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Post-exposure prophylaxis with hydroxychloroquine for the prevention of COVID-19, a myth or a reality? The PEP-CQ Study

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ABSTRACT

Many drugs have been tried for the treatment/prevention of COVID-19 with limited success. Direct household contacts of COVID-19 patients are at highest risk for SARS-CoV-2 infection. Hydroxychloroquine (HCQ) has been tried against COVID-19 owing to its in vitro virucidal action against SARS-CoV-2, but the role of HCQ as post-exposure prophylaxis (PEP) remains inconclusive. In this open-label, controlled clinical trial, asymptomatic individuals who had direct contact with laboratory-confirmed COVID-19 cases or had undertaken international travel in the last 2 weeks were offered HCQ prophylaxis and assigned to PEP ($n = 132$) or control ($n = 185$) group. The PEP group received HCQ 800 mg on Day 1 followed by 400 mg once weekly for 3 weeks. Both groups undertook home quarantine for 2 weeks along with social distancing and personal hygiene. Over 4-week follow-up, 50/317 participants (15.8%) had new-onset COVID-19. The incidence of COVID-19 was significantly ($P = 0.033$) lower in the PEP (14/132; 10.6%) compared to the control (36/185; 19.5%) group (total absolute risk reduction, –8.9% points). The NNT to prevent the occurrence of 1 COVID-19 case was 12. Overall relative risk was 0.59 (95% CI 0.33–1.05). Compliance was good. The most common adverse event was epigastric discomfort with burning sensation (three participants), with no serious adverse events. PEP with HCQ has the potential for the prevention of COVID-19 in at-risk individuals. Until definitive therapy is available, continuing PEP with HCQ may be considered in suitable at-risk individuals. Further randomised clinical trials with larger samples are required for better evaluation of HCQ as PEP for COVID-19 prevention.

1. Introduction

The epidemic caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which started in Wuhan, China, is now a well-established pandemic worldwide affecting more than 50 million people with nearly 1.3 million deaths [1]. As Italy, Spain, Germany, the UK, Brazil and USA have overtaken China in term of the highest burden of mortality, India has become the next epicentre of this pandemic, after the USA. Currently there are more than 8.8 million cases of coronavirus disease 2019 (COVID-19) in India, with a regrettable mortality of more than 130 thousand patients [2]. The clinical presentation of COVID-19 varies from asymptomatic cases and mild symptoms of fever, cough, sore throat, headache, myalgia, nasal congestion and diarrhoea to severe pneumonia, acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, and even multiple organ dysfunction syndrome and sepsis leading to death [3]. If adequate preventive and therapeutic measures are not taken, India has very a high risk of affecting millions more people with high mortality because of the large population size along with a very high population density. At present there are no definitive therapeutic drugs or vaccines available for the treatment and prevention of SARS-CoV-2 infection. Symptomatic and supportive care are being given to COVID-19 cases along with isolation and quarantine measure for suspected individuals at risk for COVID-19 to limit the spread of SARS-CoV-2 [4]. Direct household contacts of COVID-19 patients are at the highest risk of SARS-CoV-2

