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Original Article

The role of hydroxychloroquine in high-risk individuals with coronavirus disease (COVID-19)

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Abstract: Objective: This study aimed to compare the symptoms and the severity of the illness among positive Coronavirus Disease 2019 (COVID-19) high-risk individuals with or without the prophylactic use of hydroxychloroquine (HCQ). Methods: This cross-sectional study was conducted at the Pakistan Institute of Medical Sciences (PIMS), Islamabad. A total of 485 high-risk individuals with possible exposure to COVID-19 were enrolled in the study. The data were collected through a pre-designed self-reporting questionnaire inquiring about the individual's history, baseline characteristics, COVID-19 associated risk factors, exposure history, polymerase chain reaction (PCR) and antibody screening results, HCQ drug dosage, and adverse effects. The COVID-19 symptoms and the severity of the illness were also recorded. The individuals were divided into two groups as per the HCQ intake, i.e. users and non-users, and compared for statistical significance. The data of 121 PCR positive COVID-19 individuals were also compared between the two groups. Results: Out of 485 individuals, 264 (54.4%) were HCQ users. All the study demographics were comparable in both study groups. The study revealed that the COVID-19 positive cases were significantly less reported in the HCQ user group than in the non-HCQ user group (40.3% vs. 58.5%; *P*-value = 0.004). Of these 121 COVID-19 positive cases, shortness of breath (11.6%), anosmia (13%) and the severity of the illness requiring hospitalization (14.5%) were profound among non-HCQ users as compared to those who were prophylactically receiving HCQ. No serious side-effects were reported by the HCQ users. Conclusion: Voluntary pre-exposure HCQ administration significantly reduces the severity of illness, both symptomatic and radiological, among COVID-19 positive individuals.

Keywords: Coronavirus disease (COVID-19), hydroxychloroquine (HCQ), illness severity, pre-exposure prophylaxis

Introduction

The rapidly progressing coronavirus disease has immensely affected the healthcare sector, impacting public health and wellbeing. The World Health Organization (WHO) declared it a global pandemic, raising the overall national and international concerns. There has been a relentless increase in the statistics as the incidence and death rate associated with the novel coronavirus are in continuous transition [1]. It is known that the virus was first reported in Wuhan, China, by the end of 2019 and has spread unprecedentedly among several countries. According to the most recent WHO statistics, there have been 10,922,324 confirmed cases and 523,011 COVID-19 associated deaths spanning over 216 countries, areas, or territories around the world [2].

Due to the unpredictable consequences of COVID-19, the morbidity and mortality rates are likely to increase due to the diversion of all the available healthcare services towards the COVID-19 infected population, as it has left people with other serious untreated health problems [3]. With an undermined economy like that of Pakistan, COVID-19 spread, and the damage was inevitable [4]. Hence, there has been extensive ongoing research on the medical and pharmaceutical fronts for the treatment or prevention of this progressive health concern as it is a significant burden on the world's economy. There is a dire need for effective management of COVID-19, as the virus' distribution duration is rapid and mostly unlimited [5].

Among the major therapeutic agents in clinical trials as antiviral treatments include chloroquine (CQ) and the derivative molecule HCQ, Losartan, Remdesivir, Tocilizumab, intravenous immunoglobulin (IVIG), and convalescent plasma [6]. Several studies [7, 8] verified the in-vitro

activity of HCQ against SARS-CoV-2. It functions through a terminal impairment of the angiotensin-converting-enzyme 2 (ACE2) receptor glycosylation [7, 9]. The natural viral cycle depends on lysosomal fusion and the body's internal pH. CQ and HCQ act on the lysosomes and endosomes by increasing the pH, affects viral replication and prevents the cytokine activity modulating the immune response [3]. It has linear pharmacokinetics and distributes rapidly among several tissues [10, 11] with a half-life ranging from 5 to 40 days [11]. Other than these, antimalarial anthraquinones are also being used for the management of COVID-19 as per the latest guidelines [6, 7]. Hence, prophylactic HCQ (400 mg twice daily) is highly recommended for high-risk COVID-19 individuals [12].

