCW who took part in managing COVID-19 patients became infected, and several of them died [2]. These events justified the search for extra measures in addition to using personal protective equipment and isolation precautions to protect HCW before developing the disease. *In-vitro* studies demonstrated the inhibitory effect of hydroxychloroquine on virus entry to the cell [3,4]. Therefore, repurposing hydroxychloroquine to use in prophylaxis is of interest.

A recent study proposed the use of hydroxychloroquine in prophylaxis for COVID-19 [5]. Zhou, et al. also suggested that hydroxychloroquine may be useful in preventing the development of disease [6]. Many HCW obtained hydroxychloroquine before and after exposure without valid clinical evidence.

Except for one comparative study among healthcare professionals evaluating the efficacy of hydroxychloroquine in pre-exposure prophylaxis many of them have not been published so far [7-9]. In this study, we aimed to evaluate the effectiveness of hydroxychloroquine in pre-exposure and post-exposure prophylaxis on the prevention of COVID-19 among HCWs.

METHODS

Setting and Data Collection

We conducted a single-center retrospective cohort study in an affiliated tertiary care hospital. We obtained ethical approval from the Institute Ethics Committee, and signed informed consent was waived (2020/0320). The procedures followed were as per the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association.

This study was conducted between March 20 and June 20 of 2020. During the study period, the participating HCW had been informed about the use of masks in their social lives, compliance with the social distance rule, and avoiding crowded areas, and encouraged to be in line with preventive measures. We applied pre-exposure prophylaxis to HCWs according to their self-decision and willingness with hydroxychloroquine 200 mg PO weekly in consecutive weeks during the study period. Post-exposure prophylaxis was initiated with hydroxychloroquine, given 200 mg twice daily orally for three consecutive days to HCW after exposure in the hospital or social area in the first 96 hours of exposure to a SARS-CoV-2 PCR positive patient, as per the recommendations of the Ministry of Health of Turkey in April 2020 [10]. High-risk exposure was defined as exposure to a COVID-19 patient without protective equipment. Medium-risk exposure was defined as exposure using protective equipment inappropriately, while low-risk exposure was defined as exposure using personal protective equipment properly. Personal protective equipment was a surgical mask (or N95 respirator), protective eyeglasses, and disposable protective clothing. We defined the appropriate use of protective equipment as wearing a medical mask, respirator (in the presence of aerosol-generating procedures), glasses, and disposable clothing before exposure and disposing of all protective equipment followed by hand hygiene immediately after exposure. We followed the HCWs, who had a risky exposure history, with active symptom monitoring. We performed a PCR test on the symptom day if symptoms developed, and on the 7^{th} day if not.

The primary outcome for the pre-exposure prophylaxis group was symptomatic or asymptomatic COVID-19 infection confirmed by PCR during the study period. The primary outcome for the post-exposure prophylaxis group was symptomatic or asymptomatic COVID-19 infection confirmed by PCR within 5 to 14 days from exposure. PCR test was performed immediately at the onset of COVID-19 symptoms or whenever an HCW requested for a PCR test.

At the end of the study period, we conducted an online structured survey. We contacted participants where necessary to resolve conflicts among survey responses. Medical records of the hospital also validated the data.

Statistical Analysis

For statistical comparisons, we used the open-source platform R (Vienna, Austria). Variables that violate the normality assumption were presented as the median and Interquartile Range (IQR). We applied the Student's t-test or the Wilcoxon rank-sum test to analyze continuous variables and the Chi-square test or Fisher's exact test to analyze categorical variables where required.

We constructed logistic models using the "RMS" package. We fit the final logistic model using potentially confounding variables. We tested collinearity and interactions between predictors and presented estimates of marginal effects.

RESULTS

A total of 492 HCW who worked in our hospital were recruited for the study. Table 1 presents the characteristics of the study cohort. Briefly, the median (IQR) age of participants was 30 (26, 38) years, and the frequency of female gender was 64% (314). A total of 213 (43%) participants were nurses, midwives, and health technicians, and 133 (27%) were resident doctors. A total of 456 participants had a risky exposure history; 420 (92.1%) had contact in the hospital, 36 (7.9%) had contact outside the hospital (family or social exposure). 46 of 456 participants reported more than one risky exposure. Among the participants, 8.1% (40/492) and 31% (152/492) obtained pre and post-exposure prophylaxis. A total of 47 (9.6%) patients had at least one positive PCR test.

Table 1 Characteristics of the cohort

Characteristic	N	N=492*
Age (years)	479	30 (26, 38)
Gender	487	
Male		173 (36%)
Female		314 (64%)
Occupation	491	
Cleaning staff		53 (11%)
Nurse, midwife, health technician		213 (43%)
Residents		133 (27%)
Doctors		36 (7.3%)
Data entry and technical support staff		56 (11%)
Prophylaxis	492	
None		266 (54%)
Pre-exposure prophylaxis		40 (8.1%)
Post-exposure prophylaxis		152 (31%)
Both		34 (6.9%)
SARS-Cov-2 PCR	492	47 (9.6%)
*Statistics presented: median (IQR); n (%)		

Table 2 displays univariate comparisons of factors according to the PCR status of participants. Briefly, age and gender were not different, while prophylaxis status and occupation had some variations. Residents and hospital cleaners were the most frequently infected HCWs, while participants who had medium and high-risk exposures were most commonly infected.

Table 2 Characteristics of patients according to PCR results

Characteristic	PCR +ve		p-value†
	No, N = 4451	Yes, N = 47*	
Age (years)	30 (26, 39)	29 (26, 37)	0.3
Gender			
male	160 (92%)	13 (7.5%)	0.3
female	280 (89%)	34 (11%)	
Prophylaxis			
None	234 (88%)	32 (12%)	0.009
Pre-exposure	33 (82%)	7 (18%)	
Post-exposure	145 (95%)	7 (4.6%)	
Both	33 (97%)	1 (2.9%)	
Occupation			

Cleaningstaff	46 (87%)	7 (13%)	0.002
Nurse, midwife, health technician	199 (93%)	14 (6.6%)	
Residents	110 (83%)	23 (17%)	
Doctors	34 (94%)	2 (5.6%)	
Data entry and technical support staff	55 (98%)	1 (1.8%)	
Exposure risk			
Not rated	35 (97%)	1 (2.8%)	0.5
Low	33 (94%)	2 (5.7%)	
Medium	336 (89%)	40 (11%)	
High	41 (91%)	4 (8.9%)	
* Statistics presented: median (IQR); n (%); † Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independence; Fisher's exact test			

Table 3 displays the frequency of prophylaxis types according to exposure risk rating. Most patients declared that they had a medium risk exposure. The final logistic model displayed an inverse association between post-exposure prophylaxis and COVID-19 infection (effect-1.179; 95% limits, (-1.969; -0.390)) (Table 4).

Table 3 The frequency of prophylaxis types among exposure risk rating

Characteristic	Not rated N=36*	Low N=35*	Medium N=376*	High N=45*
Prophylaxis				
None	18 (6.8%)	15 (5.6%)	211 (79%)	22 (8.3%)
Pre-exposure	3 (7.5%)	4 (10%)	29 (72%)	4 (10%)
Post-exposure	14 (9.2%)	14 (9.2%)	105 (69%)	19 (12%)
Both	1 (2.9%)	2 (5.9%)	31 (91%)	0 (0%)
* Statistics presented: n (%)				

Table 4 Effect estimates from the final logistic model

Factor	Effect	Lower.0.95	Upper.0.95
Post-exposure prophylaxis	-1.179	-1.969	-0.390
Pre-exposure prophylaxis	0.273	-0.547	1.094
Risk not rated	-1.388	-3.41	0.634
Low	-0.606	-2.083	0.872
High	-0.137	-1.227	0.954
Logistic Statistic: 95% confidence interval			

Except for transient palpitations, none of the participants had severe side effects due to hydroxychloroquine utilization.

DISCUSSION

We found that hydroxychloroquine post-exposure prophylaxis had an inverse association with COVID-19 infection among HCWs. On the other hand, the hydroxychloroquine pre-exposure prophylaxis had no association with the outcome. A recently published randomized, double-blind, placebo-controlled clinical trial also reported that there was no clinical benefit of hydroxychloroquine administered daily for 8 weeks as pre-exposure prophylaxis in hospital-based HCWs exposed to patients with COVID-19 [11].

A recently published randomized controlled, double-blind study found no significant difference in post-exposure prophylaxis between participants receiving hydroxychloroquine compared to those receiving placebo. Side effects were more common in the hydroxychloroquine arm [12]. A study from South Korea reported no PCR positivity in HCWs who had potential exposure to the index case. These patients instituted 400 mg/day hydroxychloroquine prophylaxis within 58 hours of exposure and were used for 14 days. However, in this study, there was no control group, and only nine HCWs were considered high-risk exposure [13]. In a recent retrospective study conducted in Italy, patients who were in hydroxychloroquine drug regimens due to chronic dermatologic or rheumatologic diseases were phone interviewed. Among these patients, none had SARS-CoV-2 infection-related symptoms in the last two

months. However, the main limitation of the study by Lee SH et al was the absence of exposure to COVID-19 cases [14]. Other randomized controlled clinical trials evaluating the effectiveness of post-exposure prophylaxis in adults have not yet been concluded [15]. In our study, post-exposure prophylaxis was associated with a favorable outcome.

CONCLUSION AND LIMITATIONS

Interestingly, we found that PCR-proven COVID-19 infection was higher among those who received pre-exposure prophylaxis than all other groups, including those who did not receive any prophylaxis. It is also possible that the prophylactic use of hydroxychloroquine may create false confidence, and so may cause HCW to neglect personal protective measures.

The limitation of our study is that it is a single-center study, and participating groups were not randomized. Although the data were confirmed by the hospital automation system and by phone call when necessary, the data were collected through an online questionnaire. On the other hand, the inclusion of only the volunteers in the study causes selection bias.

We have observed in our hospital that hydroxychloroquine is not effective in preventing disease in pre-exposure prophylaxis. On the other hand, post-exposure prophylaxis was associated with decreased PCR-confirmed COVID-19 cases among HCW. However, to make strong inferences, more studies should be undertaken.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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