HCQ prophylaxis in COVID-19 did not show any QTc prolongation in Healthcare workers

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A B S T R A C T

Background: HCQ is a commonly recommended drug for the prophylaxis of COVID-19. One of its rare side-effect includes QTc prolongation.

Methods: This was a prospective, cross sectional and observational study conducted on Hydroxychloroquine (HCQ) among Healthcare Workers (HCWs) at Max Super Speciality Hospital, Saket, New Delhi, India. A 3-lead ECG (only limb leads, it does not require chest leads) was performed. The QTc cut offs were pre decided, QTc < 470 ms for males and <480 ms for females was considered within the normal limits and anything above this was regarded as QTc prolongation.

Results: There were 274 HCWs enrolled into the study, including 175 males and 99 females. Majority of the HCWs were young and had a mean age of 32.19 ± 9.29 years. Out of these, 218 were taking HCQ as per the Indian Council of Medical Research (ICMR) guidelines. The median cumulative dose being taken was 1600 mg and the median QTc of these participants was 390 ms in males and 391.5 ms in females. Subsequently, 33 participants were followed-up and found to have a median QTc of 389 ms and a cumulative dose of HCQ as 2000 mg.

Conclusion: In conclusion, ours is the first study in the middle of the pandemic which showed that HCQ prophylaxis in young HCWs without comorbidities did not show any QTc prolongation.

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1. Introduction

In the current era of rapidly rising cases of coronavirus illness 2019 (Covid-19) infection, multiple treatment and prophylaxis options have been tried with various degrees of success rates as well as accompanying side effects. HCQ is one of the commonly recommended medications for the population at high-risk of exposure, as it has both anti-inflammatory and antiviral effects.1-7

The Indian Council for Medical Research (ICMR), National Task Force for COVID 19 issued recommendations for HCQ to be used as a prophylaxis for the asymptomatic exposed Healthcare Workers (HCW) in late March 2020.8 Since these and similar recommendations have come up, several questions have been raised in regards to its cardiac toxicity particularly QTc prolongation. HCQ is recommended as a prophylaxis as it is a long acting drug with a terminal half-life of more than 40 days.9 There is a high-risk of side-effects on cumulative dosing. The most common side effects of HCQ include gastrointestinal symptoms, pruritus, hypoglycaemia, retinopathy, neuropsychiatric effects and dermatological changes that can occur in up to 10% of the patients.10,11 The most severe side effects have low incidence, which includes neuromyopathy of proximal muscles, cardiotoxicity, and irreversible retinopathy. A rarer side effect of HCQ is prolonged QTc interval leading to arrhythmias and on rare occasions, life threatening arrhythmia Torsades-de-pointes (TdP). Even though occurrence of TdP is very uncommon, the risk is increased in patients receiving medications that have an additive effect of prolonged QTc, such as anti-infective drugs (Macrolides, Azole anti fungi, Bedaquiline, Lopinavir, and Ritonavir, etc.), psychotropic drugs (Chlorpromazine, Haloperidol, etc.), Ondansetron, Formoterol, etc.12 However majority of these side effects have been studied in treatment doses but none in prophylactic doses. Essentially all the drugs that create LQTS (Long QT syndrome) act by blocking the rapid delayed rectifier channel (IKr) current interceded by the potassium channel encoded by the KCNQ2 quality.13
We decided to proceed quickly to understand QTc prolongation due to HCQ as large work force in our institution was recommended HCQ for prophylaxis as per the ICMR guidelines.

2. Material and methods

This was a prospective, cross sectional and observational study conducted on HCQ among HCWs at Max Super Speciality Hospital, Saket, New Delhi, India. The Institutional Ethics Committee approved the study. We enrolled Healthcare workers (HCW) coming to the hospital. The inclusion criteria were HCWs, >18 years of age and consenting to participate. Participants were recruited prospectively by convenient sampling method over duration of 15 days starting on 30.04.2020. ECG station was set up in a common accessible area with due precautions. Data was collected on their demographics, history of exposure to COVID-19 and prophylaxis if any that they are taking. The details of dose and duration of the prophylactic drug being taken were also noted. A 3 lead (only limb leads, it does not require chest leads) ECG was then performed using an automated (GE MAC 2000) machine which gives all the basic readings of the ECG including the rate, rhythm and QTc (Bazett’s formula) values.

The QTc cut offs were pre decided, QTc <470 ms for males and <480 ms for females was considered within the normal limits and anything above this was regarded as QTc prolongation. A process was set up to meet the cardiologist if the QTc was prolonged.

We decided to follow up a subset of the study population to see the effects of cumulative doses of HCQ on those HCWs who continued to take it. The follow-up was done on 33 participants and a repeat ECG was recorded after an interval of one-month of their baseline ECG.

3. Results

We enrolled 274 HCWs out of which 218 were taking HCQ prophylaxis as per the guidelines. The mean age of participants was 32.28 ± 9.29 years. The demographics of the participants is shown in Table 1.

None of the study participant was found to have COVID-19 during the study period. However during this period the hospital prevalence was also low (1.8%).

3.1. Participants on HCQ

Majority of participants were on HCQ and they had taken it as per ICMR guidelines i.e. a dose of 400 mg twice a day for 1 day only, followed by 400 mg once a week for 7 weeks. Of the 218 who were on HCQ, 138 (63.3%) were males and 80 (36.6%) were females. Mean age of these participants was 32.19 ± 9.29 years. Maximum number of participants had taken it upto 3 weeks. The median dose taken by participants was 1600 mg. The median QTc was 390 ms in males and 391.5 ms in females. Fig. 1 shows the distribution of participants in different QTc ranges. We did not have any participants having any structural/congenital heart disease and none of them revealed taking any other QTc prolonging medications.

Table 1

| S.No | Variables | Percentage (n) |
|------|-----------|----------------|
| 1.   | Gender    |                |
|      | Males     | 63.8% (175)    |
|      | Females   | 36.1% (99)     |
| 2.   | Age categories |         |
|      | 18–30     | 57.2% (157)    |
|      | 31–40     | 24.4% (67)     |
|      | 41–50     | 13.8% (38)     |
|      | >51       | 4.3% (12)      |
| 3.   | Job description |       |
|      | Doctors   | 8.0% (22)      |
|      | Nurses    | 22.9% (63)     |
|      | