Prophylactic use of Hydroxychloroquine among Physicians working in Pandemic Hospitals

Mehmet Gönenli (mgonenli@ku.edu.tr)
Koç University
İlker Kayı
Koç University
Nilüfer Alpay Kanıtez
Koç University
Tuba Baydaş
Bezmialem University Hospital
Murat Köse
Istanbul University
Emine Nalbantoğlu
Koç University
Miraç Vural Keskinler
Istanbul Medeniyet University
Timur Akpınar
Koç University
Önder Ergönül
Koç University Research Center of Infectious Diseases

Research Article

Keywords: COVID-19 , Hydroxychloroquine, Prophylaxis, Physicians

Posted Date: December 16th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-107937/v1

Abstract

Background: Throughout the pandemic, physicians working at the frontlines have embarked on various quests to protect themselves, and many physicians preferred the use of hydroxychloroquine (HQN) as a prophylactic agent. This study aimed to investigate the reasons leading physicians to use HQN and the effects of HQN use on physicians.

Methods: This study is a cross-sectional study with a target population of physicians working in pandemic hospitals in İstanbul, Turkey. We have recruited the participants from seven different hospitals via an invitation email between May 14 and June 13, 2020. An online questionnaire, including 57 questions in total, was sent to each physician.

Results: A total of 148 (26%) physicians used hydroxychloroquine for prevention. Older physicians and ones who have a story of exposure to COVID-19 patients without any protection used more prophylactic HQN. Hydroxychloroquine did not differ statistically in terms of being infected among the exposed physicians (p=0.52). Nineteen (13%) physicians using hydroxychloroquine developed side effects related to the drug. Diarrhea and nausea were the most common.

Conclusion: Prophylactic HQN use was more common among the physicians older than 40 years and who had higher exposure rates to a COVID-19 patient without any protection. The physicians working at the frontlines had the highest rate of infection. Hydroxychloroquine was not effective in the prophylaxis of COVID-19 among the exposed physicians.

Highlights

- Prevalence:
  ºAmong all the physicians participating in the study, 148 (26%) physicians used hydroxychloroquine for prevention for a while or continuously. ºOlder physicians and exposed ones used more prophylactic HQN.
- Effectiveness:
  ºHydroxychloroquine did not differ statistically in terms of being infected among the exposed physicians (p=0.52).
- Side effects:
  ºNineteen (13%) of 148 patients using hydroxychloroquine developed side effects that could be related to the drug.
  ºDiarrhea and nausea were the most common

Introduction

Healthcare workers were on the front lines of the global effort to care for patients with COVID-19, while putting themselves at risk for infection. Thousands of physicians already died, from dozens of countries,

professions, and specialties [1]. The lack of access to personal protective commitment (PPE), lack of training and workforce shortages have exposed the vulnerability of healthcare workers they desperately sought for other options to protect themselves [2].

There have been efforts for the discovery of an effective treatment and prophylaxis of coronavirus disease. At the same time hydroxychloroquine (HQN), an antimalarial drug that has been mainly used in the treatment of immune-mediated diseases, has been proposed as an option. While in vitro studies showed the ability of HQN to inhibit SARS-CoV-2 activity [3, 4], consequent clinical trials have not yielded promising results for the effectiveness of HQN in treatment and prophylaxis of COVID-19 [5–7]. Yet, there are some countries that included HQN in their national case management and prophylaxis guidelines including Turkey [8, 9].

In March 2020, the Ministry of Health declared pandemic hospitals which were responsible for the management of COVID-19 cases. Istanbul, holding one fifth of the population in Turkey and being the center of commerce and international travel soon reported to be the epicenter of the pandemic in Turkey. While physicians working in pandemic hospitals in Istanbul faced the surge of COVID-19 patients, they were also suggested to use HQN as a prophylaxis against COVID-19. Therefore, we aimed to describe the HQN use among physicians for prophylactic purposes, its association with acquisition of COVID-19 and the factors that contribute to HQN use.

Method

This is a cross-sectional study with a target population of physicians working in pandemic hospitals in İstanbul, Turkey. Pandemic hospitals are the ones assigned to respond to the COVID-19 outbreak, which have at least two physicians specialized in Infectious Diseases and Clinical Microbiology, Pulmonology or Internal Medicine, and having a level three adult intensive care bed have been assigned to be a pandemic hospital in Istanbul.

