Pre-exposure prophylaxis with hydroxychloroquine for COVID-19: initial results of a double-blind, placebo-controlled randomized clinical trial

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Abstract

Background

Pre-exposure prophylaxis (PrEP) is a promising strategy to break COVID-19 transmission. Although hydroxychloroquine was evaluated for treatment and post-exposure prophylaxis, it is not evaluated for COVID-19 PrEP yet. The aim of this study was to evaluate efficacy and safety of PrEP with hydroxychloroquine against placebo in healthcare workers at high risk of SARS-CoV-2 infection during an epidemic period.

Methods

We conducted a double-blind placebo-controlled randomized clinical trial in three hospitals in Barcelona, Spain. From 350 adult healthcare workers screened, we included 269 participants with no active or past SARS-CoV-2 infection (determined by a negative nasopharyngeal SARS-CoV-2 PCR and a negative serology against SARS-CoV-2). Participants allocated in the intervention arm (PrEP) received 400mg of hydroxychloroquine daily the first four consecutive days and subsequently, 400mg weekly during the study period. Participants in the control group followed the same treatment schedule with placebo tablets.

Results

52.8% of participants were in the hydroxychloroquine arm and 47.2% in the placebo arm. Both groups showed similar proportion of participants experiencing at least one adverse event (AE) (p=0.548). No serious AE were reported. Almost all AE (96.4%) were mild. Only mild gastrointestinal symptoms were significantly higher in the hydroxychloroquine arm compared to the placebo arm (28.3% vs 16.9%, p=0.044). Given the national epidemic incidence decay, only one participant in each group was COVID-19 diagnosed. Consequently, our study design deemed underpowered to evaluate any benefit regarding PrEP efficacy.

Conclusions

First month follow-up analysis displayed that PrEP with hydroxychloroquine at low doses is safe.

Trial registration

This trial was registered at clinicaltrials.gov (NCT04331834) on April 2nd 2020.

Background

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the causative agent of coronavirus disease 2019 (COVID-19).(1) Currently, the worldwide prevention strategies for SARS-CoV-2 infection are self-protection equipment use, hand washing, case identification, case isolation, contact tracing and exposed people quarantine of close contacts.(2–4) In these circumstances, secondary attack rate estimates of COVID-19 ranges from 3–15% in the community(5–7), which can reach 26% in healthcare professionals.(8) Prevention of healthcare workers' infection is crucial for protecting the workforce during pandemic management. Pre-exposure prophylaxis (PrEP) is a promising strategy, which proved effective in preventing other infectious diseases.(9) Thus, several trials with repurposed drugs to evaluate PrEP effectiveness in mitigating SARS-CoV-2 transmission are under development.(10)

Chloroquine was observed to effectively inhibit SARS-CoV-2 in vitro.(11, 12) In fact, its derivate hydroxychloroquine shows a better in vitro antiviral activity and safety profile.(13, 14) Hydroxychloroquine potentially inhibits entry and post-entry stages of SARS-CoV-2. (11, 13) While hydroxychloroquine was evaluated for the treatment of SARS-CoV-2 pneumonia and post-exposure prophylaxis, it is not evaluated for PrEP yet. The aim of this study is to compare efficacy and safety of PrEP with hydroxychloroquine against placebo in healthcare workers in reducing the risk of COVID-19 disease during an epidemic period.

Methods

Trial design

We conducted a multicentre double-blind, placebo-controlled randomized clinical trial. We allocated participants to one of the two study arms in a 1:1 ratio by simple randomization. Randomization list was generated prior to enrolment.

Screening of candidates was initiated on April 3rd 2020 and first recruitment on April 4th 2020.

This trial was approved by the Drug Research Ethics Committee of the Hospital Clinic of Barcelona (CEIm), Barcelona, Spain and the Spanish Agency of Medicines and Medical Products (AEMPS). It was registered at clinicaltrials.gov (NCT04331834) on April 2nd 2020.

Participants

We recruited 269 healthcare workers from three hospitals in Barcelona, Spain, (Hospital Clínic, Hospital de la Santa Creu i Sant Pau and Hospital Plató).