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infection. Presently, many scientists and doctors are recommending several existing available drugs, e.g. ribavirin, lopinavir, remdesivir, chloroquine and hydroxychloroquine (HCQ), for SARS-CoV-2 infection for therapeutic and as well as prophylactic purposes [5,6], among which HCQ, a chloroquine analogue, has given some rays of hope to battle against this deadly pandemic [7]. In an in vitro study, researchers found that HCQ has some antiviral effects against SARS-CoV-2 through a mechanism targeted at the host cell [8,9]. HCQ is a relatively safe drug as it has been used in rheumatology patients for lifelong therapy with few side effects, allowing for a higher dose without any significant side effects or drug–drug interactions [10]. A recently published clinical trial suggested that HCQ can be used for therapeutic purposes in SARS-CoV-2 infection [7], and many governments, including the USA and India, have already endorsed HCQ owing to lack of adequate better alternative drugs. The Indian Council of Medical Research (ICMR) has advised HCQ prophylaxis for people who are at risk for developing SARS-CoV-2 infection, all asymptomatic healthcare workers (HCWs) involved in caring for suspected or confirmed COVID-19 cases, and all asymptomatic household contacts of laboratory-confirmed COVID-19 cases [11]. However, there is still a lack of significant scientific data to prove or disprove the efficacy of HCQ for the treatment and post-exposure prophylaxis (PEP) for SARS-CoV-2 infection. Being a tertiary-care centre, the Post Graduate Institute of Medical Education and Research (PGIMER) caters for many states, including Punjab, Haryana, Himachal Pradesh, Uttara Khand, Uttar Pradesh and Rajasthan. Among these, Punjab has the highest population of non-resident Indians, most of whom have returned home. Initially this set our institute to handle the highest burden of suspected cases of COVID-19 in northern India. A recently published study proposed that HCQ was not useful as PEP for the prevention of COVID-19 in at-risk individuals [12]. However, in that study the majority of participants were HCWs. There is still a lack of clinical trials regarding PEP with HCQ for the prevention of COVID-19 in non-HCW individuals who are at risk of SARS-CoV-2 infection. In this open-label, controlled clinical trial, we aimed to evaluate the efficacy of PEP with HCQ for the prevention of COVID-19 in an asymptomatic non-HCW population who were at risk for SARS-CoV-2 infection.

2. Method

The aim of this study was to evaluate the efficacy of PEP with HCQ for the prevention of COVID-19 in asymptomatic non-HCW individuals who were at risk for SARS-CoV-2 infection.

2.1. Study site

At-risk individuals were recruited through the special COVID-19 screening clinic at emergency outpatient department (EMOPD) and communicable disease ward of PGIMER, Chandigarh, a tertiary-care centre in the northern India. The study was done with the collaboration of the Departments of Internal Medicine, Virology, Pharmacology and Community Medicine & School of Public Health of PGIMER.

2.2. Study design

In this open-label, controlled clinical trial, at-risk individuals who presented at the special COVID-19 screening clinic and through telephone consultation were screened for enrolment in the study. After screening of asymptomatic individuals who had undertaken international travel in the last 2 weeks or had direct contact with a laboratory-confirmed COVID-19 case, were given the option of receiving HCQ as PEP for the prevention of SARS-CoV-2 infection and were assigned into the PEP or control group. Participants who did not give consent for HCQ prophylaxis and those with a contraindication for HCQ therapy were directly included in the control group. Asymptomatic individuals with high-risk direct contact were family members, relatives, friends or colleagues who were living with or spent hours/days with COVID-19 patients without taking any personal protective precautions. The PEP group received HCQ prophylaxis, whereas the control group did not receive HCQ prophylaxis. Both groups received standard care in the form of home quarantine for 2 weeks along with social distancing and personal hygiene. Participants were followed up for 4 weeks by telephone or physically as and when required. The study was registered with ClinicalsTrial.gov (ClinicalTrials.gov ID NCT04408456).

2.3. Study duration

The study was carried out during March–July 2020.

2.4. Inclusion and exclusion criteria

Irrespective of gender and age ($\geq$18 years), all asymptomatic individuals who had undertaken international travel in last 2 weeks and all asymptomatic individuals with direct contact with laboratory-confirmed COVID-19 cases were included in the study. Individuals who did not give consent for HCQ prophylaxis and patients with a contraindication for HCQ therapy, such as known hypersensitivity to HCQ or 4-aminoquinolone derivatives as well as patients with known retinopathy, cardiac arrhythmia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, psoriasis and pregnancy, were directly included in the control group. All symptomatic individuals, non-COVID suspects and all HCWs related to suspected or confirmed COVID-19 cases were excluded from the study.

