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

Mahnaz Valizadeh [a],

Termeh Tarjoman [a],

Behnam Farhoudi [a],

Arezoo Chouhdari [a],

Masoumeh Mesgarian [a],

Seyed Ahmad Seyed Alinaghi [b],

Mehrangiz Zangeneh [a],

Zahra Hanifezadeh [a],

Hesam Adain Atashi [a],

Hamidreza Massumi naini [a],

Shahla Abolghasemi [a],

Manije Dezfulinejad [a],

Shima Haghani [c],

[a] Amir-al-momenin hospital Tehran Medical sciences, Islamic Azad University, Tehran, Iran.

[b] Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran.

[c] Nursing Care Research Center, Iran University of Medical Sciences, Tehran, Iran.

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.

Methods: In this randomized, double blind placebo-controlled clinical trial 334 healthcare workers aged 18-65 year-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 or died 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.

Keywords: SARS-CoV-2, Severe COVID-19, Hydroxychloroquine, Pre-exposure prophylaxis, Adverse reactions, Outcome.

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

Махназ Велизаде [1],

Терме Тарджоман [1],

Бехнам Фархуди [1],

Арезу Чоудари [1],

Масуме Месгарян [1],

Сейед Ахмад Сейед Алинаги [2],

Мехрангиз Зангене [1],

Захра Ханифезаде [1],

Хесам Адайн Аташи [1],

Хамидреза Массуми наини [1],

Шахла Аболгасеми [1],

Мание Дезфулинежад [1],

Шима Хагани [3]

[1] Больница Амир-аль-Моменин, Тегеранский университет медицинских наук, Исламский университет Азад, Тегеран, Иран.

[2] Иранский исследовательский центр ВИЧ/СПИДа, Иранский институт снижения поведения высокого риска, Тегеранский университет медицинских наук, Тегеран, Иран.

[3] Научно-исследовательский центр сестринского дела, Иранский университет медицинских наук, Тегеран, Иран.

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 у HCQ предотвратить тяжелые последствия COVID-19 среди медицинских работников.

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 группа плацебо. Эффективность мероприятий оценивали через три 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 или умерли от COVID-19 (значение p: 0,26). При этом 22 (14,9%) человека в группе HCQ и 15 (11,6%) человек в группе плацебо заразились COVID-19 (значение p: 0,99). О побочных реакциях сообщили 5 (3,4%) участников группы HCQ и 5 (3,9%) участников группы плацебо (значение 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, включая уровень смертности. 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.

1 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 [3-6].

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 2,000 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 [22-17].

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.

2 **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%.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 (p_1 q_1 + p_2 q_2)}{d^2} = \frac{7.8 \times (0.15 \times 0.85 + 0.05 \times 0.95)}{0.1^2} = 137$$

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 ($\chi 2$) 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.

3 **Results**

Enrollment of participants was conducted as proposed in the project. We enrolled 334 participants in the study, 278 individuals completed the research **(Figure 1)**.

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.

4 **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 between 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 [24-21]. Currently, there are many studies that reported no added benefit for the use of CQ or HCQ in the treatment of COVID-19 patients [5-8]. However; 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- 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 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 [29]. 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 [20-7], 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 [21-7], 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.

5 **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.

Funding: The project funding was provided by Islamic Azad University.

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

Acknowledgment: The study was approved by the Iran National Committee for Ethics in Biomedical Research (Ethics code: IR.IAU.PS.REC.1399.001). The

study was also registered on IRCT site (IRCT20200424047184N1). The authors would like to acknowledge Zahra Eskandari for her great cooperation in follow ups.

FIGURES

Figure 1. Flow of the participants through study.