We included adult healthcare workers working at least three days a week in a trial hospital with a negative result of SARS-CoV-2 polymerase chain reaction (PCR) assay in nasopharyngeal swab within four days before enrolment. COVID-19 serology was evaluated in all candidates with a rapid diagnostic test (Vivadiag™ COVID-19 IgM/IgG Rapid Test ©, Hangzhou, China) and confirmed with Enzyme-Linked ImmunoSorbent Assays (VITROS Anti-SARS-CoV-2 Total, © Ortho-Clinical Diagnostics, 2020). Those individuals positive for COVID-19 serology by any method were excluded. We also excluded participants with any of the following conditions: pregnancy, breastfeeding, ongoing antiviral, antiretroviral or corticosteroids treatment, chloroquine or hydroxychloroquine intake the last month or any contraindication to hydroxychloroquine.

Intervention and comparator

Randomization was generated using a computer random number generator. We used sequentially numbered sealed envelopes of identical appearance containing either hydroxychloroquine or placebo, ensuring allocation concealment. Participants allocated to intervention arm (PrEP) received 400 mg of hydroxychloroquine (two tablets of 200 mg) daily the first four consecutive days, followed by 400 mg weekly during the study period, initially scheduled to be 6 months. Participants in the control group followed the same treatment schedule with placebo tablets that were indistinguishable from hydroxychloroquine tablets.

Participants took the first two tablets at recruitment visit under direct observation by a physician, who then provided the needed tablets to complete the first month of treatment.

Participants, investigators assessing participant eligibility and recruitment, assessing outcomes and follow-up, and/or dealing with data management and analysis were all blinded to arm allocation. Only one person unrelated to participant recruitment and follow-up, clinical assistance, data management and analysis had access to this information.

Outcome

The primary outcome was the incidence of COVID-19 confirmed cases (defined by compatible symptoms with COVID-19 with seroconversion or a positive PCR for SARS-CoV-2) in the hydroxychloroquine arm compared to the placebo arm at any time during the study follow-up.

The secondary outcomes included: i) the SARS-CoV-2 seroconversion in the hydroxychloroquine group compared to the placebo group in both asymptomatic and symptomatic participants; ii) the occurrence of any adverse event (AE) related with hydroxychloroquine treatment; iii) the incidence of SARS-CoV-2 infection and COVID-19 in healthcare workers in the placebo group during the study period; iv) the risk ratio for the different clinical, analytical and microbiological conditions to develop COVID-19.

Participant’s follow-up

Passive and active surveillance was conducted to all participants to detect SARS-CoV-2 infections and any AE.

Active surveillance of each participant was conducted monthly by blinded physicians unaware of the trial arm assignments, which completed a standardized case report form (CRF) for each participant. Follow-up visits included: i) assessment of compliance with PrEP, ii) physical examination and detailed evaluation of symptoms to either detect past and current symptoms

and signs related to COVID-19, iii) venepuncture for blood determinations, including SARS-CoV-2 serology test (VITROS Anti-SARS-CoV-2 Total, © Ortho-Clinical Diagnostics, 2020), iv) assessment of COVID-19 risk factors such as known close contacts with suspected and/or confirmed COVID-19 cases or the number of weeks during which they were managing COVID-19 patients, v) standardized questions to collect past and current common side effects along with open free text and, vi) electrocardiogram to evaluate possible cardiac rhythm alterations.

During this study period, a medical doctor was available by phone 24hours a day during the study period for passive surveillance. All participants were provided with this contact number in case of presenting any COVID-19 related symptom or AE. In that instance, a standardized CRF was filled out to collect the information. A nasopharyngeal swab was performed to all those participants presenting with COVID-19 related symptoms to detect SARS-CoV-2 infection by PCR.

Medical assistance was ensured for all participants diagnosed with SARS-CoV-2 infection following hospital guidelines.

Although the protocol was designed to follow participants for 6 months, this manuscript only includes participants' first month analysis.

Sample size

We estimated sample size assuming an expected incidence of 10% of COVID-19 in healthcare workers in the control group and 2% in the hydroxychloroquine group, with a hazard ratio of 0.2. Thus, we required a total of 440 subjects (220 per group) for a significance level of 5%, statistical power of 90% and assuming a rate of lost-to-follow-up of 10%.(15)

Interim analysis

Interim analyses of the efficacy and safety of hydroxychloroquine were planned monthly, with the option of early stopping the trial for futility. We planned to restimate incidence and lost-to follow-up rate at the first month, since these data was unknown when we estimated sample size. After the first interim analysis the trial was halted on the basis of a very low incidence rate among study participants.