2.5. Methods and interventions

In this open-label, controlled clinical trial, after screening and enrolment, all at-risk asymptomatic participants were assigned into the PEP or control group as per the inclusion and exclusion criteria. The PEP group received HCQ 400 mg (200 mg $\times$ 2 tablets) every 12 h on Day 1 followed by 400 mg once weekly for 3 weeks (total cumulative dose, 2000 mg). The control group did not receive HCQ or any drug intervention. Both groups received standard care in the form of home quarantine for 2 weeks along with social distancing and personal hygiene. The prophylactic dose of HCQ was decided according to ICMR recommendations for PEP with HCQ [11]. The potential antiviral and anti-inflammatory properties of HCQ, along with its low cost, very good oral bioavailability, higher concentrations in the lungs relative to plasma levels, and acceptable safety profile supported formulation of this national advisory. After receiving informed consent, the drugs were dispensed directly to the participants during the screening clinic visit or through doorstep delivery by the concerned HCW with help of police officials. Individuals were followed up for 4 weeks by telephone or physically when required and were questioned regarding the development of any COVID-19 symptoms such as fever, cough, sore throat, shortness of breath, diarrhoea, myalgia or any adverse drug events. During follow-up, nasopharyngeal and/or throat swabs of the participants were taken for processing by reverse transcription PCR (RT-PCR) for the detection of SARS-CoV-2 RNA to confirm COVID-19. Samples for RT-PCR were taken when any asymptomatic participants became symptomatic and by 5–14 days of contact in asymptomatic participants through an in-hospital visit at the institute's communicable disease isolation ward. Only participants with RT-PCR positive for SARS-CoV-2, with or without symptoms, were defined as a definite COVID-19 case. Participants with new-onset symptoms but negative RT-PCR for SARS-CoV-2 or in whom

it could not be performed for any reason were defined as a probable COVID-19 case. Both definite and probable COVID-19 cases together were defined as COVID-19 cases. Asymptomatic participants with negative RT-PCR were defined as a non-COVID case. The incidence of COVID-19 (definite and probable COVID-19) in previously asymptomatic participants was compared between the PEP and control groups. Baseline routine investigations (e.g. blood, chest radiography, electrocardiogram) were not possible as each participant was the potential source of SARS-CoV-2 and additional contact with HCWs could spread the virus to healthy individuals. Participants who turned out to be definite COVID-19 cases were moved to the Nehru Hospital Extension, a dedicated COVID-19 centre, of PGIMER and were managed as per the institutional COVID-19 protocol. Participants with probable COVID-19 were advised to continue with home quarantine.

2.6. Outcomes

The primary outcome of this study was the incidence of COVID-19 (definite and probable) among the participants. Secondary outcomes were new-onset COVID-19 symptoms, compliance with the advised HCQ therapy and home quarantine, difficulty faced during quarantine, and incidence of adverse drug events.

2.7. Sample size and statistical analysis

At the beginning of the study there was no clinical trial available to predict the incidence of COVID-19 or the decrease in incidence of COVID-19 with HCQ prophylaxis in individuals at risk for SARS-CoV-2 infection. As this was a pilot study, we were expecting monthly around 100–150 or less asymptomatic COVID-19 suspected individuals to visit the COVID-19 screening EMOPD of the PGIMER, depending on the worsening or improving status of the ongoing pandemic. The power of the study could not be extrapolated at the beginning of the study because of the lack of clarity regarding outcome. Participants were assigned into either the control or PEP group according to the inclusion and exclusion criteria. Participants who did not give consent for HCQ therapy and those with contraindications for HCQ therapy were directly included in the control group. A total of 1582 individuals were screened for enrolment in the study, of which 836 individuals had COVID-19-like symptoms at presentation. Of the 746 asymptomatic individuals, 82 were HCWs and 339 individuals were non-COVID suspects. Finally, 325 participants were included in the study, of whom 8 were lost to follow-up. Thus, final data analysis was done among 317 individuals, including 132 in the PEP group and 185 in the control group (Fig. 1). Data were managed in a database system through Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and statistical analysis was performed using IBM SPSS Statistics v.21.0 (IBM Corp, Armonk, NY, USA). Parametric data were analysed by paired or unpaired *t*-test, binominal/categorical endpoints were analysed by non-parametric χ^2 test with Yet's correction, and proportions were compared by Fisher's exact test. The relative risk and number needed to treat (NNT) were determined for the safety and risk assessment. A *P*-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of the study population

