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Is Hydroxychloroquine prophylaxis protective for Covid-19 infection in healthcare professionals who are at risk?

Aydın Balcı[1], Şule Çilekar[2]
[1, 2] Departman of chest diseases, Turkey Afyonkarahisar Health Sciences University Medical Faculties, Turkey

Abstract
Background: Therefore, we designed a special survey to be conducted on the healthcare professionals of a pandemic hospital in Turkey who were using HCQ chemoprophylaxis in addition to all the preventive measures enforced by their hospital and by themself in an effort to present the results along with the literature.
Objective: Without the presence of strong in vitro and clinical evidence, the recommendation of usage of CQ and HCQ for COVID-19 prophylaxis still seems to be too early. We need an effective treatment for COVID-19 together with an effective pharmaceutical treatment that can be used in chemoprophylaxis to protect healthcare professionals from potential risks.
Methods: Healthcare professionals, who are working in a pandemic hospital in Turkey, of whom we learned of their usage of HCQ as prophylaxis either directly or indirectly, created the sample of our study.
Results: There were also questions of where they supplied the HCQ from, its dosage, and the frequency of its usage.
Conclusions: our study supports our perspective to predict the use of HCQ for prophylaxis as beneficial.

Keywords: COVID-19 disease, hydroxychloroquine chemoprophylaxis, Healthcare professionals

1. Introduction

Pneumonia cases with unknown causes were detected in December 2019 in the Wuhan city of China. This disease which was called 2019-nCoV initially was revealed to be caused by a newly identified coronavirus (COVID-19) infection called SARS-CoV-2 [1]. It became a pandemic around the world in a short period like 5 months after the first case.

There is a rapid increase in the spread of COVID-19 among the community, mainly due to asymptomatic or mild clinical undiagnosed cases. Moreover, the presence of uncertainties regarding the survival of the virus in the air, on surfaces, or in the form of droplets also affects the rapid spread of the virus [3]. This fast spread of the virus means potential risk to professionals working in the healthcare facilities. Therefore prevention measures like quarantine, isolation, social distancing, and barrier measure are some of the beneficial strategies which will minimize the spread of the virus and the fatalities due to the virus as well as they will take off some of the pressure on the healthcare system [4]. In addition to continuing to use barrier prevention measures, there are different opinions because of the current data on the use of some antimalarial drugs, such as chloroquine (CQ) and hydroxychloroquine (HCQ), which have been tried for COVID-19 treatment and chemoprophylaxis [5]. In studies conducted in vitro related to COVID-19, CQ and its hydroxyl analog HCQ were observed to have strong antiviral activities against SARS-CoV-2 disease. Due to the potential antiviral activity of CQ, promising results were obtained from the in vitro studies of it [6, 7]. Antiviral mechanisms of both drugs are based on their capacity to increase endosomal pH. This prevents the Coronaviridae family (eg, SARS-CoV-2) from releasing their genetic materials into the host cells and proliferation of their envelopes. Since both drugs can suppress the production and release of tumor necrosis factor (TNF) and interleukin 6 (IL-6), their anti-inflammatory effects can be considered to be important [8, 9]. HCQ which is a less toxic aminoquinoline has an N-hydroxyethyl side chain instead of an N-diethyl chloroquine group therefore HCQ is more soluble than CQ [10]. HCQ has lower toxicity compared to CQ in vitro study (especially retinal toxicity). Additionally, HCQ is preferred more against COVID-19 infection because of its strength in clinical applications which is 3 times more compared to CQ [6, 11]. It was concluded in a study in vitro that HCQ is more effective than CQ for both prophylaxis and treatment purposes [12]. Based on the results in vitro, some of the authors claimed that CQ and HCQ may be beneficial for prophylactic use against COVID - 19. Moreover, in line with these results, China's National Health Commission Guidelines for Covid-19 and U.S. Food and Drug Administration recommended the use of HCQ on the treatment of Covid-19 even though its indefinite benefits while they do not make any comments about the use of these drugs for the purpose of prophylaxis [13, 14].

