Hydroxychloroquine for Post-Exposure Prophylaxis of COVID-19 among naval personnel: study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background:

The first case of a corona virus 2019 (COVID-19) infection among Sri Lankan was reported on 11th March, 2020. The situation in Sri Lanka changed with the rapid increase of personnel contracting COVID-19 in a Naval base camp that housed more than 4000 people. This provided a unique opportunity to study the effectiveness of hydroxychloroquine (HCQ) for post-exposure prophylaxis (PEP), while taking stringent, non-pharmacologic, public health measures to prevent spread. Our aim is to answer the question “is HCQ effective and safe for PEP among naval personnel with exposure to COVID-19 positive patients?”

Methods/design:

This is a placebo-controlled, randomized, clinical trial carried out in quarantine centers of the Sri Lanka Navy, Ministry of Defense, Sri Lanka. Navy personnel who are exposed to a patient with confirmed COVID-19 infection but test negative for the virus on reverse, real-time polymerase chain reaction (rRT-PCR) at recruitment will be randomized, 200 to each arm, to receive HCQ or placebo, and monitored for the development of symptoms or rRT-PCR positivity for severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) virus for 14 days.

Discussion:

This trial will provide high-quality evidence of the efficacy of HCQ as PEP for COVID-19. The study design is unique due to the circumstances of the outbreak in a confined area among otherwise healthy adults, at a relatively early stage of its spread.

Trial registration:

This trial was registered in the Sri Lanka Clinical Trails Registry (SLCTR) – SLCTR/2020/011 on 04.05.2020 (https://slctr.lk/trials/slctr-2020-011)

Background

The novel Corona virus 2019 (COVID-19) epidemic is a massive threat to public health worldwide. Current estimates suggest that the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), responsible for COVID-19 illness, is both highly contagious (estimated basic reproductive rate, $2-3$) and five to fifty-fold more lethal than seasonal influenza (estimated mortality rate, 0.5-5%) (1). Interventions to decrease the incidence and severity of COVID-19 are urgently needed.

The first case of a Sri Lankan was reported on 11th March, 2020, in a tour guide who was exposed to European tourists in the recent past. Since then, the cumulative numbers have increased. After a critical evaluation of evidence, the use of hydroxychloroquine (HCQ) in symptomatic patients was included in a circular issued by the Ministry of Health, Sri Lanka, on 27th of March, 2020. Since then, its possible use for pre- or post-exposure prophylaxis (PEP) has been intensely debated within the medical profession.

HCQ is an anti-malarial medication with immunomodulatory effects. HCQ has been shown to clear COVID-19 infection status and reduce viral shedding early during the disease course (2, 3). Those against its introduction for prophylaxis cited the poor quality of the study designs and lack of reproducible results elsewhere. However, there were in-vitro studies showing that it elevated endosomal pH, slowed the entry of COVID-19 into cells, and inhibited its replication (4, 5). The drug is inexpensive, has a good safety profile and used extensively in the past to prevent malaria in Sri Lanka and currently used to treat autoimmune diseases.
Clinical trials have been commenced in other countries to assess the efficacy of hydroxychloroquine as pre- or PEP to reduce the severity or attack rate among contacts of known or suspected COVID-19 patients (6–9). India commenced pre-exposure prophylaxis of healthcare workers in 22 March, 2020 (10). In mid-April Indian scientists commenced mass prophylaxis of slum communities in Mumbai (11).

By late April there were four studies from USA, UK, Singapore, Canada to evaluate the role of HCQ in prophylaxis, registered in ClinicalTrials.gov (12–15).

The situation in Sri Lanka changed with the rapid increase of personnel contracting COVID-19 in a Navy camp that housed more than 4000 people in an area of about 52 acres. This was believed to have been the result of navy personnel being exposed to infected patients during contact tracing. This provided a unique opportunity to study the effectiveness of HCQ in prophylaxis while taking stringent, non-pharmacologic, public health measures to prevent spread.

Our research question is, “Is HCQ effective and safe for PEP among naval personnel with exposure to COVID-19 positive patients?”