The post-exposure prophylaxis of HCQ among individuals at a moderate to high risk of COVID-19 has been studied [13]. To the best of our knowledge, this is the first local study exploring the illness severity and symptom profile of the positive COVID-19 individuals with or without the prophylactic use of HCQ. However, internationally a HERO-HCQ trial has been registered to test the pre-exposure efficacy of HCQ in reducing COVID-19 risk [14]. While no conclusions can be drawn affirmatively, there are multiple studies in progress to confirm this at the national and international levels.

Materials and methods

A cross-sectional study was conducted at the Pakistan Institute of Medical Sciences (PIMS) of Islamabad, affiliated with Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), for one month from May to June 2020. A total of 485 high-risk individuals were enrolled in the study. Healthcare providers (HCPs) including physicians, nurses, ancillary staff members, respiratory therapists, triage personnel, primarily working in the emergency department (ED) and intensive care unit (ICU), anesthesiologists, certified registered nurse anesthetists (CRNAs), i.e. emergency medical technicians (EMTs), performing aerosol-generating procedures were considered high-risk COVID-19 individuals. Other than the HCPs, elderly individuals, diabetics, patients with chronic pulmonary diseases, hypertension, cardiovascular disease (CVD), chronic kidney disease (CKD), and immunocompromised individuals who were already taking HCQ on their own accord were also included. The people regularly praying at the mosque, medical storekeepers, and those working in highly interactive professions were also considered at high risk of attaining COVID-19 and were included. Among the excluded cases were individuals who refused to provide consent. The study protocol was approved by the Ethical Review Board of Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU) (Ref # F. 1-1/2015/ERB/SAZBMU/548; Dated April 06, 2020). The ethical guidelines were followed, and the study was conducted in accordance with the principles stated in the Declaration of Helsinki. Written informed consent was taken from the participants before enrolment.

The data were collected through a pre-designed self-reporting questionnaire inquiring about the individual's history, baseline characteristics, COVID-19 associated risk factors, exposure history, PCR and antibody screening results, HCQ drug dosages, and adverse effects, if any. The symptoms of COVID-19 and the severity of the illness were also recorded. The study sample was classified as HCQ users and non-HCQ users.

Statistical analysis

The comparative results were analyzed and presented using SPSS version 22.0. The continuous variables such as age were given as the mean and standard deviation, while all the other categorical variables were displayed as a frequency and a percentage. Further, a sub-analysis was also conducted in a sample of 121 PCR positive COVID-19 individuals with or without the prophylactic use of HCQ to investigate the study hypothesis. The associations were evaluated using Pearson's chi-square test, where a P-value < 0.05 was considered significant.

Results

The baseline characteristics of the HCQ users and the non-HCQ users were found to be comparable, as shown in **Table 1**. Out of the total of 485 participants, there were 264 HCQ users and 221 non-HCQ users, with an overall mean age of 30.5 ± 7.3 years. There were more male participants in both groups as compared to females (P = 0.011). Hypertension (3.9%),

Table 1. Demographic and clinical characteristics of the study participants

Variables	Overall (n = 485)	HCQ User (n = 264)	Non-HCQ User (n = 221)	*P*-value
Age (years)	30.5 ± 7.3	30.6 ± 7.2	30.4 ± 7.5	0.858
Age groups				
≤ 40 years	447 (92.2)	245 (92.8)	202 (91.4)	0.568
> 40 years	38 (7.8)	19 (7.2)	19 (8.6)	
Gender				
Male	274 (56.5)	163 (61.7)	111 (50.2)	0.011*
Female	211 (43.5)	101 (38.3)	110 (49.8)	
Occupation				
Doctor	429 (88.5)	235 (89)	194 (87.8)	0.527
Nurse/Paramedic Staff	31 (6.4)	18 (6.8)	13 (5.9)	
Others	25 (5.2)	11 (4.2)	14 (6.3)	
Affiliation				
Medicine	126 (26)	72 (27.3)	54 (24.4)	0.276
Anesthesia/ICU/COVID Ward/ER	90 (18.6)	44 (16.7)	46 (20.8)	
Surgeon	86 (17.7)	45 (17)	41 (18.6)	
OB/GYN	39 (8)	17 (6.4)	22 (10)	
Other Specialties	144 (29.7)	86 (32.6)	58 (26.2)	
Smoker	61 (12.6)	35 (13.3)	26 (11.8)	0.621
Presence of comorbidity	54 (11.1)	24 (9.1)	30 (13.6)	0.118
Diabetes	14 (2.9)	5 (1.9)	9 (4.1)	0.154
Hypertension	19 (3.9)	10 (3.8)	9 (4.1)	0.872
Chronic pulmonary disease	17 (3.5)	6 (2.3)	11 (5)	0.107
Others	13 (2.7)	6 (2.3)	7 (3.2)	0.543
RT-qPCR Result (n = 247)				
Positive	121 (49)	52 (40.3)	69 (58.5)	0.004*
Negative	126 (51)	77 (59.7)	49 (41.5)	
Antibody screening result (n = 426)				
IgM positive	91 (21.4)	48 (20.1)	43 (23)	0.467
IgG positive	12 (2.8)	9 (3.8)	3 (1.6)	0.181
Both IgM/IgG positive	28 (6.6)	16 (6.7)	12 (6.4)	0.909
Negative	295 (69.2)	166 (69.5)	129 (69)	0.917