Statistical analysis

We conducted an intention-to-treat analysis, with all patients fulfilling inclusion criteria and not presenting exclusion criteria. Categorical variables were expressed as absolute frequency and percentage and were compared with Fisher's exact test. Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR). We conducted all analysis with R.(16)

Results

Participants

Screening

We assessed 350 health-care workers for eligibility, 269 of them fulfilled the study criteria and were recruited after signing the informed consent form. Participants were randomly assigned to the hydroxychloroquine group (n = 142, 52.8%) and to the placebo group (n = 127, 47.2%). Figure 1 describes participants enrolment and randomization.

The participants' demographic characteristics are shown in Table 1. The trial included 197 (73.2%) female participants and the median age was 39 years (IQR: 30–50 years). Eighty-three (30.9%) had some underlying medical condition and 74 (25.5%) were under chronic treatment.

Table 1
– Participants' baseline characteristics for both hydroxychloroquine and placebo group

	Placebo (n = 127)		**Hydroxychloroquine (n = 142)**	
	n	%	n	%
Sex, female	93	73.2	104	73.2
Age (mean, SD)	40.3	(12.8)	39.6	(11.2)
Country of origin				
Spain	112	88.2	126	88.7
Other European countries	0		4	2.8
Latin America	14	11.0	12	8.5
North Africa	1	0.8	0	
Professional category				
Medical Doctor	53	42.1	67	47.2
Nurse	35	27.8	40	28.2
Nurse Assistant	12	9.5	12	8.5
Administrative	10	7.9	10	7.0
Other	16	12.7	13	9.2
Smoking	17	13.8	21	14.9
Comorbidities				
Any	42	33.1	41	28.9
Diabetes Mellitus	1	0.8	0	
Hypertension	3	2.4	2	1.4
Chronic respiratory condition	2	1.6	5	3.5
Other	38	30.4	37	26.2
Immunosuppression	0		0	
Chronic treatment				
Any	34	26.8	40	28.2
Antidiabetics	0		1	0.7
Antihypertensives	1	0.8	2	1.4
Statins	3	2.4	1	0.7
Bronchodilators	2	1.6	1	0.7
Contraceptives	9	7.1	11	7.7
Levothyroxine	6	4.7	9	6.3
Proton pump inhibitors	2	1.6	5	3.5

SD: standard deviation

	Placebo (n = 127)		Hydroxychloroquine (n = 142)	
Other	5	3.9	4	2.8
History of vaccination				
Haemophilus	9	7.8	8	6.2
Pneumococcal	5	4.2	9	6.7
Influenza	85	68.5	92	64.8
SD: standard deviation				

Almost half of the recruited individuals (44.8%) were medical doctors. A 33.1% referred contact with at least one confirmed or probable COVID-19 case without wearing it, 34.6% in the hydroxychloroquine and 30.2% in the placebo group (p-value = 0.526). From them, the median number of contacts per participants was 2.5 (IQR: 2–3). Participants were living with a median number of 2 co-habitants (IQR: 1–3) and 28.3% of the participants were living with health-care workers. All studied risk factors were similar between groups. Table 2 describes participants' risk factors for COVID-19 exposure.

Table 2
– Participant's risk factors of COVID-19 exposure at screening and first month of follow-up