We have selected seven pandemic hospitals for recruiting participants. To ensure the inclusion of a socioeconomically diverse group of hospitals, we have chosen three private university hospitals and four public hospitals. The total number of physicians working in these seven pandemic hospitals was 4,722. We have calculated the sample size in OpenEpi [10] program by taking the anticipated frequency of HQN use as 50% as recommended for unknown frequencies; 5% margin of error with a design effect of 1.7. The sample size at a 95% confidence interval was 607 participants.

The inclusion criteria for the participants were having a minimum medical doctor degree and actively working with patients in pandemic hospitals since March 11, 2020. The study was approved by The Koç University Ethics Committee on Human Research and the Turkish Ministry of Health.

Recruitment of participants was by an invitation sent via email from hospital administration to the physicians. To do so, we sought permission from each hospital for sending an invitation email to their eligible physician staff. Hospital administrations sent two reminder emails in a weekly period after the

initial invitation email. Data collection was limited to one month between May 14, 2020, and June 13, 2020. We collected the data via an online questionnaire, including 57 questions in total prepared according to the scientific literature. Upon providing consent, physicians could proceed to the survey.

The questionnaire assessed socio-demographic characteristics of participants such as age, gender, and medical specialty, ever and current use of hydroxychloroquine since the beginning of the pandemic, dose, timing and duration of hydroxychloroquine use, ever and ongoing use of any other supplements, working conditions during the pandemic, frequency of contact with COVID-19 patients, and if participants used regular medication and had any chronic health condition.

Statistical analysis

We provided a mean, median, and Standard Deviation for continuous variables and percentages for the categorical variables. We dichotomized the categorical variables and used the Chi-Square test for comparisons in univariate analysis. We conducted two separate multivariable analyses with logistic regression. The significant variables in univariate analysis and the potential confounders were included to the models. One multivariable analysis for the predictors of HQN use was performed, that included independent variables of age, gender, having any comorbidities, being exposed to a COVID-19 patient without any protection (defined as exposure) and working at frontline departments. The second multivariable analysis was performed for the predictors of infection that included the independent variables of age, gender, having any comorbidities, working at frontline departments and prophylactic HQN usage. Statistical significance was set at $P < .05$ to reject the null hypothesis in a 2-sided equation. Stata software (version 8.0) was used in the statistical analysis.

Results

At the end of the data collection period we have received 718 responses. After eliminating the participants who were out of our target population from seven pandemic hospitals there were 564 physicians remaining for analysis comprising to 93% of the initial sample size. The mean age of the physicians who participated in the study was 36 (sd:8.9), and 295 (52%) of the participants were women (Table 1).

Table 1
Basic Characteristics of Physicians

	Total n = 564 (%)	Received prophylaxis n = 148 (%)	P	Infected n = 28 (%)	p
Age > 40	170 (30)	63 (42.6)	**< 0.001**	6 (21.4)	0.27
Gender (Male)	269 (48)	65 (44)	0.284	16 (57.1)	0.305
Frontline departments	310 (55)	77 (52)	0.403	21 (75)	**0.029**
Current smoker	76 (13.5)	25 (17)	0.156	4 (14.2)	0.897
Comorbidities					
Hypertension	34 (6)	12 (8.1)	0.216	2 (7.1)	0.799
DM	12 (2)	4 (2.7)	0.572	1 (3.6)	0.587
Hyperlipidemia	19 (3.3)	7 (4.7)	0.285	0	
CVS	9 (1.6)	1 (0.7)	0.298	1 (3.6)	0.392
Arrhythmia	6 (1)	2 (1.3)	0.691	1 (3.6)	0.185
Any comorbidity	124 (22)	41 (27.7)	0.051	7 (25)	0.693
Patient care in a week			0.753		0.307
0 hrs	56 (10)	19 (12.8)		0 (0)	
< 8 hours	117 (20.8)	31 (20.9)		4 (14.2)	
8–12 hours	36 (6.4)	11 (7.4)		1 (3.6)	
12–24 hrs	66 (11.7)	15 (10.1)		5 (17.9)	
24–48 hrs	137 (24.4)	35 (23.6)		8 (28.6)	
> 48 hrs	149 (26.5)	37 (25)		10 (35.7)	
Patient care > 12 hours per week	352 (62.4)	87 (58.8)	0.289	23 (82.1)	**0.027**
History of exposure	184 (32.6)	56 (37.8)	0.115	16 (57)	**0.005**
Used HQN prophylaxis	148 (26.3)	N/A	N/A	8 (28.5)	0.774

