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EFFECT THE PRE-EXPOSURE PROPHYLACTIC OF HYDROXYCHLOROQUINE ON SEVERE COVID-19 DISEASE: A RANDOMIZED CONTROLLED TRIAL

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Abstract. *Background. In vitro* studies have shown some effects for Hydroxychloroquine (HCQ) against SARS-CoV-2 virus. Despite effective vaccination program, relatively large proportion of population remains unvaccinated. So, there still remains a need for other prophylactic measures. The present study aims to evaluate whether HCQ can prevent severe COVID-19 outcomes among health-care workers. *Materials and methods.* In this randomized, double blind placebo-controlled clinical trial 334 healthcare workers aged 18–65 years old were included of whom 278 individuals completed the study. Participants were randomly assigned to the HCQ group (800 mg at day one, followed by 400 mg weekly for the next 7 weeks); or the placebo group. Participants were followed three weeks after the last dose of drug or placebo (10 weeks from the first dose of drug or placebo). The primary outcome was hospitalization or death from COVID-19. *Results.* Of 148 people who received HCQ, none were hospitalized or died from COIVD-19, while of 130 people who received the placebo, 2 (1.5%) were hospitalized for COIVD-19 (p-value: 0.26). And, 22 (14.9%) people in the HCQ group and 15 (11.6%) people in the placebo group contracted COVID-19 (p-value: 0.99). Adverse reactions were reported by 5 (3.4%) of participants in the HCQ group and 5 (3.9%) of participants in the placebo group (p-value: 0.99). *Conclusion*. We found that HCQ has no significant prevention effect on the incidence of mild COVID-19. However, the low rate of hospitalization (the primary outcome) in this trial like most of the other clinical trials with HCQ would have required increasing the sample size considerably to be able to comment on the effectiveness of HCQ in prevention of severe forms including death rate. This justifies systematic reviews to include similar studies to further investigate the issue.

Key words: *SARS-CoV-2, severe COVID-19, hydroxychloroquine, pre-exposure prophylaxis, adverse reactions, outcome.*

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ВЛИЯНИЕ ДОКОНТАКТНОЙ ПРОФИЛАКТИКИ ГИДРОКСИХЛОРОХИНОМ НА РАЗВИТИЕ ТЯЖЕЛОГО COVID-19: РАНДОМИЗИРОВАННОЕ КОНТРОЛИРУЕМОЕ ИССЛЕДОВАНИЕ

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Резюме. *История вопроса.* Исследования *in vitro* показали ряд эффектов гидроксихлорохина (HCQ) против вируса SARS-CoV-2. Несмотря на эффективную программу вакцинации, относительно большая часть населения остается непривитой. Таким образом, по-прежнему сохраняется необходимость в других профилактических мерах. Настоящее исследование нацелено на оценку возможности HCQ предотвратить тяжелые последствия COVID-19 среди медицинских работников. *Материалы и методы.* В настоящее рандомизированное двойное слепое плацебо-контролируемое клиническое исследование были включены 334 медицинских работника в возрасте от 18 до 65 лет, из которых 278 человек завершили исследование. Участники были случайным образом распределены в группу HCQ (800 мг в первый день, затем 400 мг еженедельно в течение следующих 7 недель) или группу плацебо. Эффективность мероприятий оценивали через 3 недели после приема последней дозы препарата или плацебо (через 10 недель после первой дозы препарата или плацебо). Основная конечная точка эффективности была представлена как уровень госпитализации или смерти пациента от COVID-19. *Результаты.* Из 148 человек, получавших HCQ, ни один не был госпитализирован и не умер от COVID-19, тогда как из 130 человек, получавших плацебо, 2 (1,5%) были госпитализированы с COVID-19 ($p = 0,26$). При этом 22 (14,9%) человека в группе HCQ и 15 (11,6%) человек в группе плацебо заразились COVID-19 ($p = 0,99$). О побочных реакциях сообщили 5 (3,4%) участников группы HCQ и 5 (3,9%) участников группы плацебо ($p = 0,99$). *Вывод.* Показано, что HCQ не оказывает существенного профилактического эффекта на заболеваемость легкой формой COVID-19. Однако низкий уровень госпитализации (основной результат) в этом исследовании, как и в большинстве других клинических исследований с HCQ, потребовал бы значительного увеличения размера выборки, чтобы иметь возможность оценить эффективность HCQ в предотвращении тяжелых форм, в том числе заканчивающихся летально. Это обосновывает необходимость проведения систематических обзоров с включением аналогичных исследований для дальнейшего изучения проблемы.