	Screening				Month 1			
	Placebo (n = 127)		Hydroxychloroquine (n = 142)		Placebo (n = 116)		Hydroxychloroquine (n = 137)	
Number of cohabitants(median, IQR)	2	[1–3]	1.5	[1–3]	1	[1–3]	2	[1–3]
Confirmed cases (median, IQR)	1	[1–1]	1	[1–1]	1	[1–1]	1	[1–1]
Suspected cases (median, IQR)	3	[3–3]	3	[3–3]	3	[3–3]	3	[3–3]
Used public transportation [a]	54	43.2	55	38.7	56	48.7	58	42.3
Close contact with animals [a]	26	20.8	36	25.5	39	33.6	52	38.0
Use of COVID-19 recommended PPE at work [a] [b]								
Always	107	86.3	117	82.4	111	95.7	135	98.5
Almost always	8	6.5	11	7.7	4	3.4	2	1.5
Sometimes	2	1.6	5	3.5	1	0.9	0	0.0
Occasionally	2	1.6	1	0.7	0	0.0	0	0.0
Never	5	4.0	8	5.6	0	0.0	0	0.0
Close contact with a confirmed COVID-19 case without using PPE [a]	35	28.0	34	23.9	17	14.7	7	5.1
If yes, how many								
1	20	57.1	11	32.4	9	56.2	3	42.9
2–3	10	28.6	18	59.2	7	43.8	3	42.9
≥ 4	5	14.3	5	14.7	0	0	1	14.3
If yes, how frequently								
Every day	16	48.5	13	38.2	2	11.8	0	0.0
≥ 1 / week	8	24.2	10	29.4	8	47.1	5	83.3
< 1 / week	9	27.3	13	38.2	9	42.1	1	16.7
Close contact with a suspected COVID-19 case without using PPE [a]	19	15.2	15	10.6	5	4.3	6	4.4
If yes, how many								
1	7	36.8	6	40.0	1	20.0	3	50.0
2–3	6	31.6	7	46.7	2	40.0	2	33.3
≥ 4	6	31.6	2	13.3	2	40.0	1	16.7
If yes, how frequently								
Every day	8	44.4	3	20.0	1	20.0	1	16.7

PPE: Personal protection equipment. [a] During the last 20 days. [b] *Almost always* defined as not using the proper PPE protection 1–2 times in the last 20 days. *Sometimes* defined as not using the proper PPE 1–2 times/week. *Occasionally* defined as not using the proper PPE > 2 times/week.

	Screening				Month 1			
≥ 1 / week	6	33.3	8	53.3	2	40.0	4	67.7
< 1 / week	4	22.2	4	26.7	2	40.0	1	16.7

PPE: Personal protection equipment. [a] During the last 20 days. [b] *Almost always* defined as not using the proper PPE protection 1–2 times in the last 20 days. *Sometimes* defined as not using the proper PPE 1–2 times/week. *Occasionally* defined as not using the proper PPE > 2 times/week.

Included participants did not present any relevant abnormality in blood test (Table 3) neither in electrocardiogram. Median QTc did not differ between groups (383 ms [357–400] in hydroxychloroquine group and 384 ms [368–405] in the placebo group).

Table 3
– Laboratory parameters at screening and first month of follow-up

	Reference values	Screening				Month 1			
		Placebo		Hydroxychloroquine		Placebo		Hydroxychloroquine	
	Median	IQR	Median	IQR	Median	IQR	Median	Q1 - Q3	
WBC	4.0–11.0 × 10^9/L	6.31	(5.38–7.24)	6.13	(5.16–7.18)	5.88	(4.99–6.98)	5.92	(5.11–6.70)
Neutrophils	2.0–7.0 × 10^9/L	3.6	(2.90–4.46)	3.5	(2.95–4.44)	3.4	(2.8–4.4)	3.49	(2.6–4.2)
Lymphocytes	0.9–4.5 × 10^9/L	2.0	(1.6–2.3)	1.9	(1.6–2.2)	1.8	(1.4–2.2)	1.8	(1.6–2.1)
Eosinophils	< 0.5 × 10^9/L	0.1	(0.1–0.2)	0.1	(0.1–0.2)	0.1	(0.1–0.2)	0.2	(0.1–0.3)
Basophils	< 0.2 × 10^9/L	0	(0–0)	0	(0–0)	0	(0–0)	0	(0–0)
Monocytes	0.1–1.0 × 10^9/L	0.4	(0.3–0.4)	0.3	(0.3–0.4)	0.3	(0.3–0.4)	0.3	(0.3–0.4)
Platelets	130–400 × 10^9/L	239	(215–266)	235	(198–265)	237	(210–270)	223.5	(198.3–264.5)
Haemoglobin	130–170 g/L	137.5	(129–147.3)	138	(131–147)	136	(129–143)	138	(131–147)
Haematocrit	0.40–0.50 L/L	0.43	(0.40–0.46)	0.43	(0.39–0.45)	0.41	(0.39–0.45)	0.42	(0.40–0.44)
CRP	< 0.40 mg/dL	< 0.40	(< 0.40 - <0.40)	< 0.40	(< 0.40 - <0.40)	< 0.40	(< 0.40 - <0.40)	< 0.40	(< 0.40 - <0.40)
ASAT	5–40 IU/L	21.0	(18–26)	20	(17–23)	21	(18–25)	20	(17–23)
ALAT	5–40 IU/L	17	(13.8–26)	16	(13–20)	17	(13–22)	15	(12–20)
GGT	5–40 IU/L	18	(14–23)	16	(13–23)	17	(13–21)	16	(12–21)
AP	46–116 IU/L	63.5	(52–77.8)	57	(50–72)	65	(51–77)	54	(47–68)
Bilirubin	< 1.2 mg/dL	0.59	(0.4–0.7)	0.6	(0.5–0.8)	0.6	(0.5–0.8)	0.6	(0.5–0.8)
Creatinine	0.30–1.30 mg/dL	0.76	(0.69–0.85)	0.75	(0.66–0.86)	0.78	(0.71–0.88)	0.75	(0.69–0.88)
Na	135–145 mEq/L	140	(140–141)	141	(140–142)	140	(138–141)	139	(138–141)
Glucose	65–110 mg/dL	82	(75–87.92)	82	(77–88.75)	86.76	(78–96)	87.00	(80.25–94.75)
D-dimer	< 500 ng/mL	200	(200–300)	200	(200–300)	200	(200–300)	200	(200–300)

