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Short Communication

Withania somnifera as a safer option to hydroxychloroquine in the chemoprophylaxis of COVID-19: Results of interim analysis

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ARTICLE INFO

Keywords:

COVID-19
Chemoprophylaxis
Ashwagandha
Hydroxychloroquine
Ayurveda

ABSTRACT

Objectives: To study the efficacy and safety of *Withania somnifera* (WS, Ashwagandha) in the prophylaxis against COVID-19 in high risk health care workers (HCW) in comparison to hydroxychloroquine (HCQ). To evaluate the general physical and mental health benefits of Ashwagandha.

Methods: A 16 week randomized prospective, open-label, parallel efficacy, two arm, multi-centre study. The primary efficacy measure was 'failure of prophylaxis' as confirmed COVID-19 by quantitative Reverse Transcription Polymerase Chain Reaction (RT-PCR) at any time during the study period. This study on 400 participants from three centres was designed to establish non-inferiority for WS to HCQ for prophylaxis against COVID-19 at 80 % power and significance $p < 0.025$, one-sided. The interim analysis was carried out on 160 participants after completion of 8 weeks.

Results: Participants in both the arms were well-matched at the baseline characteristics. Forty participants in the HCQ group and 26 participants in the WS group reported mild AE. The symptoms of confirmed COVID-19 were found to be 3.7 % (95 % CI 1.3–10.5 %) in the HCQ and 1.3 % (95 % CI 0.02–6.7 %) in the WS arm amongst the first 160 participants completing 8 weeks.

Conclusion: Our intent was to explore a safer option to HCQ. We report that WS was not found inferior to HCQ and its efficacy was within the 15 % non-inferiority margin set *a priori*. WS as an immunomodulator has other clinical benefits including reducing mental stress. The final report of this study is expected by end of August 2021.

1. Introduction

A large number of health care workers (HCW) engaged in combatting COVID-19 have fallen prey to the virus. This is despite extensive use of personal protection equipment, strict personal discipline and other

preventive measures such as social distancing, use of face mask, hand-washing, and use of drugs like hydroxychloroquine HCQ as prophylactic agents. Chemoprophylaxis against SARS-CoV-2 is needed; however, there are no proven drugs yet. This study was initiated when vaccines were not available in India. Earlier studies have shown that HCQ was

Withania somnifera (WS); health care workers (HCW); hydroxychloroquine (HCQ); Reverse Transcription Polymerase Chain Reaction (RT-PCR).

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<https://doi.org/10.1016/j.ctim.2021.102768>

Received 6 July 2021; Received in revised form 11 August 2021; Accepted 12 August 2021

Available online 18 August 2021

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Table 1
Baseline Characteristics (n = 160).

Demographic variable	Ashwagandha (n = 80)	HCQ (n = 80)
Age (mean ± SD)	38.38 ± 8.25	36.86 ± 9.62
Gender (M:F)	40:40	36:44
Participants with co-morbidity (No, %)	10 (12.5 %)	7 (8.75 %)

unable to prevent SARS-CoV-2 infection among hospital-based HCW.¹ Concerns over misguided use of HCQ have been raised.² Despite insufficient evidence, the Indian Council of Medical Research (ICMR) had issued an advisory³ recommending use of HCQ. As a result, thousands of high-risk HCW consumed HCQ for a prolonged period. India has a legal system to recognize a practice of traditional, complementary and integrative medicine including Ayurveda, Yoga and Naturopathy, Unani, Siddha, Homoeopathy (AYUSH). Based on available literature and empirical evidence, the Ministry of AYUSH (MoA), Govt of India has recommended *Withania somnifera* (WS) also known as Ashwagandha for COVID-19 prophylaxis.⁴ The long-term safety of Ashwagandha is well documented.^{5–7} WS as an immunomodulator has other clinical benefits including reducing mental stress.⁸ In previous studies, selective-Th1 upregulating activity of WS was demonstrated in mouse models,⁹ which seems relevant in the management of COVID-19. Available data indicate that WS may be a good candidate for clinical repurposing in COVID-19 management.¹⁰ Against this background, the current study was undertaken to explore the use of WS as a safer prophylactic option to HCQ in COVID-19.