Of the 317 participants, 174 (54.9%) were male and 143 (45.1%) were female; only 10 participants (3.2%) had a history of international travel within 2 weeks prior to enrolment. The mean ± standard deviation age of the study population was 37.2 ± 13.9 years. The most common co-morbidity was diabetes mellitus (n =14; 4.4%), followed by hypothyroidism (n = 7; 2.2%), hypertension (n = 4; 1.3%), bronchial asthma (n = 2; 0.6%), chronic obstructive pulmonary disease (n = 1; 0.3%) and coronary artery disease (n = 1 0.3%). Among the 317 participants, 53 (16.7%) were alcohol consumers and 29 (9.1%) were smokers. The distributions of age, sex and co-morbidities were similar between the study groups (Table 1).

3.2. Primary outcome

Of the 317 participants, 50 (15.8%) had new-onset COVID-19 during follow-up. The incidence of COVID-19 was significantly (P = 0.033) lower in the PEP group (14/132; 10.6%) that received HCQ prophylaxis compared with the control group (36/185; 19.5%) that did not received HCQ prophylaxis (Table 2). The total absolute risk reduction for the incidence of COVID-19 in participants received PEP with HCQ was –8.9% points compared with participants who did not receive PEP with HCQ. The NNT was 12, suggesting that to prevent the occurrence of 1 case of COVID-19, 12 at-risk individuals would need to be treated with HCQ prophylaxis and the overall relative risk was 0.59 [95% confidence interval (CI), 0.33–1.05].

Of the 317 participants, 38 (12.0%) had definite COVID-19 (RT-PCR positive, with or without symptoms) during follow-up. The incidence of definite COVID-19 was also significantly (P = 0.041) lower in the PEP group (10/132; 7.6%) that received HCQ prophylaxis compared with the control group (28/185; 15.1%) that did not receive HCQ prophylaxis (Table 2). The total absolute risk reduction for the incidence of definite COVID-19 in participants received PEP with HCQ was –7.5% points compared with participants who did not receive PEP with HCQ. The NNT to prevent the occurrence of 1 case of definite COVID-19 in at-risk individuals was 14. The overall relative risk was 0.50 (95% CI, 0.25–0.99).

Of the 317 participants, 12 (3.8%) had probable COVID-19 (symptomatic with RT-PCR negative or RT-PCR could not be performed for any reason) during follow-up. The incidence of probable COVID-19 was also lower in the PEP group (4/132; 3.0%) that received HCQ prophylaxis compared with the control group (8/185; 4.3%) that did not receive HCQ prophylaxis, but the difference was not statistically significant (P = 0.552) (Table 2).

RT-PCR of nasopharyngeal/throat swabs was not be possible in 17 (5.4%) of the 317 participants for various reasons, including the strict lockdown, lack of adequate number of testing kits initially, and a few participants who did not show interest in testing. All of them followed the advice as per the study protocol and were co-operative to complete the follow-up. If we consider only the participants (n = 300) in whom RT-PCR could be performed, even then the incidence of definite COVID-19 was also significantly (P = 0.023) lower in the PEP group (10/130; 7.7%) that received HCQ prophylaxis compared with the control group (28/170; 16.5%) that did not receive HCQ prophylaxis.

3.3. Symptomatic COVID-19

Of 50 new-onset COVID-19 cases, 29 (58.0%) were asymptomatic and only 21 (42.0%) developed symptoms. The incidence of new-onset symptoms was higher in the control group (15/185; 8.1%) compared with the PEP group that received HCQ prophylaxis (6/132; 4.5%), but the difference was statistically insignificant (P = 0.209) (Table 2). None of the participants developed moderate-to-severe COVID-19 requiring oxygen therapy or life support. The most common symptoms were cough (13/21; 61.9%) and sore throat (9/21; 42.9%), followed by fever (7/21; 33.3%), myalgia (7/21; 33.3%) and diarrhoea (1/21; 4.8%), with 9 participants having two or more symptoms. The new-onset symptoms were not significantly different between the PEP and control groups.