Ключевые слова: *SARS-CoV-2, тяжелая форма COVID-19, гидроксихлорохин, доконтактная профилактика, побочные реакции, результат.*

Introduction

Coronaviruses are a group of RNA-coated viruses that cause widespread respiratory, intestinal, liver, and neurological diseases in humans and other mammals and birds [1]. Coronavirus disease 2019 (COVID-19) was first reported in Wuhan in December 2019 then spread the world within weeks and initiated an ongoing pandemic [3, 4, 5, 6].

As of October 28, 2021, about 299 million people worldwide have been diagnosed with COVID-19 with more than 5.4 million deaths [5]. Iran has 8th rank in COVID-19 epidemic in the world where the number of infected patients is 6 204 925 and more than 131 847 deaths have occurred by 7/1/2022 [28].

Vaccination has had a substantial impact on case numbers and hospitalization in many countries, but limitations in global access to vaccines and reluctance to receive vaccines among some people mean that many populations remain vulnerable. Even in vaccinated individuals, uncertainties remain about duration of protection and efficacy of current vaccines against emerging SARS-CoV-2 variants [27]. So, there remains a need for more effective treatment and prophylactic measures.

Since the initiation of the COVID-19 outbreak, necessary actions have been taken to decrease the virus transmission and mortality [4, 13]. Nearly 2000 ongoing clinical trials for the assessment of the efficacy of pharmacologic therapy against COVID-19 infection have been registered in the WHO International Clinical Trials Registry Platform. Nonetheless, the efficiency of no specific prophylactic drugs has been confirmed [15]. Available treatments are based on COVID-19 severity currently, which comprise corticosteroids, antiviral drugs, immunomodulators, neutralizing antibody therapies, cell therapy, and gene therapy [19].

Hydroxychloroquine (HCQ) was described to possess anti-SARS-CoV activity *in vitro* in the previous SARS outbreak. Therefore, HCQ may be a potential pharmacological agent for COVID-19 prophylaxis [30]. HCQ is a well-known disease-modifying anti-rheumatic drug (DMARDs) which have been used for rheumatic diseases treatment as well as malaria prophylactic agent for decades. HCQ has immunomodulatory effects at cellular level. Specifically, inhibition of autophagy can prevent immune activation of different types of cells which inhibits cytokine production and modulates CD154 expression on T cells [17, 18, 19, 20, 21, 22].

HCQ's immunomodulatory profile, its ability to inhibit viral replication, and large amount of knowledge about the safety of this drug deriving from its use

in malaria prophylaxis and in the treatment of rheumatologic diseases, lead us to conduct this clinical trial to evaluate the pre-exposure prophylactic effect of HCQ on the incidence of severe COVID-19 disease in healthcare workers (HCW) in Iran.

Materials and methods

Study design. This study was a double-blind randomized placebo controlled clinical (field) trial with two parallel groups in 1 to 1 ratio. Written informed consent was obtained from all participants. The study was approved by the Iran National Committee for Ethics in Biomedical Research.

Study participants. Participants were randomly divided into HCQ and placebo groups. Healthcare workers of three hospitals affiliated to Islamic Azad University, Tehran Medical Unit (IAUTMU) and two day-surgery clinics in Tehran were invited to participate in the study. Between April 4, 2020 and October 21, 2020, we assessed 440 people for eligibility and enrolled 334 participants, of whom 278 individuals completed the study.

We estimated sample size using G*Power version 3.1.9.2. We estimated the minimum sample size assuming an expected incidence of 15% of COVID-19 in healthcare workers in the control (placebo) group and 5% in the HCQ group. Thus we required of a total 274 subjects (137 per group) for a significance level of 0.05, statistical power of 80% and assuming a rate of lost- to- follow up of 10%.

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})(p_1q_1 + p_2q_2)}{d^2} =$$

$$= \frac{7.8 \times (0.15 \times 0.85 + 0.05 \times 0.95)}{0.1^2} = 137$$

Inclusion criteria. Healthcare workers aged 18–65 years who registered for the call, consented to participate in the study, had no suspected COVID-19 symptoms at the time of enrollment, and no previous history of COVID-19 disease were included in the study.