	Total n = 564 (%)	Received prophylaxis n = 148 (%)	P	Infected n = 28 (%)	p
pre-exposure HQN Use	*118*	*N/A*	*N/A*	*6 (21.4)*	*0.946*
post-exposure HQN Use	*30*	*N/A*	*N/A*	*2 (7.1)*	*0.659*

During this study, 28 out of 564 physicians (5%) were infected. Pneumonia developed in 15 of 28 (54%) infected physicians.

In the study group, 148 (26%) physicians used hydroxychloroquine for prevention for a while or continuously. Among the physicians who used HQN, 8 of 148 (5.4%) infected, compared to 20 of the 416 (4.8%) physicians who did not use HQN (p = 0.773, Fig. 1).

There were 310 (55%) physicians that worked more than 12 hours a week with COVID-19 patients. These frontline physicians were from 18 different departments including Infectious diseases, Emergency, Pulmonology, Internal Medicine, Intensive Care, ENT and Pediatrics departments. Out of these 310 physicians 21 (6.7%) were infected while only seven physicians (2.7%) from other departments were infected (p = 0.029). Also, physicians providing care for COVID-19 patients more than 12 hours a week were infected more than physicians working for fewer hours (23/352 p = 0.027, Table 1).

In the study, 184 physicians stated that they had contacted at least one COVID-19 patient without having appropriate personal protective equipment. Among the physicians with suspected contact, 16 (8.7%) were infected (p = 0.005).

Fifty six (30.4%) physicians out of 184 used hydroxychloroquine for prophylaxis. While 26 physicians were using HQN before any exposure with a COVID-19 patient, 30 began HQN after exposure. It was also found that hydroxychloroquine did not differ statistically in terms of being infected among the exposed physicians (p = 0.52).

Diarrhea (7.4%) was the most common side effect among physicians using HQN, and only one patient who has diarrhea was infected. Arrhythmias (3.4%), nausea (3.4%), abdominal pain (2.7%), weakness (3%), rash (1.3%), and dizziness (1.3%) were other side effects, respectively.

While 68% of the physicians never used a loading dose, those who took the loading dose mostly received 400 mg for a day (17%). Eleven different maintenance dosages were documented in the study and 200 mg once a week (17.6%) was the most preferred dose for maintenance among physicians (Table 2).

Table 2
HQN Dosages used for prophylaxis among physicians

	HQN use N = 148 (%)
Loading dose	
No loading dose	101 (68%)
400 mg one day	25 (17%)
800 mg one day	8 (5.4%)
200 mg 3 days	8 (5.4%)
400 mg 3 days	6 (4%)
Maintenance	
200 mg for once	20 (13.5%)
400 mg for once	12 (8.1%)
200 mg every 3 weeks	20 (13.5%)
400 mg every 3 weeks	6 (4%)
200 mg every 2 weeks	5 (3.4%)
400 mg every 2 weeks	5 (3.4%)
200 mg once a week	26 (17.6)
400 mg once a week	13 (8.8%)
200 mg twice a week	20 (13.5%)
200 mg once a day	3(2%)
200 mg twice a day	18 (12.2)

Of the 148 physicians using hydroxychloroquine prophylaxis, 44 were still on prophylaxis when the study was terminated. Five of the 144 (3.4%) physicians who stopped the drug stated that after stopping prophylaxis, they developed a complaint or finding related to COVID.

In the multivariable analysis conducted to determine who preferred hydroxychloroquine prophylaxis, we found that physicians over 40 years of age ($p < 0.001$) and who had unprotected exposure to a COVID-19 patient ($p = 0.032$) preferred prophylaxis (Table 3).