**Methods**

**Study design**

This will be a placebo-controlled, randomized, clinical trial. The study will be carried out among all eligible persons meeting the inclusion/exclusion criteria directed to be quarantined in quarantine centers (QCs) of the Sri Lanka Navy, Ministry of Defense, Sri Lanka. A patient information leaflet will be provided and informed written consent will be obtained. Those willing to undergo the trial will be randomized and monitored for development of symptoms or reverse, real-time polymerase chain reaction (rRT-PCR) positivity for SARS-CoV-2 virus. All eligible participants who test negative for the virus on rRT-PCR at baseline, will be randomly assigned to the following study arms within 48 hours of admission. Permission will be obtained through the Navy to commence a double-blind randomized trial of HCQ to investigate its efficacy to prevent development of COVID-19 infection in persons who are not yet infected.

**Study setting**

Designated QCs maintained by the Sri Lanka Navy, Ministry of Defense, Sri Lanka.

**Study population**

All the Naval personal who are currently being quarantined in QCs of the Sri Lanka Navy, Ministry of Defense, Sri Lanka.

**Study participants**

All eligible persons directed to be quarantined in QCs of the Sri Lanka Navy, Ministry of Defense will be considered as potential study participants in the study.

**Inclusion criteria**

1. All consenting male and female adult Naval personnel (18-59.9 years of age)
2. Exposure to a patient with confirmed COVID-19 infection (rRT-PCR positive for SARS-CoV-2 virus)
3. The exposure should be for > 30 min within 2 meters of the infected individual and should be within ONE WEEK at the time of inclusion in the study
4. Recruited within 48 hours of admission to these centers
5. Willing to take study drug as directed for 5 days.

**Exclusion criteria**
1. Pregnant and lactating females
2. Suspected or confirmed to have COVID-19 infection (i.e. Navy personnel having positive rRT-PCR test for COVID-19 or presence of fever with cough, shortness of breath, sore throat, anosmia or diarrhoea at the time of recruitment)
3. Presence of pre-existing cardiovascular disease including being on medication for ischaemic heart disease
4. Presence of contraindication to the use of HCQ (on other medications predisposing to long QT or presence of long QT on baseline ECG)
5. Prior diagnosis of retinopathy, G6PD, malignancy or advanced kidney disease
6. Known sensitivity or allergy to hydroxychloroquine

**Sample size**

Altogether 400 participants will be recruited to the study. Among them, 200 each will be allocated to the intervention arm and control arm.

**Sample size calculation**

We used a simulation-based method to estimate design power. Required sample size was determined by simulating 1000 samples for different sample sizes, and the minimum sample size which resulted in an 80% power to detect a significant intervention effect was selected. We considered below assumptions to simulate data.

**Assumptions**

1. Sensitivity of the rRT-PCR is considered as 70% which leaves behind 30% (i.e. 100% − 70%) of COVID-19 infected persons unidentified.
2. Study population of interest includes NAVY personnel who have been exposed to a patient with confirmed COVID-19 infection, and who are not having a positive PCR test for COVID-19 infection or presence of fever with cough, shortness of breath, sore throat, anosmia or diarrhoea at the time of recruitment.
3. We assumed 50% of the study population have COVID-19 infections (i.e. but not diagnosed) at the time of recruitment.
4. If no intervention is adopted (i.e. control arm), we assumed that the COVID-19 infections would increase by 66.7% after 2 weeks.
5. If intervention initiated, we expect 25% reduction in the natural increase of COVID-19 infections after 2 weeks.

Our simulation-based experiment showed the required minimal sample size as 180 for each arm to achieve 80% power. We considered additional 10% (i.e. 180 × 10% = 18) to allow loss to follow ups and non-response bias. Therefore, the total required sample size for the study will be 198 (i.e. 180 + 18) persons. We rounded off the required sample size to 200 and will recruit 200 for each arm.

**Data collection method**

Two trained doctors of the Sri Lanka Navy, in personal protective equipment, will obtain informed written consent from all the participants. Demographic details, co-morbidities and exposure history will be collected via an interviewer administered questionnaire at the recruitment. An ECG will be performed at the Navy Hospital, on all participants to assess for pre-existing prolonged QT interval. A rRT-PCR for SARS-CoV-2 virus will done on all participants on admission to the quarantine center and after the completion of the quarantine period. This sample collection for rRT-PCR will be performed by the already available trained SL Navy personnel designated to perform this task with the necessary precautions including personal protective equipment.

Samples from the naso-pharynx will be obtained and transported in viral transport media and shipped at 4° C to the laboratory at The Center for Dengue Research, Faculty of Medical Sciences, University of Sri Jayawardenapura, Sri Lanka,
for analyses by one of the authors (NM) who will be blinded to the randomization. Confirmation of cases of COVID-19 will based on detection of unique nucleic acid sequences of virus RNA by reverse real-time-transcription polymerase chain reaction (rRT-PCR) (16).