*Age is given as the Mean ± SD and the all categorical variables are given as n (%). *HCQ: Hydroxychloroquine; ICU: intensive care unit; ED: emergency department; OB/GYN: obstetrics/gynecology. **P*-value < 0.05 is considered significant.

Chronic Pulmonary Disease (3.5%), and diabetes (2.9%) were the most common comorbid conditions observed in the overall studied population, where the majority were non-HCQ users. Moreover, there was a significant difference in the PCR test results among the HCQ users and non-users (P = 0.004), i.e. more than 50% of the COVID positive cases were non HCQ users compared to the HCQ users (40.3%). While the serology test results were comparatively insignificant (P > 0.05), with slightly higher frequencies of positive antibodies observed among those administering HCQ.

Table 2 shows a comparison of the symptoms, the severity of the illness, and the exposure history of the PCR positive COVID-19 individuals. Among the COVID-19 positive cases, symptoms including shortness of breath, anosmia, and the severity of the illness requiring hospitalization were profound among the non-HCQ users compared to those who were prophylactically receiving HCQ, with significant *P*-values of 0.045, 0.028, and 0.017 respectively. There was no significant association between HCQ use and exposure to COVID-19 patients as the exposure rates were comparable in the two

Table 2. Comparison of the symptoms, the severity of the illness, the exposure history and the other investigations between the prophylactic HCQ users and the non-users in the RT-qPCR positive individuals