There is no well-structured convincing evidence in the current clinical trials that support the use of HCQ in efficacy and safety in the prophylactic treatment of COVID-19.It is also difficult to conduct such clinical trials at a very fast pace with high quality while the healthcare professionals are working in an intense schedule as well as at circumstances with a high risk of developing COVID-19 disease [15]. While there is no clear evidence supporting the effectiveness of CQ or HCQ for the prophylaxis of the disease, quarantine, social distancing, and personal hygiene methods seem to be the proven preventive measures up to now [16]. Without the presence of strong in vitro

and clinical evidence, the recommendation of usage of CQ and HCQ for COVID-19 prophylaxis still seems to be too early. We need an effective treatment for COVID-19 together with an effective pharmaceutical treatment that can be used in chemoprophylaxis to protect healthcare professionals from potential risks. Although HCQ shows prophylactic efficacy in ongoing clinical trials, more clinical trials are needed. Therefore, we designed a special survey to be conducted on the healthcare professionals of a pandemic hospital in Turkey who were using HCQ chemoprophylaxis in addition to all the preventive measures enforced by their hospital and by themself in an effort to present the results along with the literature.

2. Materials and Methods

Healthcare professionals, who are working in a pandemic hospital in Turkey, of whom we learned of their usage of HCQ as prophylaxis either directly or indirectly, created the sample of our study. The study was conducted with them between 11-16 June 2020 through using the survey designed by the researchers. Questions related to sociodemographic characteristics such as age, gender, the habit of smoking, the department where they work, experience in their professions, etc. were added into the questionnaire. Additionally, there were questions on if they had anyone with COVID-19 diagnosis around them and their level of contact with these individuals. They were questioned about whether they were using any medical or herbal supplies for their immune system improvement. There were also questions of where they supplied the HCQ from, its dosage, and the frequency of its usage. Lastly, there were questions on if they had COVID-19 Polymerase chain reaction (PCR) and a rapid antigen test.

2.1 Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Afyonkarahisar Health Sciences University Faculty of Medicine (approval No. 2020/224). Informed consent was submitted by all subjects when they were enrolled.

3. Results

When looked at the demographic parameters of the 61 participants, 42(68.9%) of them were males, and the other 19(31.1%) of them were females. The mean age of the participants was 33.66±6.45. A total of 48(78.7%) of the participants were married while 11(18.0%) were singles and 2(3.3%) were divorced. A total of 34(55.8) of the participants were the doctors (Table 1).

When we evaluated the answers of the participants to the survey questions, 37 (60.7%)of the participants gave the answer of "Yes" to the question of " *Has anyone around you been diagnosed with COVID-19?*". While a total of 5 (12.5%) of them mentioned their family members who share the same accommodation and a total of 16 (40.0%) of them mentioned their patients of whom they had contact with. The quick test results and the PCR samples of all the healthcare professionals with contact history came out all negative in the 1st week. The polymerase chain reaction (PCR) and rapid antigen test results of healthcare professionals were presented in Table 2 together with their contact status with individuals tested positive.

Among 56 people who responded to the question "*When did you start using HCQ for the purpose of COVID-19 chemoprophylaxis?*"; 34 (60.7%) of them stated " After the presence of the disease was declared in the country" and 13 (23.2%) of them gave the answer of " after the contact with a patient with the diagnosis" while 9 (16.1%) of them gave the answer of " the day I started to work in the risky department where treatment and the follow up of COVID-19 patients were happening".

Question of "*What dosage are you using if you started using HCQ for prophylaxis?*" was answered by 57 participants. 52.5 % of those reported using HCQ for chemoprophylaxis by taking 1 tablet in 21 days. Usage doses are shown in Figure 1.

Question of "*Where did you get the information about the use of HCQ prophylaxis*?" was answered by 58 of the participants. A total of 29 (50.0%) of them stated that their doctor friends recommended while 15 (25.9%) of them stated to obtain the information from the literature.