2. Methods

A randomized, open-label, parallel efficacy, non-inferiority, two arm, multi-centre, 16-week duration clinical trial was initiated in September 2020 to compare WS to HCQ for pre-exposure chemoprophylaxis. The trial protocol was approved by respective institutional ethics committees and was registered on August 14, 2020 at the Clinical Trial Registry – India.¹¹ Four hundred eligible participants from three centres (Mumbai, Hasan and Nagpur) were enrolled after the informed consent. The participants were randomized in two arms to receive 2 tablets of 250 mg standardized extract of WS twice daily or 400 mg HCQ weekly. Details of quality control and standardization of WS extract are provided as Supplementary File Number 1. The participants were jointly evaluated by Ayurvedic and Modern Medicine physicians. The participants were tracked on a daily basis for adverse events (AE) using a specially designed mobile App (named as Covid Kavach). The primary efficacy measure was the incidence of symptomatic COVID-19 confirmed by a positive RT-PCR test for SARS-CoV-2. The study was powered at 80 % with 95 % confidence interval (CI), one-sided significance $p < 0.025$. Statistical analysis was carried out as per Wilson's recommended method using CIA software by BMJ group, London, 2002. An interim analysis of the first 160 participants, 80 in each arm and completing 8 weeks presented here was planned *a priori*.

3. Results

Participants in both the arms were well-matched at the baseline characteristics (Table 1). One participant in the WS arm and 3 in the HCQ arm contracted COVID-19 during the initial 8 weeks. Results indicate that WS was not inferior to HCQ and its efficacy was within the 15 % non-inferiority margin set *a priori*. The symptoms of confirmed COVID-19 were found to be 3.7 % (95 % CI 1.3–10.5 %) in the HCQ and 1.3 % (95 % CI 0.02–6.7 %) in the WS arm amongst the first 160 participants completing 8 weeks. The difference percentage between HCQ and WS among symptomatic and RT-PCR positive COVID-19 estimated as 2.4 % (3.5 % to 9.3 %) was within the pre-specified margin of 15 %. Forty participants in the HCQ group and 26 participants in the WS group reported mild AE; however, none required withdrawal from the study.

4. Conclusion

This study was planned when the vaccination option was not available and the need for chemoprophylaxis was obvious. Our intent was to explore a safer option to HCQ, which was standard care recommended by the ICMR. The interim analysis suggests that WS is not inferior to HCQ. The results show non-inferiority for both symptomatic COVID-19 with RT-PCR and asymptomatic COVID-19 with RT-PCR and also for all RT-PCR positives. Given the long history of use of Ashwagandha in the community and available data on its efficacy and safety, it can be considered as a safer option to HCQ. The final report of this study is expected by end of August 2021.

Author contributions

All authors have made substantial contributions to this study. AC, BP and NS contributed to the conceptualization, methodology, and design of the study as well as its analysis and interpretation. ACRG includes a team of clinical investigators and statistician. AC and NS contributed to coordination and acquisition of data. BP and AC prepared draft article and attended reviewers comments and revision.

Funding statement

This study was sponsored by Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, Government of India, New Delhi.

Declaration of Competing Interest

None of the authors have any competing interest regarding this study. Narayanam Srikanth work at CCRAS, MoA, Government of India, New Delhi. Arvind Chopra is chief clinical coordinator designated by MoA. Bhushan Patwardhan is Chairman Interdisciplinary AYUSH R & D Task Force on COVID-19 established by MoA. AR is a member of Data Safety Monitoring Board that reviewed the study data.

Acknowledgment

A special thanks to Vaidya Rajesh Kotecha, Secretary, Ministry of AYUSH, Government of India, for his invaluable guidance and inspiration. We thank Vaidya KS Dhiman, former DG and other non-author contributors from the CCRAS project team - Ravindra Singh, Babita Yadav, Sophia Jameela, Amit Kumar Rai, Azeem Ahmed, BS Sharma. We thank Dr Lal Hingorani, Pharmanza Herbals Pvt Ltd, India for supply of standardised extracts and tables of Ashwagandha ex gratia. We also thank all reviewers who helped in improving the quality of the protocol.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ctim.2021.102768>.

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