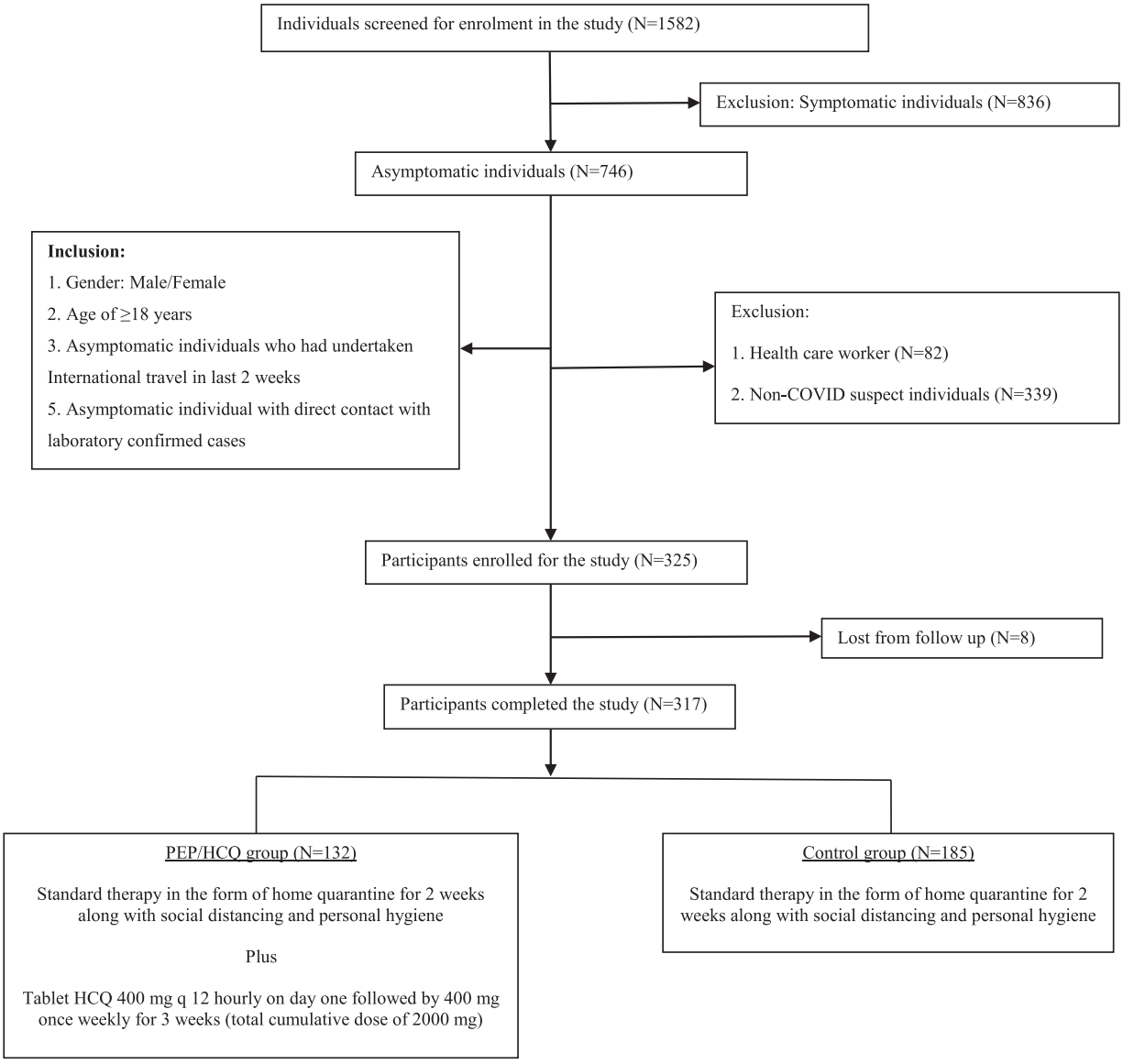

Fig. 1. Study design, screening and enrolment. PEP, post-exposure prophylaxis; HCQ, hydroxychloroquine.