Exclusion criteria. Those with a history of allergy or intolerance to HCQ, any known drug contraindication including previous history of retinopathy or long QT syndrome, porphyria, HIV-positive patients, patients with autoimmune diseases, current use of immunosuppressive drugs, body mass index (BMI) > 40, moderate to severe renal insufficiency, history of arrhythmia and pregnancy were excluded from the trial.

Intervention. For the assessed drug, placebo was made in the same size, shape and packaging as the original drug by the drug manufacturer (Tehran Darou pharmaceutical Co.). Randomization was performed by an epidemiologist and a statistician (computer based randomization with blocks of 4). Drugs and placebos were coded based on the codes specified in the Balanced-Blocked Randomization table.

Participants entered the assigned groups based on their entry sequence. The participant and the personnel who delivered the drugs and placebo were blind to them. The person designated for coding drugs and placebos had no role in drug delivery, data gathering or data analysis. Individuals who measured the variables during the study were also blind about individuals belonging to the groups (two-way blindness).

All the participants were assessed on day 1 (enrollment day) for eligibility according to the inclusion and exclusion criteria and written consents were obtained.

The HCQ group received HCQ 800 mg (i.e. four 200 mg tablets in two divided doses) on day 1 at first week, followed by 400 mg (i.e. two 200 mg tablets in a single dose) weekly for the 7 doses. The control group received placebo pills in the same way. Participants were advised to take the pills after their meals.

Participants were evaluated weekly by trained staff. Symptoms of COVID-19 disease, drug adverse reaction (i.e. frequency and severity of drug related adverse events), medication adherence (i.e. treatment and number of drugs taken) were assessed in telephone interviews and recorded on pre-printed questionnaires. Participants were advised to call and see the designated staff in each facility within 24 hours if they experience any symptoms for assessment of health status and collection of nasopharyngeal swabs if indicated. Suspected cases of COVID-19 were managed according to the protocol of the Iran Ministry of Health.

All participants were followed for 3 weeks after the last received dose or more in cases of COVID-19 disease.

Outcomes. Primary outcome of the study was severe forms of COVID-19 disease (shortness of breath, persistent chest pain or pressure, decreased level of consciousness, cyanosis of the lips and face) requiring hospital admission (including ward or ICU) or death. The secondary outcomes were confirmed or probable COVID-19 and HCQ side effects. Probable COVID-19 was defined based on compatible clinical characteristics and/or computerized tomography (CT) finding. Confirmed cases were those with positive SARS-CoV-2 PCR testing.

Statistical analysis. Data were presented as numbers and proportions for categorical variables and mean±standard deviation (SD) for continuous variables. For assessment of the difference of demographic data, COVID-19 status, symptom of COVID-19, method of COVID-19 diagnosis, drug adverse reactions, and types of adverse drug reaction between HCQ and placebo groups chi-square (χ^2) test, fisher exact test, and independent t-test were used. To find an equation for the best prediction of the probability of COVID-19 incidence, multivariable logistic regression was applied. Odds ratios (ORs) and its 95% confidence intervals (CIs) were obtained. Two-sided p-value less than 0.05 was considered statistically significant. All analyses were conducted using SPSS version 19.

Results

Enrollment of participants was conducted as proposed in the project. We enrolled 334 participants in the study, 278 individuals completed the research (Fig.).

Demographics characteristics. One hundred forty-eight in HCQ group and 130 in placebo group completed the study. As it is shown in Table 1, there were no statistically significant differences in the demographic characteristics of the participants between the two groups.

COVID-19 status and adverse drug reaction. There were no statistically significant differences in the number of mild cases of COVID-19 between the two groups (Table 2). Of 56 people who left the study, two people developed mild COVID-19 disease as well.

We found no severe cases in individuals of HCQ arm. Two cases of the placebo group required hospitalization due to severe forms of COVID-19 disease which was not statistically significant. However, it might be clinically significant as 11.7% of COVID-19 cases in the placebo group required hospitalization (Table 2) versus no cases in HCQ arm.

In total, about 50% of cases were diagnosed based on clinical findings compatible with COVID-19 and there were no statistically significant differences between the two groups in the method of diagnosis of COVID-19 (P-value = 0.45, Table 2). Both cases of severe COVID-19 had positive PCR test results. Among patients with positive clinical plus positive chest CT scan findings, 3 cases (37.5%) had negative PCR tests.