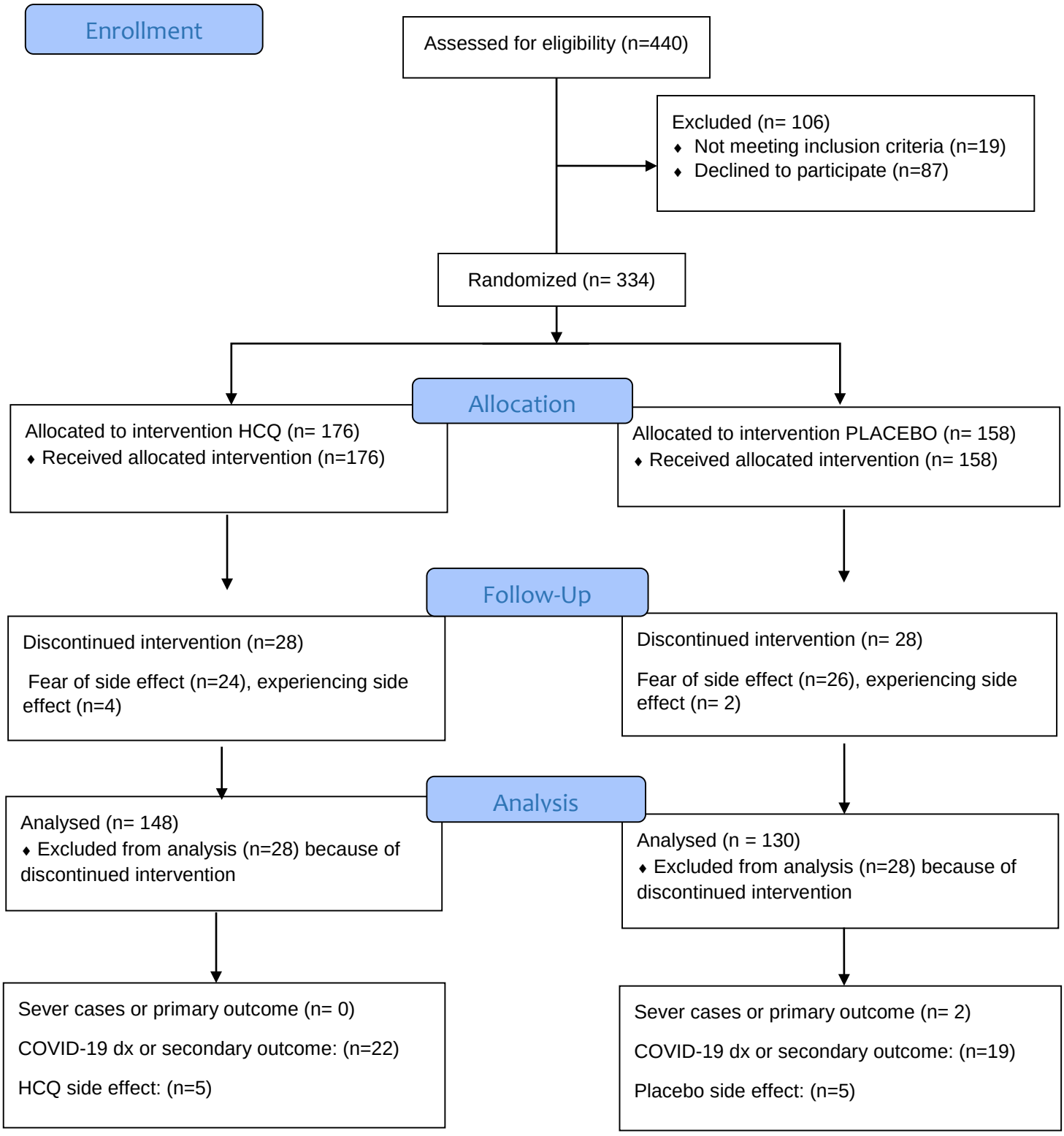
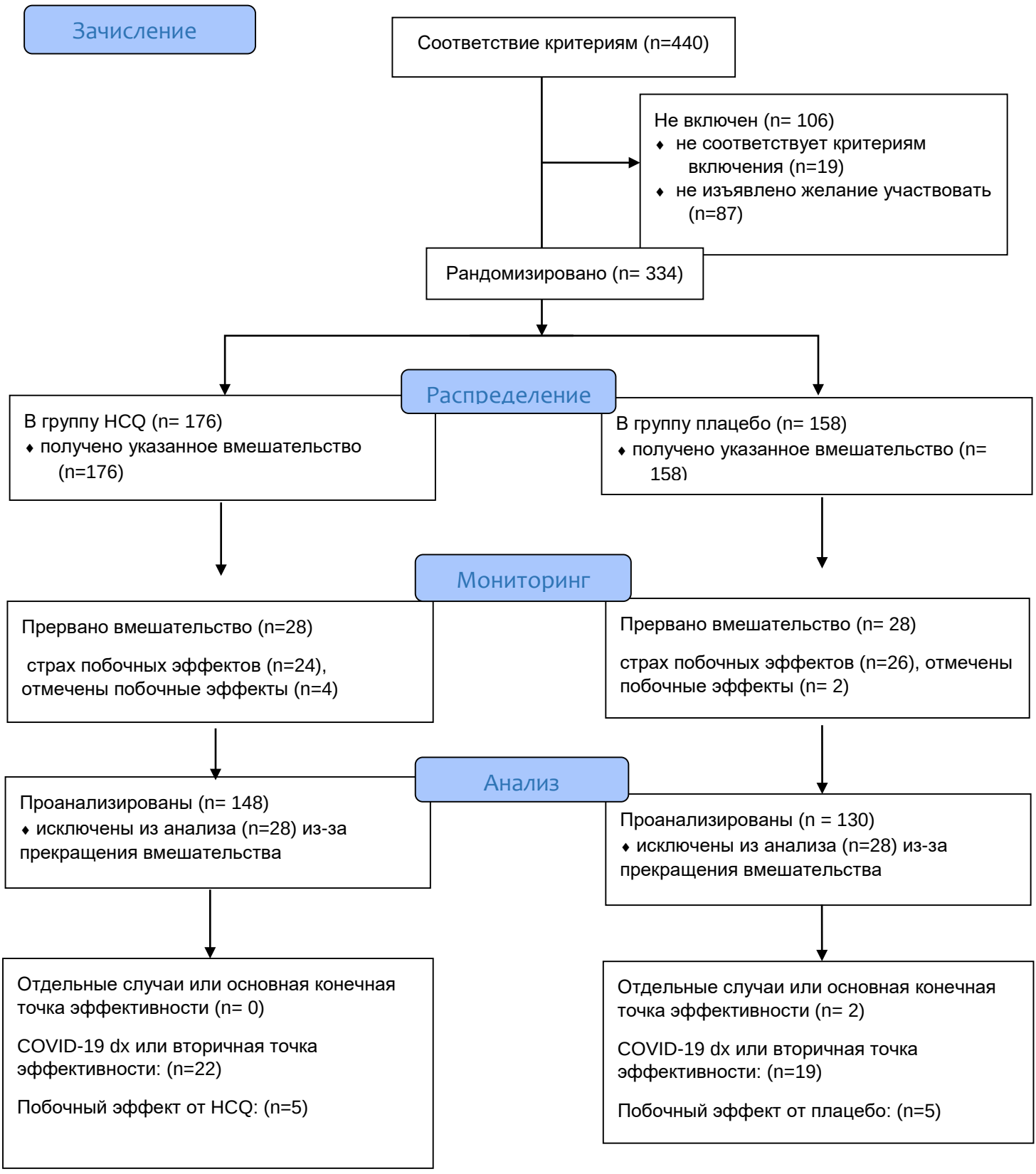