3.4. Secondary outcomes

Compliance with HCQ prophylaxis was not adequate in 7 (5.3%) of 132 participants, of whom 6 participants took drugs (800 mg) on Day 1 and stopped thereafter because of anxiety related to possible side effects as explained to them during enrolment. Otherwise, overall compliance with HCQ prophylaxis was very good. Four participants consumed HCQ 200 mg daily for 10 days. No serious adverse drug events were noted during the study. The most common adverse drug reaction (ADR) was epigastric abdominal discomfort with burning sensation reported by 3 participants (2.3%), that resolved with antacid. Itching, low mood, back ache and palpitation were reported by one participant each. The occurrence of palpitation was a single self-limiting episode for which no specific treatment was required. All of the participants reported adequate compliance with the quarantine norm. Stress and depression were the most common problems felt by 12 (3.8%) of 317 participants during the period of quarantine. Getting essentials and foods were difficult for 13 participants (4.1%). Misbehaviour by neighbour and police officers were faced by 7 participants (2.2%).

4. Discussion

Since the advent of the deadly COVID-19 pandemic, many available drugs have been tried for the treatment and prevention of COVID-19, but none of them have succeeded confidently [4–6]. HCQ is being tested as a therapeutic and preventive option against COVID-19 in view of its in vitro virucidal action against SARS-CoV-2 [8,9]. The proposed mechanisms for the virucidal effect of HCQ are inhibition of viral fusion to the cell membrane by changing the pH of the cell surface as well as inhibition of viral nucleic acid replication, protein glycosylation, virus assembly and transportation, and release of new virus particles [8,9].

The role of HCQ in COVID-19 is still inconclusive and evolving. The study that attracted the attention of the whole world projected the therapeutic potential of HCQ and azithromycin combination by decreasing the viral load [7]. A systematic meta-analysis of COVID-19 patients suggested that HCQ can prevent the radiological progression of lung disease [13]. An interim analysis of the 'Solidarity' clinical trial performed by the World Health Organization (WHO) has recommended not to use HCQ for COVID-19 therapy as it does not have any mortality benefit [14]. Boulware et al.

Table 1
Baseline demographic and clinical characteristics of the study population[a].

Characteristic	PEP group (n = 132)	Control group (n = 185)	P-value
Age (years) (mean ± S.D.)	36.4 ± 11.8	37.7 ± 15.2	0.428
Male	78 (59.1)	96 (51.9)	0.204
Female	54 (40.9)	89 (48.1)	0.204
Smoker	15 (11.4)	14 (7.6)	0.248
Alcohol consumer	23 (17.4)	30 (16.2)	0.776
Diabetes mellitus	8 (6.1)	6 (3.2)	0.229
Hypertension	1 (0.8)	3 (1.6)	0.497
Coronary artery disease	0 (0.0)	1 (0.5)	0.398
Hypothyroidism	3 (2.3)	4 (2.2)	0.947
Bronchial asthma	1 (0.8)	1 (0.5)	0.809
COPD	0 (0.0)	1 (0.5)	0.398

PEP, post-exposure prophylaxis; S.D., standard deviation; COPD, chronic obstructive pulmonary disease.
[a] Data are n (%) unless otherwise stated.