No statistically significant differences were observed in the incidence and type of adverse drug reactions between the two groups (P-value = 0.99 and 0.94, respectively, Table 2). No serious HCQ related side effects were seen.

COVID-19 symptoms. The most frequent symptoms were fever, musculoskeletal pain and chills in both groups. There were no statistically significant differences in the symptoms of the involved cases between the two groups (Table 3).

Considering that none of the variables were statistically significant in the chi-square analysis and p-value was not below 0.1 in any of the analyzes, so to predict the incidence of COVID-19 in the two groups of HCQ and placebo, we entered all variables with a level of $p < 0.5$ into multivariable logistic regression analysis by backward stepwise method. However, in multivariable logistic regression analysis, none of the variables were statistically significant for predicting COVID-19 infection.

Discussion

In this randomized, double-blind, placebo-controlled trial, we investigated the efficacy of HCQ as COVID-19 pre-exposure prophylaxis. Our study showed no statistically significant difference be-

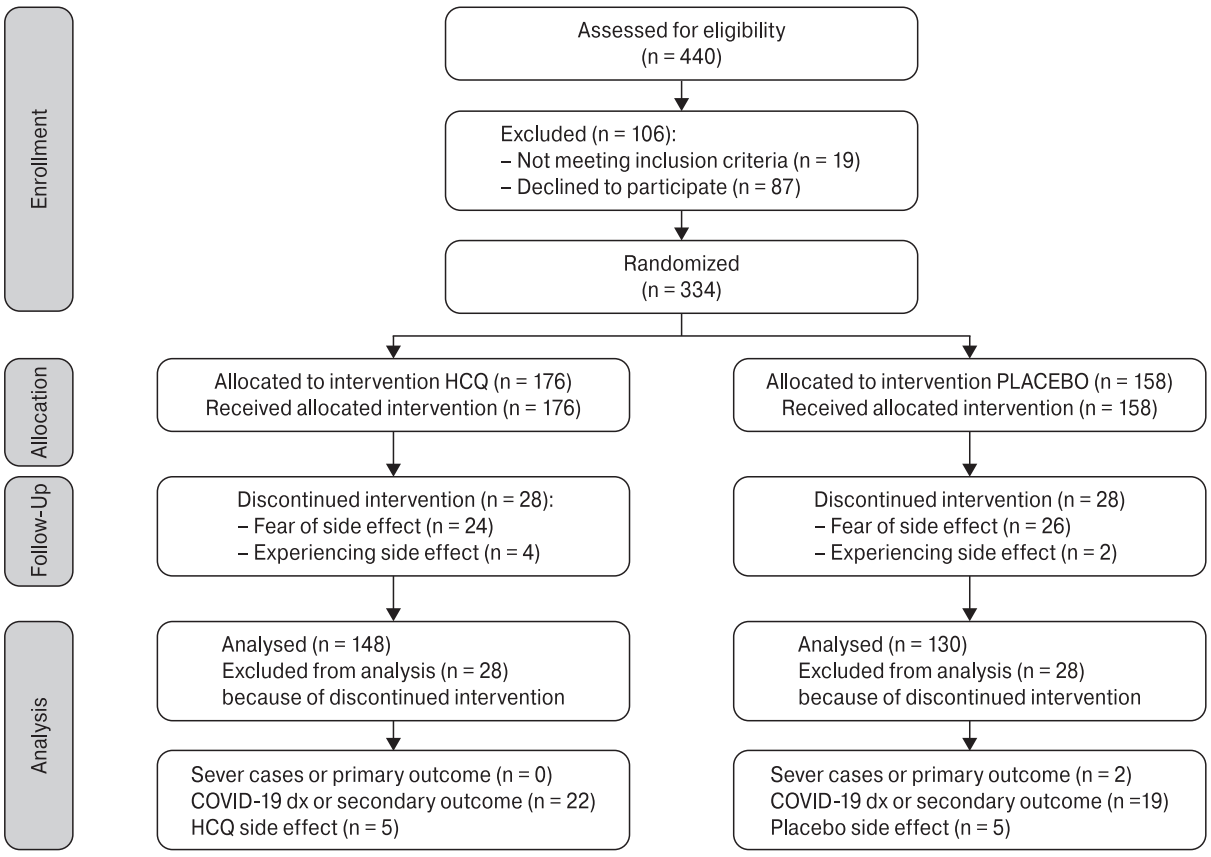

Figure. Flow of the participants through study

tween placebo and HCQ in preventing COVID-19 infection; however, we believe that the low event rate of hospitalization in our study like many other studies could have affected the result of the study.