ALAT: alanine aminotransferase. AP: alkaline phosphatase. ASAT: aspartate aminotransferase. CRP: C-reactive protein. GGT: Gamma-glutamyl transpeptidase. IQR: Interquartile range. Na: Sodium. WBC: white blood cells.

Withdrawal and lost to follow-up

On June 12th, a total of 253 (94.1%) participants had completed the first month of follow up. In the hydroxychloroquine group, 137 (96.5%) completed follow-up at first month. The reasons of no completion were withdrawal of consent (n = 1, 0.7%), AE (n = 1, 0.7%) and others(n = 3, 2.1%). In the placebo group, 116 (91.3%) completed the course of prophylaxis. Their reasons of no completion were withdrawal of consent (n = 3, 2.4%), participant unable to receive study drug as per protocol (n = 1, 0.8%), AE (n = 5, 3.9%), SARS-CoV-2 infection (n = 1, 0.8%) and others (n = 1, 0.8%) (Fig. 1).

COVID-19 risk factors at month 1

After a month of follow-up, 39.9% of participants ceased to work in a COVID-19 hospital unit, with similar proportion between both groups. In addition, only seven participants denied having used always PPE when assisting patients.The proportion of participants in contact with a confirmed and/or a suspected COVID-19 case showed to be lower compared with the screening visit (p-value < 0.001 in the hydroxychloroquine group, p-value = 0.002 in the placebo group). Participants from the hydroxychloroquine group had lower contact with confirmed COVID-19 cases without using PPE compared to the placebo (p-value = 0,018). (Table 2)

Efficacy

During the first month of follow-up, the overall accumulated incidence of COVID-19 among the study participants was 0.8%. Only one participant, from placebo arm, was diagnosed with COVID-19 by SARS-CoV-2 PCR and serology test. The participant presented with fever, respiratory symptoms and headache 6 days after randomization. The participant did not received specific treatment for COVID-19 or required hospitalization.

The risk ratio of collected risk factors and clinical and analytical conditions for developing COVID-19 could not be calculated due to low COVID-19 incidence.

Safety

A total of 95 participants experienced at least one AE during the first month of follow-up, posing an overall accumulated prevalence of 35.3%. The proportion of participants experiencing at least one AE was similar in both groups. Eighty-one events (33.0% in the hydroxychloroquine group and 26.0% in the placebo group, p = 0.207) were judged to be related to the study intervention (hydroxychloroquine or placebo). No serious AE were reported. Almost all AE (96.4%) were considered mild. Only four were reported as moderate: prostate adenocarcinoma in the hydroxychloroquine group and dental infection, hypertensive crisis and myalgia in the placebo group.

Gastrointestinal symptoms (diarrhea, abdominal pain and nausea) were the most common AE and they were more commonly reported in the hydroxychloroquine group. The median number of days from first dose to intake to AE appearance was 2.5 in the hydroxychloroquine group [0-10.5] and 6 in the placebo group [2–18].

Headache, rash, respiratory and general symptoms were also observed. They appeared similarly in time between both groups, the median number of days to appearance was 4.5 [0–17] in the hydroxychloroquine group and 5 [1–18] in the placebo group.