Figure 1. Flow of the participants through study.

Рисунок 1. Поток участников во время исследования.



TABLES

Table 1. Demographics characteristics of the participants.

Таблица 1. Демографические характеристики участников.

Characteristics **Характеристики**	**HCQ (n=148)** **N (%)** **mean± SD** **среднее±с.о.**	**Placebo (n=130)** **Плацебо** **N (%)** **mean± SD**	**P-value** **Р-величина**
Gender Пол Male М Female Ж	 74 (50) 74 (50)	 73 (56.2) 57 (43.8)	0.31
Marital status Семейное положение Single Не в браке Married В браке	 37 (25) 111 (75)	 35 (26.9) 95 (73.1)	0.57
Ethnicity Этническая принадлежность Persian	 77 (52)	 72 (55.4)	0.57

Перс Non-Persian Не перс	71 (48)	58 (44.6)	
Education level Образование Diploma and lower Аттестат и ниже Bachelor Бакалавр Student Студент Master and higher Магистр и выше	 29 (19.6) 75 (50.7) 17 (11.5) 27 (18.2)	 27 (20.8) 70 (53.8) 12 (9.2) 21 (16.2)	0.87
Smoking Курение No Нет Yes Да	 134 (90.5) 14 (9.5)	 118 (90.8) 12 (9.2)	0.94
Comorbidity* Сопутствующие заболевания No Нет Yes Да	 138 (93.2) 10 (6.8)	 119 (91.5) 11 (8.5)	0.59
Medication			

Лечение No Нет Yes Да	138 (93.2) 10 (6.8)	120 (92.3) 10 (7.7)	0.76
Age (year) **Возраст (лет)**	38.98±10.71	39.39±10.33	0.74

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

*Включая сахарный диабет, гипертонию, хроническую обструктивную болезнь легких (ХОБЛ), астму.

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

Таблица 2. Сравнение статуса COVID-19 и побочных реакций на лекарства в группах HCQ и плацебо.