Variables	Overall (n = 121)	HCQ User (n = 52)	Non-HCQ User (n = 69)	*P*-value
Signs & symptoms				
Flu-like illness	54 (44.6)	22 (42.3)	32 (46.4)	0.656
Fever	67 (55.4)	28 (53.8)	39 (56.5)	0.769
Cough	50 (41.3)	22 (42.3)	28 (40.6)	0.848
Sore throat	47 (38.3)	21 (40.4)	26 (37.7)	0.763
Shortness of breath	9 (7.4)	1 (1.9)	8 (11.6)	0.045*
Anosmia	10 (8.3)	1 (1.9)	9 (13)	0.028*
Ageusia	6 (5)	1 (1.9)	5 (7.2)	0.182
Myalgia	5 (4.1)	1 (1.9)	4 (5.8)	0.289
Severity of illness				
No Illness	34 (28.1)	14 (26.9)	20 (29)	0.803
Illness with outpatient observation	75 (62)	37 (71.2)	38 (55.1)	0.071
Illness with hospitalization	11 (9.1)	1 (1.9)	10 (14.5)	0.017*
Illness with ICU Admission/Ventilator Support	1 (0.8)	-	1 (1.4)	0.733
Other medications	29 (24)	10 (19.2)	19 (27.5)	0.289
Exposed to COVID-19 Patients				
Yes	105 (86.8)	46 (88.5)	59 (85.5)	0.635
Unsure	16 (13.2)	6 (11.5)	10 (14.5)	
Number of times exposed to COVID-19 confirmed patients				
No exposure	7 (5.8)	1 (1.9)	6 (8.7)	0.114
1 to 5 times	59 (48.8)	25 (48.1)	34 (49.3)	0.896
6 to 10 times	22 (18.2)	11 (21.2)	11 (15.9)	0.462
> 10 times	16 (13.2)	7 (13.5)	9 (13)	0.950
Don't know	17 (14)	8 (15.4)	9 (13)	0.714
Involved in patient sample taking	43 (35.5)	19 (36.5)	24 (34.8)	0.842
PPE used while taking patient samples				
No	84 (69.4)	33 (63.5)	51 (73.9)	0.217
Yes	37 (30.6)	19 (36.5)	18 (26.1)	
Type of PPE used while taking patient's sample (n = 37)				
Mask (N95/Surgical)	37 (100)	19 (100)	18 (100)	NA
Gloves	24 (64.9)	14 (73.7)	10 (55.6)	0.248
Other (PPE uniform/face-shield/goggles)	15 (40.5)	10 (52.6)	5 (27.8)	0.124
CXR finding (n = 105)				
Normal	80 (76.2)	38 (86.4)	42 (68.9)	0.038*
Abnormal	25 (23.8)	6 (13.6)	19 (31.1)	
CT scan finding (n = 14)				
Normal	10 (71.4)	5 (62.5)	5 (83.3)	0.393
Abnormal	4 (28.6)	3 (37.5)	1 (16.7)	
Duration of symptoms				
1 to 3 days	70 (57.9)	30 (57.7)	40 (58)	0.975
4 to 5 days	26 (21.5)	9 (17.3)	17 (24.6)	0.331
6 to 9 days	20 (16.5)	12 (23.1)	8 (11.6)	0.092
10 or more days	5 (4.1)	1 (1.9)	4 (5.8)	0.289
Hospital stay				

Not required	108 (89.3)	50 (96.2)	58 (84.1)	0.033*
1-3 days	7 (5.8)	1 (1.9)	6 (8.7)	0.114
4 days & above	5 (4.1)	-	5 (7.2)	0.382
Oxygen therapy received	7 (5.8)	-	7 (10.1)	0.018*

*Values are given as n (%). **P*-value < 0.05 is considered statistically significant. *HCQ: Hydroxychloroquine; ICU: intensive care unit; CXR: chest x-ray; CT: computed tomography, NA: not applicable.

Table 3. Drug dosages and Adverse effects reported by HCQ users

Variables		All HCQ Users (n = 264)	COVID-19 Positive Cases in HCQ User (n = 52)
*HCQ dosage	200/400 mg once weekly	71 (26.9)	14 (11.6)
	200/400 mg every 3 weekly	90 (34.1)	23 (19)
	200/400 mg single dose	103 (39)	15 (12.4)
Adverse effects	Nausea	17 (6.4)	11 (21.2)
	Abdominal pain	11 (28.6)	6 (11.5)
	Vomiting	10 (48.6)	9 (17.3)
	Headache	10 (22.9)	7 (13.5)
	Diarrhea	08 (28.6)	8 (15.4)

Values are given as n (%). *HCQ: Hydroxychloroquine.

groups, i.e. 88.5% HCQ users and 85.5% non-users. Moreover, both HCQ users and non-users were barely taking any preventive measures; only 30.6% of the HCPs used PPE while taking the patients' samples. Interestingly, abnormal chest X-ray results were more common (31.1%) among the non-HCQ users and were found to be statistically significant (P = 0.038). In the non-HCQ user group, a hospital stay was required in 16% of the individuals compared to 2% of the HCQ users. Oxygen therapy was only required in the non-HCQ users (10.1%) and was found to be statistically significant (P = 0.018).

The findings relating to drug dosages and the adverse effects in the overall HCQ users and HCQ users who tested positive for COVID-19 are presented in **Table 3**. Out of 264 HCQ users, 103 (39%) were administered a HCQ 200/400 mg single dose, 90 (34.1%) were on 200/400 mg every three weeks, and the rest were taking 200/400 mg once weekly. Overall, 35 (13.3%) patients reported adverse effects, and these included nausea, abdominal pain, vomiting, headache and diarrhea, which were minor and non-serious.