Four cardiovascular AE (two in each study group) were detected during the first month of treatment: two pre-excitation syndromes (Wolf-Parkinson-White), one with hypertensive crisis and two participants presenting with heart palpitations. Only hypertensive crisis was moderate, the rest were mild and none of them was considered related to the study drug. None of the participants presented prolonged QTc intervals at first month (388 ms [365–402] in the hydroxychloroquine group and 393 ms in [371–405] in the placebo group).

Only one participant in the hydroxychloroquine group presented mild visual disturbances.

Five participants discontinued the prophylaxis due to AE in the hydroxychloroquine group and one in the placebo group. Table 4 shows a detailed description of the AE presented in both study groups.

Table 4
– Comparison of Adverse Events (AE) between study groups after one month of follow-up.

	Placebo (n = 127)		Hydroxychloroquine (n = 142)		
	n	%	n	%	*p-value*
At least 1 adverse event	42	33.1	53	37.3	0.548
Syndromic approach					
General symptoms	9	7.7	10	7.0	> 0.999
Fever	6	4.7	4	2.8	0.553
Chills	0	0.0	2	1.4	0.552
Sweating	0	0.0	0	0.0	
Malaise	4	3.1	4	2.8	> 0.999
Myalgia	2	1.6	3	2.1	> 0.999
Arthralgia	0	0.0	0	0.0	
Gastrointestinal symptoms	20	15.7	39	28.3	*0.046
Nausea	3	2.4	10	7.0	0.160
Abdominal pain	11	8.3	15	10.9	0.825
Diarrhea	8	6.3	24	16.9	*0.028
Dysgeusia	0	0.0	0	0.0	
Dermatological symptoms	2	1.6	3	2.2	> 0.999
Itching	0	0.0	2	1.4	0.546
Rash	2	1.6	2	1.4	> 0.999
Respiratory symptoms	9	7.1	5	3.7	0.257
Rhinorrea	3	2.4	0	0.0	0.190
Sore throat / odynophagia	5	3.9	3	2.2	0.556
Cough	3	2.4	2	1.5	0.851
Pleuritic pain	0	0.0	0	0.0	
Dyspnoea	0	0.0	0	0.0	
Neurological symptoms	12	9.4	14	9.9	> 0.999
Headache	12	9.4	13	9.1	0.987
Visual disturbances	0	0.0	1	0.7	> 0.999
Cardiovascular symptoms	2	1.6	2	1.4	0.999
Other symptoms	10	8.0	7	4.9	0.427
Severity					0.249
Mild	43	33.8	63	44.4	

% according to available data

	Placebo (n = 127)		Hydroxychloroquine (n = 142)		
Moderate	3	2.4	1	0.7	
Severe	0	0.0	0	0.0	
Potential relationship with the study drug					
Related (at least one AE)	33	26.0	49	34.5	0.206
Non related (at least one AE)	17	13.4	14	9.9	0.476
Withdrawal due to AE	5	3.9	1	0.7	0.270
% according to available data					

No relevant laboratory abnormalities occurred. Most abnormalities were transient, with no significant changes in the two groups (Table 3).

Discussion

We conducted a multicentre double-blind placebo-controlled randomized clinical trial to evaluate whether PrEP with hydroxychloroquine was an effective intervention for preventing COVID-19 among healthcare workers during a COVID-19 epidemic period. These initial data showed that prophylaxis with hydroxychloroquine at the study doses had an excellent safety profile. Nevertheless, the community incidence of SARS-CoV-2 events decreased during the first month of follow-up as a consequence of country's control and mitigation strategies. Thus, the overall incidence in the cohort was 0.8% and the study design was deemed underpowered to answer the main objective.

In this trial, AE were similar between the hydroxychloroquine and the placebo group. Mild gastrointestinal events were higher in the hydroxychloroquine group than in the placebo group. Our safety data contrast with available data from a recently published placebo-controlled clinical trial post-exposure prophylaxis with hydroxychloroquine to prevent COVID-19, in which the intervention arm had a higher rate of AE (40.1%) compared to the placebo arm (16.8%).(17) The reasons for these discrepancies may include the high loading doses of hydroxychloroquine required for the post-exposure prophylaxis strategies (3200 mg compared to 1200 mg in 4 days in our intervention). Moreover, the loading dose during 4 consecutive days in PrEP strategies could be avoided since the patient has not yet been exposed to the virus, potentially decreasing the number of AE.