All enrolled participants will be monitored for possible adverse effects of the intervention and the placebo for the period of the study.

**Randomization**

Participants will be allocated to the study arms using simple randomization where each personnel will be considered as a unit. A list of the Navy personnel in the QCs along with their names and national identity card numbers will be obtained. Each personnel will be given a unique number starting from 1 up to the total number of personnel undergoing quarantine in all the QCs. This will be used as a sampling frame for selecting study participants.

A random number generator will be used to generate 400 random numbers without replacement from an integer vector starting from 1 to total number of persons in the QCs and the resulted numbers will be recorded in the exact order which they are generated. The personnel belong to the first 200 random identification numbers in the list will be selected to the intervention group (i.e. receive the envelops numbered from 1 to 200) and the second 200 will be selected to the control group (i.e. receive the envelops numbered from 201 to 400).

Allocation concealment will be maintained by packing the interventional product and the placebo in similar envelopes. Placebo will be produced similar to HCQ tablets in both size and shape. The first 200 envelops will contain the interventional product and the second 200 will contain placebo. These envelops will be numbered sequentially from 1 to 400 and will be handed over to the identified QCs without revealing which envelops contain HCQ and placebo to ensure double blindness.

Each of the study participant will be given a random number from an integer vector starting from 1 to 400 without replacement and each personnel will receive the relevant envelop based on the allocated random number.

- **Arm 1: Intervention arm (n = 200)**

Participants will receive a loading dose of oral HCQ 400 mg 12 hourly Day 1 followed by oral HCQ 200 mg 12 hourly for the next 4 days.

- **Arm 2: Control arm (n = 200)**

Participants will receive an oral matching placebo (oral tablet containing 100 mg of elemental calcium) 2 tablets 12 hourly Day 1, 12 hourly on Day 1, followed by 1 tablet orally, 12 hourly for the next 4 days.

**Outcome measure**

All participants will undergo a rRT-PCR test for SARS-CoV-2 virus at the end of their quarantine period.

*Primary outcome measure;*

1. Number of participants testing positive for SARS-CoV-2 virus using rRT-PCR on day 14 from the time of recruitment)

*Secondary outcome measures;*

1. Number of participants symptomatic for COVID-19 (symptomatic illness will be defined as presence of fever with cough, shortness of breath, sore throat, anosmia or diarrhoea from the time of recruitment until the completion of 14 days).
Data analysis

Descriptive statistics of the study population will be presented. Post interventional prevalence of SARS-CoV-2 virus for the control and intervention group will be calculated and population prevalence of SARS-CoV-2 virus for will be estimated with 95% Confidence Intervals for the non-intervention and intervention groups. A generalized linear mixed effect model will be used to evaluate the effectiveness of HCQ as PEP after accounting for confounders if any.

Ethical clearance

Ethical clearance for the study was obtained from the Ethics Review Committee (ERC) of the Faculty of Medicine, University of Kelaniya, Ragama – P/22/04/2020

Trial registration

This trial was registered in the Sri Lanka Clinical Trails Registry (SLCTR) – SLCTR/2020/011 on 04.05.2020 (https://slctr.lk/trials/slctr-2020-011) and authorization for the trial was obtained from the National Medicinal Regulatory Authority (NMRA) – CLITRI/2020/00032. Universal trial number (UTN) for the study is U1111-1251-3613.

Main ethical issues

All participants will be provided with a detailed information sheet in their preferred language. They will be allowed to provide informed written consent without undue influence.

HCQ has been used for a long period of time for treatment of a variety of illnesses and its safety profile is well documented. At the dosage given in this study investigators do not envisage significant challenges with its safety. However, participants will be monitored daily, and all instances of adverse events will be documented. Furthermore, this trial will include generally fit participants (i.e. Navy personnel on active duty) who have had medical examinations. All participants will have an ECG to exclude prolongation of the QT interval.

All serious adverse events and suspected unexpected serious adverse reactions (SUSARs) will be reported according to guidelines issued by the National Medicines Regulatory Authority, Sri Lanka (NMRA) to the NMRA and ERC. Serious adverse events and SUSARs that require expedited reporting will be reported within stipulated timelines. All adverse events will be managed as appropriate by the trial physicians.

Trial progress will be monitored by an unblinded trial statistician. The trial will be terminated if there is an unexpectedly high serious adverse events rate among trial participants and / or evidence of futility. Further, unblinded data will be sent weekly to the Ethical Review Committee (which will in effect act as a data monitoring committee for this study).