Table 3
Univariate and multivariate analysis for the predictors of hydroxyquinoline use

	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Age > 40	2.14	1.44–3.17	< 0.001	2.20	1.44–3.36	< 0.001
Any comorbidity	1.53	0.99–2.37	0.052	1.23	0.78–1.95	0.366
High risk exposure	1.36	0.92–2.02	0.116	1.55	1.03–2.32	0.032
Working at frontline	0.85	0.58–1.24	0.403	0.87	0.59–1.28	0.499
Female gender	1.22	0.84–1.79	0.285	1.42	0.96–2.10	0.078

We also examined the predictors of COVID-19 infection, and in both univariate and multivariable analysis, working at the front line was the single significant variable for developing an infection while using HQN was not found to be protective (Table 4).

Table 4
Univariate and multivariate analysis for the predictors of COVID-19 infection

	Univariable			Multivariable		
	OR	CI	p	OR	CI	p
Working at frontline	2.56	1.07–6.13	0.034	2.62	1.08–6.31	0.031
Age > 40	0.61	0.24–1.55	0.307	0.52	0.19–1.43	0.212
Female gender	0.67	0.31–1.44	0.307	0.58	0.26–1.27	0.176
Any comorbidity	1.19	0.49–2.87	0.693	1.44	0.56–3.68	0.446
Hydroxychloroquine	1.13	0.48–2.62	0.774	1.2	0.54–3.03	0.576

Discussion

Prophylaxis with hydroxychloroquine is still suggested in some countries although its effectiveness has not been proven by clinical studies [8]. The physicians working in pandemic hospitals tried to treat patients and protect themselves at the same time. Since the hydroxychloroquine in prophylaxis was highly controversial, physicians had to make their own decisions about whether to use this drug for protection.

Of all the physicians participating in the study, 148 (26%) physicians used HQN for a while or continuously. 118 of these doctors preferred to begin prophylaxis without any suspicious contact, while 30 doctors started HQN after an exposure (Fig. 1).

Older age and having chronic diseases are considered as well known risk factors for COVID-19 [11]. In our study, older age and having any comorbidities were associated with increased HQN use (Table 3). However in multivariate analysis the association with being older than 40 was significant, whereas having any comorbidities was not.

In multivariable analysis, working at the frontline was found to be the single significant variable for development of infection (Table 4). Using HQN was not found to be protective. There was no statistical significance between the physicians working at the frontline and the others in terms of HQN use (25% vs 28>%, p = 0.403). Moreover, among the physicians working in the frontline departments, there was not significant association between using HQN and infection (7.7% vs 6.4%, p = 0.682).

It was found that 28 (5%) of 564 physicians who participated in the study had COVID infection. Pneumonia developed in 15 (54%) of 28 infected doctors. In June, when this study ended, Boulware et al. reported that after exposure to Covid-19, HQN usage did not prevent COVID infection [5]. In our study, no statistically significant relationship was found between the use of HQN and the development of COVID infection (p = 0.774).

A total of 19 (12.8%) physicians out of 148 reported a side effect during their HQN prophylaxis. Loose stool (7.4%) and nausea (3.4%) were the most commonly reported side effects. Only one physician out of 11 who reported diarrhea had COVID infection. A recent randomized controlled study on HQN prophylaxis among healthcare workers, reported no significant difference in terms of infection rates, in parallel with our results [12]. In the same study, it was reported that 20% of 65 patients developed diarrhea during HQN prophylaxis. Cases of serious adverse cardiac events related to hydroxychloroquine prophylaxis among physicians were reported [13].

Inclusion of 564 physicians out of 4722 (12%) was one of the strongest aspects of our research. However, this was a self-administered online survey. Access to the site was tightly controlled and restricted with only physicians from selected hospitals to ensure that study represents the targeted population. In addition, 74% of the physicians participating in the study shared their email addresses to respond to any conflict related to the questionnaire to increase the reliability of the study.

In conclusion, prophylactic HQN use was common among physicians in pandemic hospitals. Prophylactic HQN use was more common among the physicians older than 40 years and the ones who had higher risk of exposure. The physicians working at the frontline had the highest rate of infection. Hydroxychloroquine was not effective in prophylaxis of COVID-19 among the exposed physicians. Diarrhea and nausea were the most common side effects of HQN.

Declarations

Funding:

No funding was received for conducting this study.