Large observational studies evaluating the hydroxychloroquine effect on SARS-CoV-2 pneumonia showed that higher doses of the drug could be associated with QTc interval prolongation and death due to cardiovascular events; especially when administered with other drugs which favor QT interval prolongation.(18, 19) The relationship of high doses of hydroxychloroquine with severe AE was also supported by a recent study evaluating high doses of hydroxychloroquine (up to 600 bid during 10 days) for treating COVID-19 patients. This study showed that 15% of participants prolonged QTc interval and two of them presented ventricular tachycardia. In this specific case, the authors suggested that this outcome could have been influenced by most of their participants receiving oseltamivir, which also prolongs QT, and the elder age of them.(20) In our case, no cardiovascular events related to the study drug were observed.

The adequate safety profile of the preventive (low) doses of hydroxychloroquine found in our study is supported by many studies on hydroxychloroquine short-term use as antimalarial and long-term use for rheumatic diseases demonstrated to be safe as well. (21–24)

As mentioned above, this trial has some limitations. The main one is low power in our study design to assess the efficacy of PrEP with hydroxychloroquine in healthcare workers at the first interim analysis. The principal reason was the low incidence of COVID-19 during the study follow-up in the study area. The analysis presented in this manuscript was conducted during April, May and June 2020 in Barcelona. During that period, COVID-19 reported cases were already decreasing in Catalonia region: while 1208 cases were reported in April 3rd, 77 cases were reported in June 12th. Accordingly, SARS-CoV-2 attack rate declined from 0.9 at

the initiation of the study to 0.77 at the end of the analysis.(25) In addition, we noticed that healthcare workers risk perception decreased as national epidemic vanished. That had an impact not only on participants' recruitment but also on participant's adherence and follow-up.

Moreover, other healthcare workers factors influenced their participation. Some study candidates had already self-prescribed hydroxychloroquine assuming its role on COVID-19 prevention, so although displaying interest they were excluded to participate. In addition, a fraction of recruited participants dropped out from the study the following day of test results notification. Hence, this set of circumstances prompted us to stop trial recruitment by 8th of May even though we had not reached our estimated sample size. Consequently, both study groups were unevenly distributed (52.8% vs 47.2%).

Conclusions

This trial displayed that administering 400 mg of hydroxychloroquine during 4 consecutive days followed by 400 mg of hydroxychloroquine weekly in adults during a month was safe. The question if COVID-19 could be prevented with hydroxychloroquine PrEP was unanswered. Since the epidemiological situation happening in our country is expected to be reproduced in other areas where similar trials are being conducted, our group will make all efforts to share databases with clinical trials with similar design, doses of hydroxychloroquine, and similar study endpoints, in an effort to answer the main question that initially fostered the design of this and similar studies. Preventing healthcare workers from COVID-19 is critical to control the pandemic. Thus, further studies in countries in the head of the pandemic are needed to break the transmission.

Abbreviations

AE
adverse event
AEMPS
Spain and the Spanish Agency of Medicines and Medical Products
CEIm
Drug Research Ethics Committee of the Hospital Clinic of Barcelona
CRF
case report form
CT
Cycle threshold
IQR
median and interquartile range
PCR
Polymerase chain reaction
PrEP
Pre-exposure prophylaxis
SARS-Cov-2
Severe Acute Respiratory Syndrome Coronavirus 2
SD
standard deviation
WHO
World Health Organization

Declarations

Ethics approval and consent to participate

This trial was approved by the Drug Research Ethics Committee of the Hospital Clinic of Barcelona (CEIm), Barcelona, Spain and the Spanish Agency of Medicines and Medical Products (AEMPS).

The study was performed according to the Declaration of Helsinki (version of Fortaleza, Brazil, October 2013), current ICH-GCP guidelines and all applicable national and local regulatory requirements (Spanish Royal Decree 1090/2015).

Informed consent was signed by all participants before their inclusion in the study. Participation in this study was voluntary, and under no circumstances the clinical management of the participants was affected by the decision to participate or not in the study. The participant was free to withdraw at any time of the study.

Consent for publication

Not applicable.