Budget

This clinical trial will be done in collaboration with the State Pharmaceutical Manufacturing Cooperation and Sri Lanka Navy, Ministry of Defense. All the necessary rRT-PCR test kits, drug and placebo for the study have been donated to the SL Navy. rRT-PCR testing will be done free of charge at the Department of Microbiology, Faculty of Medical Sciences, University of Sri Jayewardenepura, in accordance with the already existing protocol of assessment of quarantined persons.

Gantt Chart

The study is planned to conduct from 04 May 2020 to 31 May 2020 after obtaining ethical clearance.
Discussion

The study has a unique design due to the outbreak of COVID-19 infection in a confined area, among otherwise healthy adults at a relatively early stage of its spread. The space of 52 acres houses naval personnel in dormitory-type accommodation was ideal for rapid spread, and immediate measures were taken to send the initial positive cases to hospitals, transfer contacts to other QCs, and for segregation of personnel to minimize contact. Other preventive measures such as handwashing and physical distancing are also stringently followed.
**Trial Status**

Trial protocol version 2.0 dated 02 May 2020 was granted ethical approval and regulatory registration. Recruitment began on 4th May, 2020, and the approximate date on which recruitment will be completed is 30 May, 2020.

**Abbreviations**

SARS-CoV-2 Severe acute respiratory syndrome corona virus 2

COVID-19 Novel coronavirus infection 2019

HCQ Hydroxychloroquine

PEP post-exposure prophylaxis

QCs quarantine centers

rRT-PCR real-time reverse-polymerase chain reaction

ERC Ethic Review Committee

SLCTR Sri Lanka Clinical Trails Registry

NMRA National Medicinal Regulatory Authority

**Declarations**

**Ethics approval and consent to participate**

Ethical clearance for the study was obtained from the Ethics Review Committee (ERC) of the Faculty of Medicine, University of Kelaniya, Ragama – P/22/04/2020. Written, informed consent to participate will be obtained from all participants.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Individual participant data which is used to generate results will be shared immediately following publication after de-identification (text, tables, figures and appendices). Study protocol, statistical analysis plan and analytic code will be made available. Data will be shared with investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Data will be shared to achieve the aims in an approved proposal. Proposals should be directed to maduniln@yahoo.co.uk. To gain access, data requestors will need to sign a data access agreement.

**Competing interests**
The authors declare that they have no competing interests.

**Authors' contributions**

MAN, HJdeS and SJ are the Chief Investigators; MAN, KDD and SJ she conceived the study, led the proposal and protocol development. ADeS, BHRP, DSE, PB, GNM, CW, SL, SAMK, SS contributed to study design and to development of the proposal. MAN, DSE, HJdeS, and SJ are the lead trial methodologists. All authors read and approved the final manuscript.

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**Funding and sponsor**

This clinical trial will be done in collaboration with the State Pharmaceutical Manufacturing Cooperation and Sri Lanka Navy, Ministry of Defense. All the necessary rRT-PCR test kits, drug and placebo for the study have been donated to the SL Navy. rRT-PCR testing will be done free of charge at the Department of Microbiology, Faculty of Medical Sciences, University of Sri Jayewardenepura, in accordance with the already existing protocol of assessment of quarantined persons.

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Figures

| TIME POINT | STUDY PERIOD |
|------------|--------------|
|            | Enrolment    | Allocation | Post-allocation | Close-out |
|            | -t₀          | 5 days     | Week 1          | Week 2   | Week 3   | tₜ     |
| ENROLMENT: |             |            |                |          |          |        |
| Eligibility screen | X            |            |                |          |          | 31 May 2020 |
| Informed consent | X            |            |                |          |          | 31 May 2020 |
| Allocation   | X            |            |                |          |          | 31 May 2020 |
| INTERVENTIONS: |            |            |                |          |          |        |
| HCQ         | X            |            |                |          |          | 31 May 2020 |
| Placebo     | X            |            |                |          |          | 31 May 2020 |
| ASSESSMENTS: |            |            |                |          |          |        |
| Symptoms of COVID-19 | X            | X          | X              |          |          | 15 June 2020 |
| rRT-PCR for COVID-19 | X            |            | X              |          |          | 15 June 2020 |

Figure 1

SPIRIT Figure for the trial - the schedule of enrolment, interventions, and assessments

Supplementary Files

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