Variables **Переменные**	**HCQ group** **Группа HCQ** **(n=148)**	**Placebo group** **Группа плацебо** **(n=130)**	**OR** **(95%CI)** **ОШ (95% ДИ)**	**P-value** **Величина P**
	N (%)	**N (%)**		
COVID-19 Status **Статус**			-	0.26
None Нет	126 (85.1)	113 (86.9)		
Mild Легкая	22 (14.9)	15 (11.6)		
Severe Тяжелая	0 (0)	2 (1.5)		
Adverse Reactions **Неблагоприятные реакции**			1.18 (0.42-3.27)	0.99
No Нет	143 (96.6)	125 (96.1)		
Yes Да	5 (3.4)	5 (3.9)		
Diagnosis Method				

Постановка диагноза Clinical only Только клиническая картина Clinical+ PCR клиническая картина + ПЦР Clinical+ CT клиническая картина _КТ Clinical+ PCR+ CT клиническая картина +ПЦР+КТ	11 (50) 6 (27.3) 3 (13.6) 2 (9.1)	9 (52.9) 6 (35.3) 0 (0) 2 (11.8)	-	0.45
Adverse Reaction Types **Типы неблагоприятных реакций** None Нет Gastrointestinal (GI) Желудочно-кишечный тракт (ЖКТ) Headache	142 (94) 3 (2) 1 (0.7) 1 (0.7) 2 (1.3)	129 (94.9) 2 (1.5) 1 (0.7) 1 (0.7) 1 (0.7)	-	0.94

Головная боль Cardiac Сердечные GI and headache ЖКТ и головная боль Eye Зрение Fatigue Усталость	0 (0) 2 (1.3)	1 (0.7) 1 (0.7)		

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

Таблица 3. Сравнение симптомов пациентов с COVID-19 в группе HCQ и плацебо.

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

Симптомы	**Группа HCQ (n=22)** **N (%)**	**Группа плацебо (n= 17)** **N (%)**	**P**
Высокая температура	15 (68.2)	14 (82.4)	0.46
Озноб	14 (63.6)	11 (64.7)	0.94
Кашель	10 (45.5)	6 (35.3)	0.52
Одышка	10 (45.5)	3 (17.6)	0.06
Анорексия	11 (50)	4 (23.5)	0.09
Насморк	6 (27.3)	1 (5.9)	0.11
Снижение обоняния	9 (40.9)	4 (23.5)	0.25
Снижение вкуса	2 (9.1)	0 (0)	0.49
Головная боль	7 (31.8)	5 (29.4)	0.87
Больное горло	4 (18.2)	1(5.9)	0.36
Боль в груди	3 (13.6)	1 (5.9)	0.62
Миалгия	16 (72.7)	13 (76.5)	0.79
Тошнота	4 (18.2)	1 (5.9)	0.36
Рвота	1 (4.5)	0 (0)	0.99
Диарея	5 (22.7)	2 (11.8)	0.44

TITLE PAGE_METADATA

Блок 1. Информация об авторе ответственном за переписку

Behnam Farhoudi, Associate Professor, Department of infection disease, Faculty of medicine, Amir-al-momenin hospital Tehran Medical sciences, Islamic Azad University Tehran, Iran, b_farhoudi@yahoo.com

Блок 2. Информация об авторах

Mahnaz Valizadeh, Assistant Professor, Department of internal Medicine, Faculty of medicine, Amir-al-momenin hospital Tehran Medical sciences, Islamic Azad University, Tehran, Iran, valizadehmahnaz@yahoo.com

Termeh Tarjoman, Assistant Professor, Social determinants of health research center, Amir-al-momenin hospital, Tehran Medical sciences, Islamic Azad University Tehran, Iran, termehtarjoman@gmail.com

Arezoo Chouhdari, Assistant Professor, Social Determinants of Health Research Center, Amir-al-momenin Hospital, Tehran Medical sciences, Islamic Azad University, Tehran, Iran, chouhdariarezoo@gmail.com

Masoumeh Mesgarian, Assistant Professor, Department of Infectious Diseases, Faculty of medicine, Amir-al-momenin hospital, Tehran Medical Sciences, Islamic Azad University Tehran, Iran, m88mesgarian@gmail.com

SeyedAhmad SeyedAlinaghi, Associate Professor, Iranian Research Center for HIV/AIDS, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, Tehran, Iran. s.a.alinaghi@gmail.com

Mehrangiz Zangeneh, Associate Professor, Department of Infectious Diseases, Faculty of medicine, Amir-al-momenin hospital, Tehran Medical Sciences, Islamic Azad University Tehran, Iran, zangeneh4@yahoo.com

Zahra Hanifezadeh Bachelor of Midwifery, Amir-al-momenin hospital Tehran Medical Sciences, Islamic Azad University Tehran, Iran, Zahra.hanifeofficial@gmail.com