Competing Interests:

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval:

The study was carried out in accordance with the declaration of Helsinki and with the term of local legislation and approved by The Koç University Ethics Committee on Human Research (IRB No: 2020.183.IRB1.051) and the Turkish Ministry of Health (Mehmet Gökhan Gönenli-2020-05-06T16_18_41).

Consent to participate:

Informed consent was obtained from all individual participants included in the study.

Consent for publication:

The authors also affirm that human research participants provided informed consent for publication of their data.

Availability of data and materials:

We also declare that the datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Authors Contributions:

Conceptualization: Mehmet Gökhan Gönenli, Nilüfer Alpay Kanıtez, Timur Selçuk Akpınar

Methodology: İlker Kayı, Mehmet Gökhan Gönenli, Nilüfer Alpay Kanıtez

Data Collection: Tuba Baydaş, Murat Köse, Emine Ayça Nalbantoğlu, Miraç Vural Keskinler, Mehmet Gökhan Gönenli

Formal Analysis: Önder Ergönül, İlker Kayı, Mehmet Gökhan Gönenli

Writing - original draft preparation: Mehmet Gökhan Gönenli, İlker Kayı, Önder Ergönül

Supervision: Önder Ergönül, Timur Selçuk Akpınar

Acknowledgements:

The authors thank all the doctors, nurses and other healthcare providers working at the Istanbul Pandemic Hospitals and caring for COVID-19 patients.

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Figures

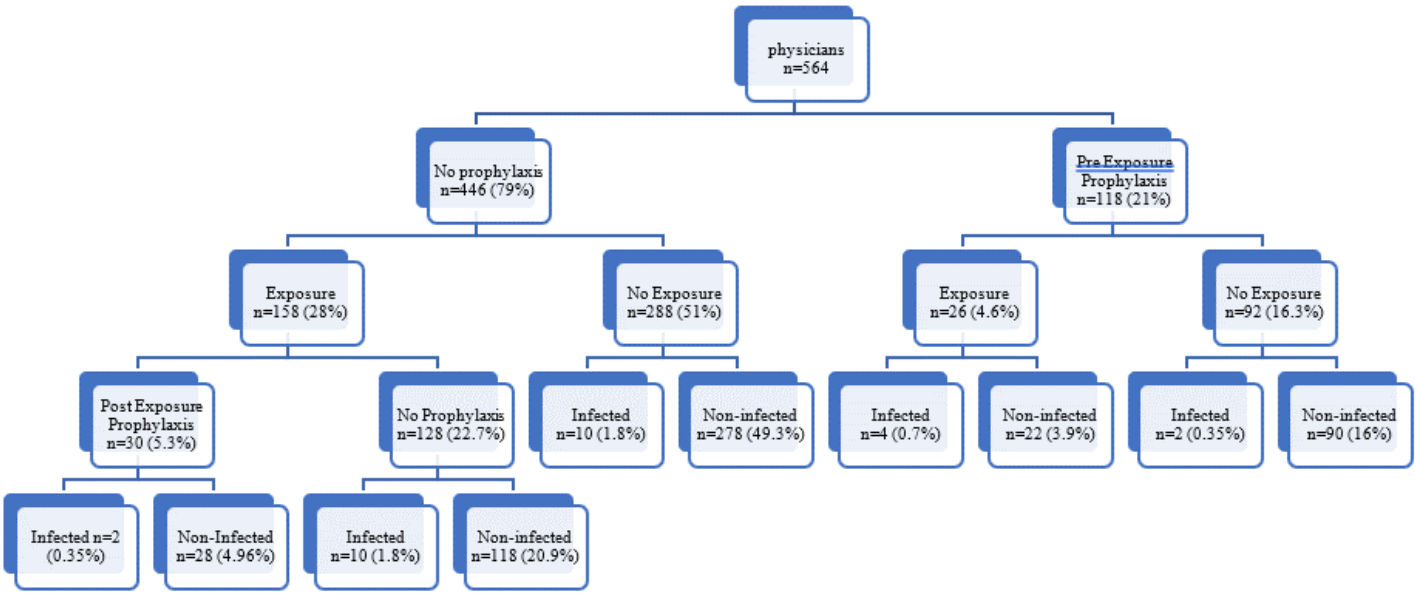

Figure 1

Hydroxychloroquine use and infection rates among physicians