Table 2
Incidence of COVID-19 after post-exposure prophylaxis (PEP) with hydroxychloroquine (HCQ) and in the control group (no HCQ)

Outcome	n (%) PEP group (n = 132)	Control group (n = 185)	P-value
COVID-19 [a]	14 (10.6)	36 (19.5)	0.033
Definite COVID-19 [b]	10 (7.6)	28 (15.1)	0.041
Probable COVID-19 [c]	4 (3.0)	8 (4.3)	0.552
New-onset symptoms	6 (4.5)	15 (8.1)	0.209
Moderate-to-severe COVID-19	0	0	–

COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] Participants with either definite or probable COVID-19 were defined as a COVID-19 case.
[b] Participants RT-PCR positive for SARS-CoV-2, with or without symptoms, were defined as a definite COVID-19 case.
[c] Participants with new-onset symptoms but RT-PCR negative for SARS-CoV-2 or RT-PCR could not be performed for any reason were defined as a probable COVID-19 case.

concluded that HCQ is not useful for PEP in at-risk individuals for the prevention of COVID-19 [12]. However, the majority (66.4%) of participants in their study were HCWs. There is still a lack of clinical trials evaluating HCQ for PEP in high-risk household contacts of laboratory-confirmed COVID-19 cases. Whilst HCWs and non-HCWs both have a risk of COVID-19 post-exposure, practically the risk category is completely different. HCWs are supposed to come into contact with COVID-19 patients after taking all necessary precautions, for example wearing protective equipment, whereas non-HCW individuals are exposed to COVID-19 unknowingly without any precautions or personal protective equipment, as most of the time patients are their family members or friends or relatives. HCWs usually spend a fixed duration of time with COVID-19 patients and most of the time maintain a safe distance, but non-HCW individuals live with COVID-19 patients for days to weeks without maintaining a safe distance. Post-exposure, non-HCW individuals have a higher risk for COVID-19 compared with HCWs, thus the incidence of COVID-19 after PEP with HCQ may differ in HCWs and non-HCWs. In our study, we aimed to evaluate the efficacy of HCQ as PEP for prevention of COVID-19 in asymptomatic non-HCW individuals at risk for SARS-CoV-2 infection.

Boulware et al. defined COVID-19 cases as symptomatic illness confirmed by a positive molecular assay or COVID-19-related symptoms [12]. Although fever, cough, sore throat, respiratory difficulty and diarrhoea are common presentations of COVID-19, up to 80% of cases may be asymptomatic [3,15]. Radiological imaging may be normal in mild cases and show interstitial pneumonia with ARDS in severe cases. Influenza A virus H1N1 and other influenza A infections can also present with similar clinical and radiological pictures, causing diagnostic difficulty for COVID-19 with concurrence of seasonal viral pneumonia. According to Boulware et al., only 16 of 107 symptomatic cases were PCR-confirmed [12]. Molecular diagnostic assay of nasopharyngeal/bronchoalveolar lavage samples is the investigation of choice for a definitive diagnosis and differentiation of COVID-19 from other seasonal viral pneumonias. So only PCR-positive cases should be designated as definite COVID-19, and PCR-negative symptomatic cases may be designated as probable COVID-19 in view of the ongoing pandemic and variable sensitivity of RT-PCR to detect SARS-CoV-2 in different specimens [16]. Similarly, all asymptomatic high-risk contacts should be tested by molecular diagnostic assay within the incubation period of 2 weeks, as ~80% of COVID-19 cases can be asymptomatic [15]. There was a possibility of missing asymptomatic COVID-19 in the study by Boulware et al. as molecular testing for SARS-CoV-2 was done only for symptomatic individuals, in contrast to the present study where samples from asymptomatic individuals were also tested by RT-PCR for SARS-CoV-2. That is why the present study was able to detect asymptomatic COVID-19 cases in individuals at risk for SARS-CoV-2 infection. According to our study, 58.0% of the COVID-19 cases were asymptomatic. Regarding the 'Solidarity' clinical trial showing no mortality benefit in COVID-19 patients treated with HCQ [14], we would like to re-emphasise that prevention is better than cure. As nearly 80% of COVID-19 patients are asymptomatic and hardly require any specific therapy, prevention of COVID-19 in high-risk individuals is of upmost importance to contain this deadly pandemic.