Hesam Adain Atashi, researcher, Amir-al-momenin hospital, Tehran medical sciences branch, Islamic Azad University Tehran, Iran, Hero4p@gmail.com

Hamidreza Massumi naini, Assistant Professor, Department of Internal Medicine, Faculty of

medicine, Amir-al-momenin hospital Tehran Medical Sciences, Islamic Azad University Tehran, Iran, massumi44@yahoo.com

Shahla Abolghasemi, Assistant Professor, Department of Internal Medicine, Faculty of medicine, Buali hospital, Tehran Medical Sciences, Islamic Azad University Tehran, Iran,

shahlamarmin@yahoo.com

Manije Dezfulinejad, Assistant Professor, Department of Infectious Diseases, Faculty of medicine, Buali hospital, Tehran Medical Sciences, Islamic Azad University Tehran, Iran,

dr.dezfuli2011@yahoo.com

Shima Haghani, Nursing Care Research Center, Iran University of Medical Sciences, Tehran, Iran, shima_haghani@yahoo.com

Блок 1. Информация об авторе ответственном за переписку

Бехнам Фархуди, доцент кафедры инфекционных заболеваний медицинского факультета больницы Амир-аль-Моменин Тегеран Медицинские науки Исламского университета Азад Тегеран, Иран, b_farhoudi@yahoo.com

Блок 2. Информация об авторах

Махназ Вализаде, доцент, кафедра внутренней медицины, медицинский факультет, больница Амир-аль-Моменин, Тегеранский университет медицинских наук, Исламский университет Азад, Тегеран, Иран, valizadehmahnaz@yahoo.com

Терме Тарджоман, доцент, Центр исследований социальных детерминант здоровья, больница Амир-аль-Моменин, Тегеранский университет медицинских наук, Исламский университет Азад, Тегеран, Иран, termehtarjoman@gmail.com

Арезу Чохдари, доцент, Центр исследований социальных детерминант здоровья, Больница Амир-аль-Моменин, Тегеранский университет медицинских наук, Исламский университет Азад, Тегеран, Иран, chouhdariarezoo@gmail.com

Масуме Месгарян, доцент кафедры инфекционных болезней медицинского факультета больницы Амир-аль-Моменин, Тегеранский университет

медицинских наук Исламского университета Азад Тегеран, Иран, m88mesgarian@gmail.com

СейедАхмад СейедАлинаги, доцент, Иранский исследовательский центр ВИЧ/СПИДа, Иранский институт снижения поведения высокого риска, Тегеранский университет медицинских наук, Тегеран, Иран. s.a.alinaghi@gmail.com

Мехрангиз Зангене, доцент кафедры инфекционных болезней медицинского факультета больницы Амир-аль-Моменин Тегеранский университет медицинских наук Исламского университета Азад Тегеран, Иран, zangeneh4@yahoo.com

Захра Ханифезаде, Бакалавр акушерства, больница Амир-аль-Моменин, Тегеранский университет медицинских наук, Исламский университет Азад, Тегеран, Иран, Zahra.hanifeofficial@gmail.com

Хесам Адайн Аташи, научный сотрудник, больница Амир-аль-моменин, филиал Тегеранского университета медицинских наук, Исламский университет Азад, Тегеран, Иран, Hero4p@gmail.com

Хамидреза Массуми Наини, доцент кафедры внутренней медицины факультета медицины, больница Амир-аль-Моменин, Тегеранский университет медицинских наук, Исламский университет Азад, Тегеран, Иран, Massumi44@yahoo.com

Шахла Аболгасеми, доцент кафедры внутренней медицины медицинского факультета больницы Буали, Тегеранский университет медицинских наук Исламского университета Азад Тегеран, Иран, shahlamarmin@yahoo.com

Манидже Дезфулинежад, доцент кафедры инфекционных болезней медицинского факультета больницы Буали, Тегеранский университет медицинских наук Исламского университета Азад Тегеран, Иран, dr.dezfuli2011@yahoo.com

Шима Хагани, Исследовательский центр сестринского ухода, Иранский университет медицинских наук, Тегеран, Иран, shima_haghani@yahoo.com

Блок 3. Метаданные статьи

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

Running head:

PRE-EXPOSURE PROPHYLACTIC OF HYDROXYCHLOROQUINE ON COVID-19

Keywords: SARS-CoV-2, Severe COVID-19, Hydroxychloroquine, Pre-exposure prophylaxis, Adverse reactions, Outcome.

Original article.

9 pages, 3 table, 1 figure.