Question of " *Are you using any other preparate for supportive purposes except HCQ?*" was answered by 54 of the participants. A total of 30 (55.6%) of them stated that they do not use anything. The most common answer to this question was the vitamin supplement with 20 (32.78%) of the participants. Moreover, 1 (1.63%) of the professionals claimed to use ivermectin regularly as a preparate.

A total of 36 of the participants gave the answer of " No" to the question of " *Did you have any of the most common clinical signs of the disease?*". The most common answer from the participants who answered the initial question with "Yes" was " dry cough" with 16.7% of them and their rapid antigen results were negative (Figure 2).

The question of " *Did you have any side effects of HCQ while using?*" was answered by 58 of the participants. A total of 9 (15.5%) of them gave the answer of "Yes" of whom 5 (55.5%) stated diarrhea while 1 (11.1%) stated headache, nausea, and tachycardia. In terms of side effects, gastroenterological findings were statistically significant compared to other findings ($p < 0.01$).

A total of 56 of the participants answered the question of " *How did you obtain the HCQ?*". A total of 23 (41.1%) of those claimed to obtain from their pharmacist friends while 19 (33.9%) of them obtained from their relatives with rheumatic disease. Remaining 14 (25.0%) of them claimed to obtain it with a prescription. A total of 28 (50.0%) of the participants who use HCQ stated that they recommend HCQ prophylaxis to their relatives.

The question of " *Did you perform any of the interventions determined as the high-risk group by the Ministry of Health on any COVID-19 diagnosed patients?*" was answered by 54 of the participants. A total of 20 (37.0%) of the participants stated of performing the procedure of taking the respiratory tract and secretion (Figure 3).

The test results of all the participants who had the COVID-19 PCR and rapid antigen test were negative. The test results were shown in Table 3.