Safety concerns have been raised against the use of HCQ as it can cause life-threatening cardiac arrhythmias, QT prolongation, hypoglycaemia, vision loss due to irreversible retinopathy, and haemolysis in patients with G6PD deficiency. However, these side effects are not common in routine practice and HCQ appears to be safe with prolonged use [10,13]. Fortunately, none of the study participants complained of any serious ADRs. The drug was tolerable to most of the participants and compliance was good. Only

three participants complained of mild epigastric abdominal discomfort with burning sensation after the first dose that was self-limiting thereafter. The incidence of side effects was higher in the study by Boulware et al., which may be because of the higher dose (3800 mg) of HCQ used compared with the present study (2000 mg) [12]. Direct household contacts of COVID-19 patients are at the highest risk for SARS-CoV-2 infection. To date, there is no clinical trial available regarding PEP with HCQ for the prevention of COVID-19 in asymptomatic high-risk direct household contacts of laboratory-confirmed COVID-19 patients. Recently published studies also supported the role of HCQ for the prevention and treatment of COVID-19 [17–19]. Also according to Boulware et al., there was an absolute risk reduction of –2.4% points in participants who received HCQ prophylaxis, but it did not reach statistical significance [12]. Looking at the disastrous nature of this enormous pandemic, even a 2.4% risk reduction may have a significant impact in preventing further spread when millions of people are infected or will be infected. According to the present study, the absolute risk reduction for the incidence of COVID-19 in participants receiving PEP with HCQ was –8.9% points, which was statistically significant ($P = 0.033$). With this open-label clinical trial, we absolutely do not claim or recommend PEP with HCQ for the prevention of COVID-19 in asymptomatic direct contacts. Nevertheless, based upon the one or two studies we should not completely disregard or reject the potential of HCQ as PEP in asymptomatic high-risk contacts for the prevention of COVID-19. Based upon the safely profile of HCQ and as definitive therapy is still awaited, even a few percentage points of risk reduction for COVID-19 will have a huge impact against this global pandemic of the worst nature. The present study will hopefully make researchers around the globe recognise the potential of HCQ as a virucidal agent and will encourage researchers to further study in order to prove the virucidal effect of HCQ in vivo as well as to reconsider further randomised clinical trials with larger sample size for better evaluation of the efficacy of HCQ as PEP for the prevention of COVID-19 in asymptomatic at-risk individuals.

A limitation of our study is it being an open-label clinical trial and not randomised [20]. We could not conduct a randomised double-blind clinical trial owing to ethical issues as the off-label use of HCQ was not completely safe for conducting a double-blind study. Randomisation and blinding was not permissible as HCQ prophylaxis was recommended by the ICMR for all individuals at risk for COVID-19 [11]. HCQ is approved as an antimalarial and immunomodulator in rheumatic diseases, and the in vitro virucidal effect of HCQ is yet to be proven in an in vivo study [9]. Use of HCQ is not completely safe, as it can cause life-threatening complications. It was very difficult to get preliminary work-up done before starting HCQ in high-risk contacts of COVID-19 in order to restrict the spread of highly contagious SARS-CoV-2 in HCWs and it was also difficult to follow-up physically owing to lockdown factors. To our knowledge, this is the only clinical trial dedicated to evaluating the efficacy of HCQ as PEP to prevent COVID-19 in asymptomatic, high-risk household contacts of laboratory-confirmed COVID-19 cases.

5. Conclusion

PEP with HCQ has the potential for the prevention of COVID-19 in asymptomatic individuals at risk for SARS-CoV-2 infection, as there was a significant risk reduction for the incidence of COVID-19 in participants who received PEP with HCQ. Until definitive therapeutic drugs or preventive vaccines are available, there is no harm in continuing PEP with HCQ in suitable at-risk individuals for the prevention of COVID-19, as endorsed by many national/international health authorities. Better pharmacovigilance is required for monitoring ADRs and to prevent the misuse of HCQ. Further randomised clinical trials with larger sample sizes are encouraged for better evaluation of the efficacy of HCQ as PEP for the prevention of COVID-19 in asymptomatic, high-risk, direct contacts of COVID-19 patients.

Data availability: All data requests should be submitted to the corresponding author (DPD) for consideration.

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