Availability of data and material

Data will be available from the author on reasonable request (jose.munoz@isglobal.org).

Competing interests

The authors declare no competing interests.

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Author Contributions

Grau-Pujol and Camprubí contributed equally to this manuscript.

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Supervision: Muñoz

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Figures

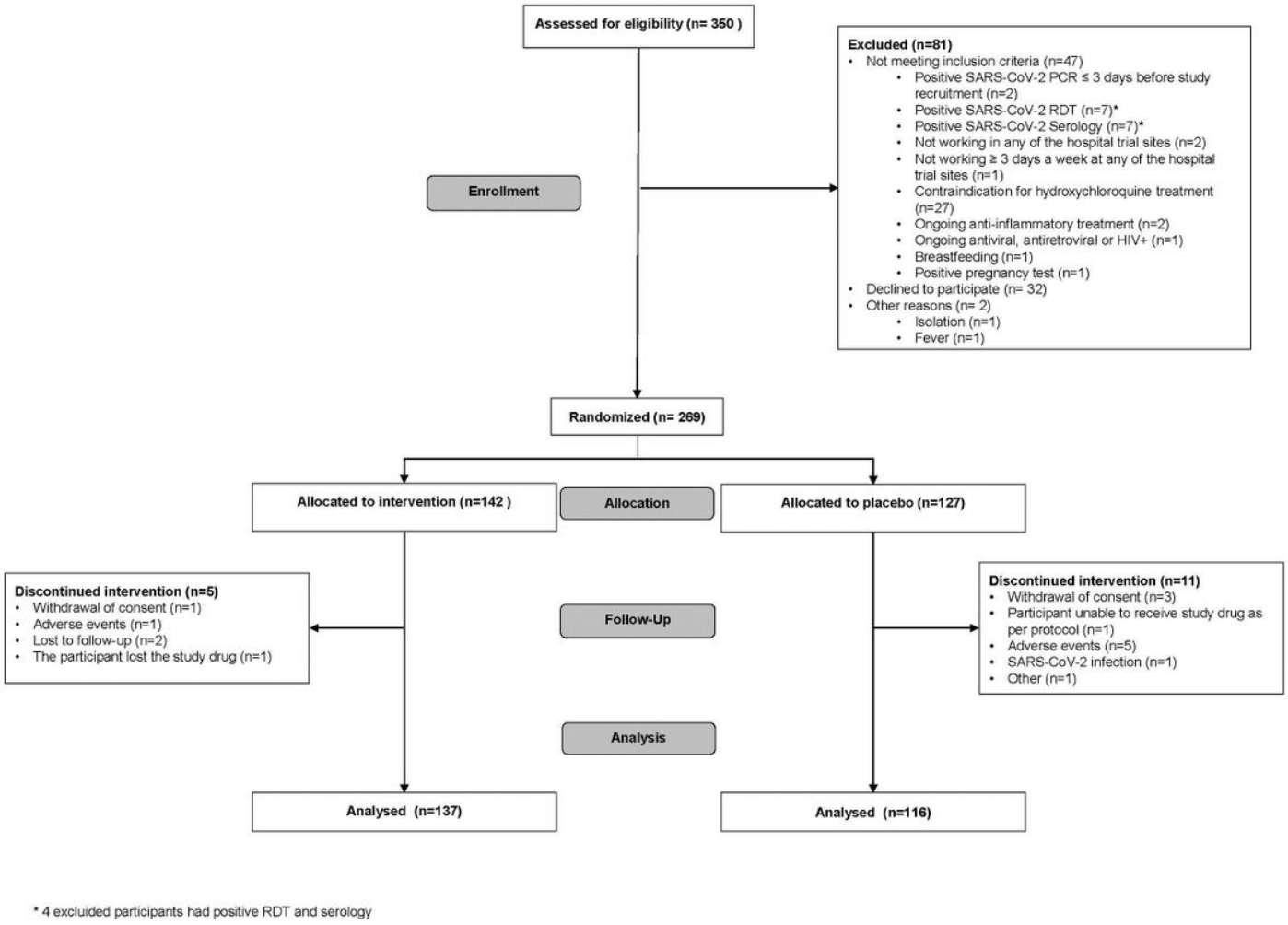

Figure 1

Flow diagram of trial participants at screening, recruitment and follow-up.

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