Contradictory results have been observed in various studies investigating the effects of HCQ on COVID-19 outcomes [21, 22, 23, 24]. Currently, there are many studies that reported no added benefit for the use of CQ or HCQ in the treatment of COVID-19 patients [5, 6, 7, 8]. Howeverб most of these studies are reported to be underpowered to comment on the mortality as primary outcome because of the low event rate of mortality. Skipper et al. mentioned increasing the sample size to about 6000 would have been needed to evaluate the effectiveness of HCQ while they recruited 423 participants. For this reason, they changed the primary outcome from severe forms of COVID-19 to "change in overall symptom severity over 14 days" [25]. A recent multicenter, population-based national retrospective-cohort study of 28 759 adults with mild COVID-19 showed that the odds of hospitalization or death was reduced significantly in patients who were given HCQ early in the course of COVID-19 disease [18]. Ip et al. also reported that in SARS-CoV-2 infected non-hospitalized patients, HCQ exposure was associated with a decreased rate of subsequent hospitalization (OR 0.53; 95% CI, 0.29, 0.95) [10].

On the other hand, the available evidence indicates that the drug should be started early in the course of the disease to show outcome benefits. Other studies that investigated whether post-exposure prophylaxis could prevent COVID-19 failed to show preventive effect on the illness [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23].

However, there is some concern that the post-exposure drug may have not achieved adequate concentrations early enough to show a benefit [23]. Rajasingham R. et al. investigated the efficacy of HCQ as pre-exposure prophylaxis for COVID-19 in healthcare workers and reported no statistically significant difference. They recruited the study from a broad geographic area to increase the generalizability of the findings [20]. We also tried to enroll our study participants from different

Table 1. Demographics characteristics of the participants

Characteristics		HCQ (n = 148) N (%)	Placebo (n = 130) N (%)	P-value
Gender	Male	74 (50)	73 (56.2)	0.31
	Female	74 (50)	57 (43.8)	
Marital status	Single	37 (25)	35 (26.9)	0.57
	Married	111 (75)	95 (73.1)	
Ethnicity	Persian	77 (52)	72 (55.4)	0.57
	Non-Persian	71 (48)	58 (44.6)	
Education level	Diploma and lower	29 (19.6)	27 (20.8)	0.87
	Bachelor	75 (50.7)	70 (53.8)	
	Student	17 (11.5)	12 (9.2)	
	Master and higher	27 (18.2)	21 (16.2)	
Smoking	No	134 (90.5)	118 (90.8)	0.94
	Yes	14 (9.5)	12 (9.2)	
Comorbidity*	No	138 (93.2)	119 (91.5)	0.59
	Yes	10 (6.8)	11 (8.5)	
Medication	No	138 (93.2)	120 (92.3)	0.76
	Yes	10 (6.8)	10 (7.7)	
Age (year), mean± SD		38.98±10.71	39.39±10.33	0.74

Note. *Including Diabetes Mellitus, hypertension, Chronic Obstructive Pulmonary Disease (COPD), Asthma.

Table 2. Comparison of COVID-19 status and adverse drug reaction in HCQ and Placebo groups

Variables		HCQ (n = 148) N (%)	Placebo (n = 130) N (%)	OR (95%CI)	P-value
COVID-19 status	None	126 (85.1)	113 (86.9)	–	0.26
	Mild	22 (14.9)	15 (11.6)		
	Severe	0 (0)	2 (1.5)		
Adverse reactions	No	143 (96.6)	125 (96.1)	1.18 (0.42–3.27)	0.99
	Yes	5 (3.4)	5 (3.9)		
Diagnosis method	Clinical only	11 (50)	9 (52.9)	–	0.45
	Clinical+PCR	6 (27.3)	6 (35.3)		
	Clinical+CT	3 (13.6)	0 (0)		
	Clinical+PCR+CT	2 (9.1)	2 (11.8)		
Adverse reaction types	None	142 (94)	129 (94.9)	–	0.94
	Gastrointestinal (GI)	3 (2)	2 (1.5)		
	Headache	1 (0.7)	1 (0.7)		
	Cardiac	1 (0.7)	1 (0.7)		
	GI and headache	2 (1.3)	1 (0.7)		
	Eye	0 (0)	1 (0.7)		
	Fatigue	2 (1.3)	1 (0.7)		