06.07.2023

REFERENCE

No.	Authors, Title	DOI/URL
1	Abella BS, Jolkovsky EL, Biney BT, Uspal JE, Hyman MC, Frank I, Hensley SE, Gill S, Vogl DT, Maillard I, Babushok DV, Huang AC, Nasta SD, Walsh JC, Wiletyo EP, Gimotty PA, Milone MC, Amaravadi RK; Prevention and Treatment of COVID-19 With Hydroxychloroquine (PATCH) Investigators. Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial. JAMA Intern Med. 2021 Feb 1; 181(2):195-202. doi: 10.1001/jamainternmed.2020.6319. PMID: 33001138; PMCID: PMC7527945.	doi: 10.1001/jamainternmed.2020.6319.
2	Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, Skipper CP, Nascene AA, Nicol MR, Abassi M, Engen NW, Cheng MP, LaBar D, Lother SA, MacKenzie LJ, Drobot G, Marten N, Zarychanski R, Kelly LE, Schwartz IS, McDonald EG, Rajasingham R, Lee TC, Hullsiek KH. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med. 2020 Aug 6; 383(6):517-525. doi: 10.1056/NEJMoa2016638. Epub 2020 Jun 3. PMID: 32492293; PMCID: PMC7289276.	DOI: 10.1056/NEJMoa2016638
3	Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S,	DOI: 10.1056/NEJMoa2001282

	Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 May 7;382(19):1787-1799. doi: 10.1056/NEJMoa2001282. Epub 2020 Mar 18. PMID: 32187464; PMCID: PMC7121492.	
4	Dadras O, Alinaghi SAS, Karimi A, MohsseniPour M, Barzegary A, Vahedi F, Pashaei Z, Mirzapour P, Fakhfouri A, Zargari G, Saeidi S, Mojdeganlou H, Badri H, Qaderi K, Behnezhad F, Mehraeen E. Effects of COVID-19 prevention procedures on other common infections: a systematic review. Eur J Med Res. 2021 Jul 3; 26(1):67. doi: 10.1186/s40001-021-00539-1. PMID: 34217366; PMCID: PMC8253677.	https://doi.org/10.1186/s40001-021-00539-1
5	Eze P, Mezue KN, Nduka CU, Obianyo I, Egbuche O. Efficacy and safety of chloroquine and hydroxychloroquine for treatment of COVID-19 patients-a systematic review and meta-analysis of randomized controlled trials. Am J Cardiovasc Dis. 2021 Feb 15; 11(1):93-107. PMID: 33815925; PMCID: PMC8012280.	https://pubmed.ncbi.nlm.nih.gov/33815925/
6	Girum T, Lentiro K, Geremew M, Migora B, Shewamare S. Global strategies and effectiveness for COVID-19 prevention through contact tracing, screening, quarantine, and isolation: a systematic review. Trop Med Health. 2020 Nov 23; 48(1):91.	https://doi.org/10.1186/s41182-020-00285-w

	doi: 10.1186/s41182-020-00285-w. PMID: 33292755; PMCID: PMC7680824.	
7	Grau-Pujol B, Camprubí-Ferrer D, Marti-Soler H, Fernández-Pardos M, Carreras-Abad C, Andrés MV, Ferrer E, Muelas-Fernandez M, Jullien S, Barilaro G, Ajanovic S, Vera I, Moreno L, Gonzalez-Redondo E, Cortes-Serra N, Roldán M, Arcos AA, Mur I, Domingo P, Garcia F, Guinovart C, Muñoz J. Pre-exposure prophylaxis with hydroxychloroquine for COVID-19: a double-blind, placebo-controlled randomized clinical trial. Trials. 2021 Nov 15; 22(1):808. doi: 10.1186/s13063-021-05758-9. PMID: 34781981; PMCID: PMC8591593.	doi: 10.1186/s13063-021-05758-9.
8	Group RECOVERY Collaborative; Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, Prudon B, Whitehouse T, Felton T, Williams J, Faccenda J, Underwood J, Baillie JK, Chappell LC, Faust SN, Jaki T, Jeffery K, Lim WS, Montgomery A, Rowan K, Tarning J, Watson JA, White NJ, Juszczak E, Haynes R, Landray MJ. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 Nov 19; 383(21):2030-2040. doi: 10.1056/NEJMoa2022926. Epub 2020 Oct 8. PMID: 33031652; PMCID: PMC7556338.	doi: 10.1056/NEJMoa2022926.
9	Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY,	DOI: 10.1056/NEJMoa2002032

	Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720. doi: 10.1056/NEJMoa2002032. Epub 2020 Feb 28. PMID: 32109013; PMCID: PMC7092819.	
10	Ip A, Ahn J, Zhou Y, Goy AH, Hansen E, Pecora AL, Sinclaire BA, Bednarz U, Marafelias M, Sawczuk IS, Underwood JP 3rd, Walker DM, Prasad R, Sweeney RL, Ponce MG, La Capra S, Cunningham FJ, Calise AG, Pulver BL, Ruocco D, Mojares GE, Eagan MP, Ziontz KL, Mastrokyriakos P, Goldberg SL. Hydroxychloroquine in the treatment of outpatients with mildly symptomatic COVID-19: a multi-center observational study. BMC Infect Dis. 2021 Jan 14; 21(1):72. doi: 10.1186/s12879-021-05773-w. PMID: 33446136; PMCID: PMC7807228.	https://doi.org/10.1186/s12879-021-05773-w
11	Jorge A. Hydroxychloroquine in the prevention of COVID-19 mortality. Lancet Rheumatol. 2021 Jan; 3(1):e2-e3. doi: 10.1016/S2665-9913(20)30390-8. Epub 2020 Nov 5. PMID: 33521667; PMCID: PMC7836264.	DOI: 10.1016/S2665-9913(20)30390-8
12	Kuznik A, Bencina M, Svajger U, Jeras M, Rozman B, Jerala R. Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. J Immunol. 2011 Apr 15; 186(8):4794-804. doi: 10.4049/jimmunol.1000702. Epub 2011 Mar 11. PMID: 21398612.	DOI: https://doi.org/10.4049/jimmunol.1000702

13	Lahiri A, Jha SS, Bhattacharya S, Ray S, Chakraborty A. Effectiveness of preventive measures against COVID-19: A systematic review of In Silico modeling studies in indian context. Indian J Public Health. 2020 Jun; 64 (Supplement): S156-S167. doi: 10.4103/ijph.IJPH_464_20. PMID: 32496248.	DOI: 10.4103/ijph.IJPH_464_20
14	Li X, Wang Y, Agostinis P, Rabson A, Melino G, Carafoli E, Shi Y, Sun E. Is hydroxychloroquine beneficial for COVID-19 patients? Cell Death Dis. 2020 Jul 8; 11(7):512. doi: 10.1038/s41419-020-2721-8. PMID: 32641681; PMCID: PMC7341710.	https://doi.org/10.1038/s41419-020-2721-8
15	Lin SN, Rui J, Chen QP, Zhao B, Yu SS, Li ZY, Zhao ZY, Wang Y, Zhu YZ, Xu JW, Yang M, Liu XC, Yang TL, Luo L, Deng B, Huang JF, Liu C, Li PH, Liu WK, Xie F, Chen Y, Su YH, Zhao BH, Chiang YC, Chen TM. Effectiveness of potential antiviral treatments in COVID-19 transmission control: a modelling study. Infect Dis Poverty. 2021 Apr 19; 10(1):53. doi: 10.1186/s40249-021-00835-2. PMID: 33874998; PMCID: PMC8054260.	https://doi.org/10.1186/s40249-021-00835-2
16	Meo SA, Klonoff DC, Akram J. Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19. Eur Rev Med Pharmacol Sci. 2020 Apr; 24(8):4539-4547. doi: 10.26355/eurrev_202004_21038. PMID: 32373993.	DOI: 10.26355/eurrev_202004_21038
17	Mohan Kapoor Krishan and A K. Role of Chloroquine and Hydroxychloroquine in the Treatment of COVID-19 Infection-	DOI: 10.1101/2020.03.24.20042366.