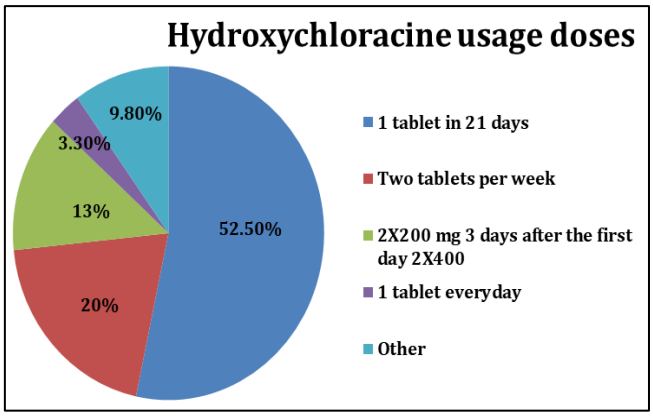

Fig 1: HCQ (Hydroxychloracine) usage dose intervals of the participants

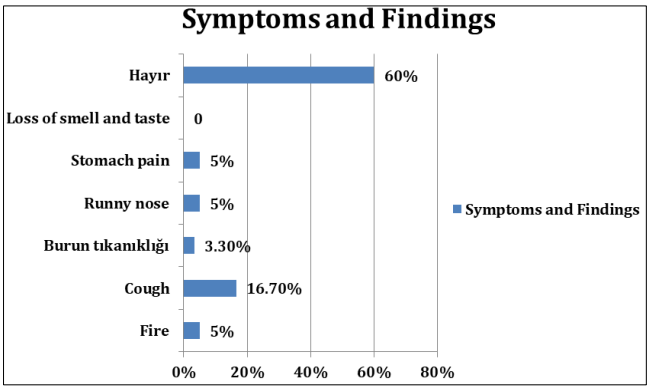

Fig 2: Clinical findings seen in the participants

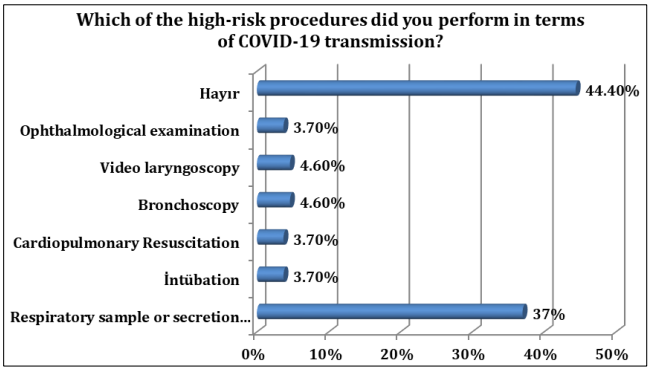

Fig 3: High-risk transactions for COVID-19 transmission

Table 1: Demographic features

		n	%
The average age	33,66±6,45		
Gender	Male	42	68,9
	Female	19	31,1
Profession	Doctor	34	55,8
	Assistant Health Personnel	27	44,2
Marital status	The married	48	78,7
	Single	11	18
	Divorced	2	3,3
Smoking History	Yes	22	36,1
	No	39	63,9
Cigarette Packet Year	16,36±10,215		
Chronic Disease	Hypertension	6	9,8
	Diabetes Mellitus	3	4,9
	Asthma	2	3,3

Table 2: Polymerase Chain Reaction and rapid antigen test results in healthcare workers with positive patient contact status.

Contact Status	COVID-19		Polymerase Chain reaction		Rapid Antigen test	
	N	%	-	+	-	+
In-Home Contact	5	%12.5	5	-	5	-
Treated Patient Contact	16	%40,0	8	-	7	-
Disease in her/his colleague	9	%22,5	7	-	7	-

Table 3: COVID-19 PCR and rapid antigen test cases

	Did You Have A Covid-19 Polymerase Chain Reaction Test?		Have you had a Covid-19 Rapid Antigen Test?	
	N	%	N	%
YES	26	(%42.6)	26	(%42.6)
Positif	-	-	-	-
Negative	26	%100	26	%100

4. Discussion

This study was conducted with healthcare professionals using HCQ chemoprophylaxis after COVID-19 disease started to appear within our country. It is planned to evaluate the possible effects of the HCQ drug and to determine the effectiveness of prophylaxis by asking some questions to some extent. Our study evaluated the survey responses of the healthcare professionals using HCQ prophylactically, as retrospective style. The most remarkable result of our study was the negative results of PCR or rapid antigen tests in healthcare professionals who use HCQ prophylaxis and had contact with COVID-19 positive patients. It gives us a reason to ask the question of " *Is the use of HCQ prophylaxis protective against COVID-19 disease?*".

There has been a great interest in the prevention of the disease, prophylaxis, and the treatment approaches due to the rapidly progressing nature of the COVID-19 pandemic. There is no approved prophylaxis or treatment regimen for COVID-19 disease currently. Some clinical studies have been initiated which include treatments such as HCQ, favipiravir, losartan, remdesivir, tocilizumab, intravenous immunoglobulin, and healing plasma [17]. Although reports regarding the use of CQ and HCQ, which have been used for malaria treatment for years, have been revealed, there is still uncertainty in terms of their effectiveness for the treatment of COVID-19 [18].

HCQ is being recommended as a prophylactic agent for individuals who are in contact with immunosuppressive or infected patients [19]. Healthcare professionals following these

kinds of studies have started to use HCQ prophylaxis in different doses similar to our study.

Scientifically there is no proven effective treatment and a dose for either COVID-19 management or prophylaxis. Although pharmacometrics modeling and simulation experiments have been used by several groups, potential regimens are intended for hospitalized patients with serious conditions, and there are no models that have been specifically evaluated in the context of prophylaxis [20, 21]. While there was the usage of different doses of HCQ prophylaxis among the participants in our study, the most common dose was 1 tablet in 21 days among 32 (52.5%) of the participants.

What is known about the pharmacokinetics of HCQ is its use in indications other than COVID-19, such as malaria, rheumatoid arthritis, and systemic lupus erythematosus. HCQ has a very high volume of distribution and linear kinetics, therefore, it is easily distributed to a range of tissues [22, 23]. There are pharmacokinetic studies that show that elimination half-life of HCQ ranges from 5-40 days [23]. Due to its long half-life duration, HCQ concentrations are still high even on days of completion of treatment regimens. Therefore the doses of hydroxychloroquine used for malaria might be used for the treatment and prophylaxis of COVID-19 [19]. Since the preclinical models reveal that the accumulation of HCQ happens 30 times more in the lung tissues, the therapeutic effect of the drug can be preserved for a long time [24]. The maximum dose we observed in our study was 1 tablet every 21 days. Unlike malaria treatment, which is recommended to begin dosing 2 weeks prior to traveling to an endemic site, in the use of prophylaxis for COVID-19, therapeutic concentrations require faster acquisition, so a loading dose in the pre-exposure prophylaxis setting supports this logical approach [19]. Our study shows that the participants started HCQ prophylaxis as soon as the risk started to form. However, the reliability of the drug has not been proven. In some patients, it has been reported to cause severe adverse cutaneous reactions, fulminant hepatic insufficiency, and ventricular arrhythmias (especially when prescribed with azithromycin) and even rare potential fatality [25, 26]. The most common side effects of HCQ are gastrointestinal symptoms and itching [27]. Some of our participants also observed side effects of the drug, However, none of the participants stopped prophylaxis due to side effects. The most common side effect in our participants is gastrointestinal symptoms in line with the literature and it is more significant than other symptoms.

Some of the World leaders including Donald TRUMP, president of the US, admitted the frequent use of HCQ and its safety through the media. The statements made by a world leader like the President of the US increased the demand for the HCQ. In the notifications made by the French president, it was stated that French doctors were pressured to prescribe the drug, despite its unapproved efficacy and many possible side effects [28]. Due to the policy of the Ministry of Health in our country, HCQ was removed from public access. Before its removal from public access, some people managed to obtain it through prescription. Apart from this, some people also managed to obtain it through their relatives or pharmacists acquaintances due to its use in the treatment of rheumatic diseases in our country.

In summary, there is still no effective treatment and prophylaxis for COVID-19. While hydroxychloroquine prophylaxis is promising, we do not have sufficient evidence to recommend the use of it to the general population. We must consider the long-term consequences of hydroxychloroquine prophylaxis administration and show respect to the scientific approach. There is a need for further similar studies with control groups.

5. Conclusion

The workload of healthcare systems is increasing against a virus with a high infectious rate. Rapid solutions are needed to ensure the continuity of the system and rectify its destructive effects on the world economy. Prophylactic treatments or vaccines are the key elements of stopping the outbreak or reducing the prevalence, in the case of a pandemic. Vaccines are one of the primary preventive measures against communicable diseases. In addition to this, The novelty of the COVID-19 virus, its ambiguous reaction to the immune system, and its rapid spread raised the expectations of creating a successful vaccine in a short term. Self-quarantine and social distancing are now considered as proven preventive measures currently.The presence of negative PCR and rapid antigen test results even after the participants' unprotected contact with COVID-19 diagnosed patients, and the small-scale of a sample group of our study supports our perspective to predict the use of HCQ for prophylaxis as beneficial.

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7. Disclosure

He made no influence on this work in relation with the company or its products. Other authors have no potential conflicts of interest to disclose.

8. Author Contributions (Use CRediT terms)

Conceptualization: Balcı A. Methodology: Balcı A. Formal analysis:Çilekar Ş. ; Data curation: Çilekar Ş; Writing - original draft preparation:Balcı A Approval of final manuscript: all authors.

8.1 ORCID

Aydın Balcı https://orcid.org/0000-0002-1111-2211
Şule Çilekar https://orcid.org/0000-0004-3333-2001

9. Referances

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