Table 3. Comparison of symptoms of COVID-19 patients in two HCQ and Placebo groups

Symptoms	HCQ group (n = 22) N (%)	Placebo group (n = 17) N (%)	P-value
Fever	15 (68.2)	14 (82.4)	0.46
Chills	14 (63.6)	11 (64.7)	0.94
Cough	10 (45.5)	6 (35.3)	0.52
Shortness of breath	10 (45.5)	3 (17.6)	0.06
Anorexia	11 (50)	4 (23.5)	0.09
Running nose	6 (27.3)	1 (5.9)	0.11
Decreased sense of smell	9 (40.9)	4 (23.5)	0.25
Decreased taste	2 (9.1)	0 (0)	0.49
Headache	7 (31.8)	5 (29.4)	0.87
Sore throat	4 (18.2)	1(5.9)	0.36
Chest pain	3 (13.6)	1 (5.9)	0.62
Myalgia	16 (72.7)	13 (76.5)	0.79
Nausea	4 (18.2)	1 (5.9)	0.36
Vomiting	1 (4.5)	0 (0)	0.99
Diarrhea	5 (22.7)	2 (11.8)	0.44

health settings to increase the generalizability of our study. In their study the total number of PCR confirmed COVID-19 patients among total cases of COVID-19 were 18% [20], in comparison to ours of 36%. Another randomized double-blind placebo-controlled clinical trial reported no clinical benefit for HCQ when administered daily for 8 weeks as pre-exposure prophylaxis in COVID-19 patients [1]. This study was limited by early termination. The primary outcome of this study was the incidence of SARS-CoV-2 infection as determined by a nasopharyngeal swab. In comparison, in our study the primary outcome was severe COVID-19. We decided to do that because our main hypothesis was that HCQ as a disease modifying agent may prevent severe disease. Another similar study was conducted by Berta et al., among healthcare workers. However, the community incidence of SARS-CoV-2 events decreased during their study. So this study was also deemed underpowered to answer the main objective [7].

Similar to these studies [20, 21, 23, 24, 25, 27], our study did not show any significant differences in infection incidence between HCQ and control groups. We did not also see a statistical difference in incidence of symptoms of COVID-19 cases between the two groups. The most frequent symptoms in both groups were fever and chills. However, we found two severe cases in the control group with no severe cases in HCQ group. These may have clinical importance and rationalize further investigations with more cases in the future studies. At this time, with the current status of pandemic and availability of effective vaccines, it is unlikely to have the opportunity to run new original studies that investigate the effect of HCQ prophylaxis on COVID-19. However, there are some studies on the same issue not published yet. We recommend systematic reviews to include the data of studies similar to ours' that are pending to be published and also inclusion of the studies that HCQ has started early in the course of COVID-19 to further illuminate the issue.

Similar to other studies of HCQ for either prophylaxis or COVID-19 treatment [21, 23, 24, 25, 27], we found that the medication was generally well tolerated. In our study we had advised the participants to take the medication after meal knowing that the gastrointestinal side effect is the most frequently reported side effect of the HCQ and we observed that HCQ is better tolerated after meal.

Study limitations. The most important limitation of our study was the small sample size of the study. Like many other studies with HCQ, our study suffered from the exclusion of the old age group which we know is the most vulnerable. The other limitation was free testing shortages which made it impossible to frequently check the PCR status to detect the asymptomatic COVID-19 infections.

Conclusion

Our study showed no differences in COVID-19 incidence between HCQ and control group. However, we found no severe cases in the HCQ arm but in the placebo group two cases required hospitalization. The low rate of hospitalization (the primary outcome) in this trial like most of the above mentioned clinical trials with HCQ would have required increasing the sample size considerably to be able to comment on the effectiveness of HCQ in prevention of severe forms including death rate. It justifies systematic reviews to include similar studies to further investigate the issue.

Additional information

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Declaration of competing interest. All authors declare no conflict of interest.

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