	A Systematic Literature Review. medRxiv, 2020. doi: https://doi.org/10.1101/2020.03.24.20042366	
18	Mokhtari M, Mohraz M, Gouya MM, Namdari Tabar H, Tabrizi JS, Tayeri K, Aghamohamadi S, Rajabpoor Z, Karami M, Raeisi A, Rahmani H, Khalili H. Clinical outcomes of patients with mild COVID-19 following treatment with hydroxychloroquine in an outpatient setting. Int Immunopharmacol. 2021 Jul; 96:107636. doi: 10.1016/j.intimp.2021.107636. Epub 2021 Apr 6. PMID: 34015598; PMCID: PMC8023208.	doi: 10.1016/j.intimp.2021.107636
19	Rahman A. Effectiveness of Current Treatments for Covid-19. Preprints 2020, 2020110372. https://doi.org/10.20944/preprints202011.0372.v1	DOI:10.20944/preprints202011.0372.v1
20	Rajasingham R, Bangdiwala AS, Nicol MR, Skipper CP, Pastick KA, Axelrod ML, Pullen MF, Nascene AA, Williams DA, Engen NW, Okafor EC, Rini BI, Mayer IA, McDonald EG, Lee TC, Li P, MacKenzie LJ, Balko JM, Dunlop SJ, Hullsiek KH, Boulware DR, Lofgren SM; COVID PREP team. Hydroxychloroquine as Pre-exposure Prophylaxis for Coronavirus Disease 2019 (COVID-19) in Healthcare Workers: A Randomized Trial. Clin Infect Dis. 2021 Jun 1; 72(11):e835-e843. doi: 10.1093/cid/ciaa1571. PMID: 33068425; PMCID: PMC7665393.	https://doi.org/10.1093/cid/ciaa1571
21	Saghir SAM, AlGabri NA, Alagawany MM, Attia YA, Alyileili SR, Elnesr SS, Shafi ME, Al-Shargi OYA, Al-Balagi N, Alwajeeh AS, Alsalahi OSA, Patra AK, Khafaga AF, Negida A,	DOI: 10.2147/TCRM.S301817.

	Noreldin A, Al-Amarat W, Almaiman AA, El-Tarabily KA, Abd El-Hack ME. Chloroquine and Hydroxychloroquine for the Prevention and Treatment of COVID-19: A Fiction, Hope or Hype? An Updated Review. Ther Clin Risk Manag. 2021 Apr 28; 17:371-387. doi: 10.2147/TCRM.S301817. PMID: 33953559; PMCID: PMC8092643.	
22	Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020 Mar; 16(3):155-166. doi: 10.1038/s41584-020-0372-x. Epub 2020 Feb 7. PMID: 32034323.	DOI: 10.1038/s41584-020-0372-x
23	Shabani M, Totonchi M, Rezaeimirghaed O, Gachkar L, Hajiesmaeili M, Khoshkar A, Amirdosara M, Saffaei A, Shokouhi S, Mardani M, Alavi Darazam I, Karami A, Sharifi M, Zaman M, Abedheydari E, Sahraei Z. Evaluation of the prophylactic effect of hydroxychloroquine on people in close-contact with patients with COVID-19. Pulm Pharmacol Ther. 2021 Oct; 70:102069. doi: 10.1016/j.pupt.2021.102069. Epub 2021 Aug 10. PMID: 34389507; PMCID: PMC8353977.	https://doi.org/10.1016/j.pupt.2021.102069
24	Singh H, Chauhan P, Kakkar AK. Hydroxychloroquine for the treatment and prophylaxis of COVID-19: The journey so far and the road ahead. Eur J Pharmacol. 2021 Jan 5; 890:173717. doi: 10.1016/j.ejphar.2020.173717. Epub 2020 Nov 3. PMID: 33152333; PMCID: PMC7606072.	doi: 10.1016/j.ejphar.2020.173717.

25	Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, Williams DA, Okafor EC, Pullen MF, Nicol MR, Nascene AA, Hullsiek KH, Cheng MP, Luke D, Lother SA, MacKenzie LJ, Drobot G, Kelly LE, Schwartz IS, Zarychanski R, McDonald EG, Lee TC, Rajasingham R, Boulware DR. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial. Ann Intern Med. 2020 Oct 20; 173(8):623-631. doi: 10.7326/M20-4207. Epub 2020 Jul 16. Erratum in: Ann Intern Med. 2021 Mar; 174(3):435. PMID: 32673060; PMCID: PMC7384270.	https://doi.org/10.7326/M20-4207
26	van den Borne BE, Dijkmans BA, de Rooij HH, le Cessie S, Verweij CL. Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. J Rheumatol. 1997 Jan; 24(1):55-60. PMID: 9002011.	https://pubmed.ncbi.nlm.nih.gov/9002011/
27	WHO Dashboard. https://covid19.who.int/ Accessed: January 7, 2022.	https://covid19.who.int/
28	Worldometer.com	https://www.worldometers.info/coronavirus/country/iran/ Accessed: January 7, 2022.
29	Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Mar; 579(7798):265-269. doi: 10.1038/s41586-	https://doi:10.1038/s41586-020-2008-3

	020-2008-3. Epub 2020 Feb 3. Erratum in: Nature. 2020 Apr; 580(7803):E7. PMID: 32015508; PMCID: PMC7094943.	
30	Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Jul 28; 71(15):732-739. doi: 10.1093/cid/ciaa237. PMID: 32150618; PMCID: PMC7108130.	DOI: 10.1093/cid/ciaa237.