

LETTER

Open Access



Pre-exposure prophylaxis with hydroxychloroquine for high-risk healthcare workers during the COVID-19 pandemic: A structured summary of a study protocol for a multicentre, double-blind randomized controlled trial

Berta Grau-Pujol^{1,2,3*} , Daniel Camprubí¹, Helena Marti-Soler¹, Marc Fernández-Pardos¹, Caterina Guinovart¹ and Jose Muñoz¹

Abstract

Objectives: The aim of this study is to assess the efficacy of the use of pre-exposure prophylaxis (PrEP) with hydroxychloroquine against placebo in healthcare workers with high risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in reducing their risk of coronavirus disease 2019 (COVID-19) disease during an epidemic period.

As secondary objectives, we would like to: i) assess the efficacy of the use of PrEP with hydroxychloroquine against placebo in healthcare workers with high risk of SARS-CoV-2 infection in reducing their risk of exposure to SARS-CoV-2 (defined by seroconversion) during an epidemic period, ii) evaluate the safety of PrEP with hydroxychloroquine in adults, iii) describe the incidence of SARS-CoV-2 infection among healthcare workers at high risk of SARS-CoV-2 infection, iv) identify clinical, analytical and microbiological predictors of COVID-19 among healthcare workers at high risk of SARS-CoV-2 infection, v) set up a repository of serum samples obtained from healthcare workers at high risk of SARS-CoV-2 infection for future research on blood markers to predict SARS-CoV-2 infection.

Trial design: Multicentre double-blind parallel design (ratio 1:1) randomized controlled clinical trial.

Participants: Approximately 440 healthcare workers of four Spanish hospitals (Hospital Clínic of Barcelona, Hospital de la Santa Creu i Sant Pau of Barcelona, Hospital Plató of Barcelona, Hospital General de Granollers, Barcelona) will be recruited. Participants are considered to be at high-risk of SARS-CoV-2 infection due to their frequent contact with suspected and confirmed cases of COVID-19.

For eligibility, healthcare workers with 18 years old or older working at least 3 days a week in a hospital with both

(Continued on next page)

* Correspondence: berta.grau@isglobal.org

¹Barcelona Institute for Global Health (ISGlobal), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain

²Fundación Mundo Sano, Argentina, Spain

Full list of author information is available at the end of the article



© The Author(s). 2020 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

(Continued from previous page)

negative SARS-CoV-2 polymerase chain reaction (PCR) assays and serological COVID-19 rapid diagnostic tests (RDT) are invited to participate. Participants with any of the following conditions are excluded: pregnancy, breastfeeding, ongoing antiviral, antiretroviral or corticosteroids treatment, chloroquine or hydroxychloroquine uptake the last month or any contraindication to hydroxychloroquine treatment.

Intervention and comparator: Eligible participants will be allocated to one of the two study groups:

- Intervention group (PrEP): participants will receive the standard of care and will take 400mg of hydroxychloroquine (2 tablets of 200 mg per Dolquine® tablet) daily the first four consecutive days, followed by 400 mg weekly for a period of 6 months.
- Control group: participants will receive placebo tablets with identical physical appearance to hydroxychloroquine 200 mg (Dolquine®) tablets following the same treatment schedule of the intervention group.

Both groups will be encouraged to use the personal protection equipment (PPE) for COVID-19 prevention according to current hospital guidelines.

Main outcomes: The primary endpoint will be the number of confirmed cases of a COVID-19 (defined by a positive PCR for SARS-CoV-2 or symptoms compatible with COVID-19 with seroconversion) in the PrEP group compared to the placebo group at any time during the 6 months of the follow-up in healthcare workers with negative SARS-CoV-2 PCR and serology at day 0.

As secondary endpoints, we will obtain: i) the SARS-CoV-2 seroconversion in the PrEP group compared to placebo during the 6 months of follow-up in healthcare workers with negative serology at day 0; ii) the occurrence of any adverse event related with hydroxychloroquine treatment; iii) the incidence of SARS-CoV-2 infection and COVID-19 among healthcare workers in the non-PrEP group, among the total of healthcare workers included in the non-PrEP group during the study period; iv) the risk ratio for the different clinical, analytical and microbiological conditions to develop COVID-19; v) a repository of serum samples obtained from healthcare workers confirmed COVID-19 cases for future research on blood markers to predict SARS-CoV-2 infection.

Randomisation: Participants meeting all eligibility requirements will be allocated to one of the two study arms (PrEP with hydroxychloroquine or non-PrEP control group) in a 1:1 ratio using simple randomisation with computer generated random numbers.

Blinding (masking): Participants, doctors and nurses caring for participants, and investigators assessing the outcomes will be blinded to group assignment.

Numbers to be randomised (sample size): Each intervention group will have 220 participants, giving a total of 440 participants.

Trial Status: The current protocol version is 1.5, 2nd of June 2020. Two hundred and seventy-five participants were recruited and completed first month follow-up until date. The estimated sample size could not be reached yet due to the declining national epidemic curve. Thus, 275 is the total number of participants included until date. The study has been suspended (26th of June) until new epidemic curve occurs.

Trial registration: This trial was registered on April 2nd 2020 at clinicaltrials.gov with the number NCT04331834.

Full protocol: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

Keywords: COVID-19, Randomised controlled trial, protocol, pre-exposure, prophylaxis, hydroxychloroquine, healthcare workers, Spain, double-blinded

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13063-020-04621-7>.

Additional file 1.

Acknowledgements

The authors will like to thank María José Cavallín for her disposal and assistance during protocol writing. They will also like to acknowledge Dolores Soy for her guidance on study hydroxychloroquine dosage.

Authors' contributions

BGP, DC, HMS, MFP, CG and JM designed and wrote the trial protocol. All authors read and approved the final manuscript.

Funding

The study is currently supported by funds from ISGlobal and Hospital Clínic's International Health's department.

Laboratorios Rubió has partially contributed to the funding of this project and with the required doses of Hydroxychloroquine (Dolquine®). The funding body did not participate on the design of the study and collection, analysis, data interpretation or manuscript writing.

Availability of data and materials

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

Ethics approval and consent to participate

This clinical trial has received ethical and regulatory approvals from the appropriate ethical and regulatory committees in order to safeguard the health of the participants. It was first approved by the Hospital Clínic's Drug Research Ethics Committee (CEIm) with date April 2nd 2020 and the Spanish Agency of Medicines and Medical Products (AEMPS) with date April 3rd 2020. The last protocol amendment was approved June 9th 2020 with AEMPS reference number PGFPP7W635.

Participation in this study is voluntary, and under no circumstances the clinical management of participants will be affected by their decision to participate or not in the study. Informed consent will be signed by all participants before their inclusion in the study. The study consent form reflects the risks and benefits of participating in the study, and the specific sampling procedures to be done to each participant. Sufficient time will be given to the participant's guardians to decide whether or not to participate in the study. Candidates will be given the opportunity to enquire about the details of the study and any question regarding the study will be answered.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

¹Barcelona Institute for Global Health (ISGlobal), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain. ²Fundación Mundo Sano, Argentina, Spain. ³Centro de Investigação em Saúde da Manhica, Maputo, Mozambique.

Received: 14 July 2020 Accepted: 16 July 2020

Published online: 29 July 2020

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