Discussion

The current scenario of COVID-19 has not only shattered the world's economy but has also created a healthcare crisis among the majority of countries. There has been extensive research concerning COVID-19 prevention and treatment. Several clinical trials investigating the efficacy of repurposed drugs have been carried out, but none has discovered a completely safe and effective COVID-19 treatment or prevention [14-17]. On the contrary, HCQ has comparatively attained recognition as it effectively reduces the risk of COVID-19 [18].

Our study aimed to compare the symptoms and severity of the illness among positive COVID-19 individuals with or without the prophylactic use of HCQ. It was observed that the illness severity, both symptomatic and radiological, was mild among the HCQ users as compared to the non-users. Fever (55.4%) was reported as one of the most prevalent symptoms among the positive COVID-19 individuals with or without the prophylactic use of HCQ, followed by flu-like illness (44.6%). Our comparative analysis found that shortness of breath (11.6%) and anosmia (13%) were significantly higher among the positive COVID-19 non-HCQ users as compared to the HCQ users (P < 0.05). Conversely, a randomized controlled trial observed increased shortness of breath among patients on standard medical care plus HCQ compared to those receiving standard medical care alone [16].

Although the two groups were comparable in terms of age, comorbidities, and exposure history, 88.5% HCQ users and 85.5% non-HCQ

users were exposed up to 10 times or more with confirmed COVID-19 patients. Still, the HCQ users displayed a significantly reduced severity of the illness, i.e. 14.5% of the non-HCQ users were extremely ill and required hospitalization compared to the HCQ users (1.9%; P = 0.017). One study indicated comparable disease severity and poor outcomes among both the COVID-19 HCQ users and non-users [19]. Furthermore, another study indicated that triple therapy with ivermectin, atorvastatin, and N-acetylcysteine could be a useful therapeutic approach in addition to the standard of care for COVID-19 [20]. Hence, it can be stated that despite the increased COVID-19 exposure history among the HCQ users, the severity of the illness and the frequency of symptoms among the HCQ users are insignificant as compared to the non-HCQ users.

As per the personal preventive practices, WHO recommended that high-risk individuals such as those dealing with COVID-19 cases must use an N95 mask and other personal protective equipment (PPE) [21]. Almost all of the HCQ users were using PPE, and there was not much difference between the two groups. Moreover, the hospital stays among the non-HCQ users were prolonged (1-3 days) compared to the HCQ users, i.e. 8.7% and 1.9%, respectively, and the same was the case for the patients requiring oxygen therapy (P = 0.018). With the current findings, this study concludes that HCQ effectively reduces the severity of illness and causes no serious side-effects. Nausea, vomiting, diarrhea, and headache were a few of the adverse effects reported by the enrolled HCQ users. In support, a similar study also reported diarrhea as the most common adverse effect associated with the pre-exposure prophylactic use of HCQ among the COVID-19 individuals, but the frequency of the side-effects was lower, and their intensity was mild among the individuals obtaining standard medical care (9%) as compared to those receiving HCQ (30%) [16]. Hence, the use of HCQ in terms of severity of illness and symptomatic relief might be effective, but its nature is still dubious in terms of the safety profile. HCQ use is only recommended in clinical trials as its general administration may cause other health problems, as stated by the US Food and Drug Administration [22]. Moreover, WHO also remains unsatisfied in claiming the drug as effective for COVID-19 and even for prophylaxis, halting one large clinical trial involving data from multiple countries to test the efficacy of HCQ in COVID-19 patients [23]. Among the major limitations were the non-randomized and observational aspects of the study. Further validation is required; large scale randomized controlled trials (RCTs) are recommended to further investigate the role of HCQ in lowering disease severity and symptomatic decline among positive COVID-19 cases.

Conclusion

In conclusion, this cross-sectional study involving COVID-19 exposed individuals found that the use of HCQ significantly reduces the illness severity and also manages the symptom profiles of the positive COVID individuals, suggesting that the drug supports pre-exposure prophylactic management. To better understand this phenomenon, clinical trials should be conducted in Pakistan involving the local population to provide more definite outcomes relating to the study's objective.

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Disclosure of conflict of interest

None.

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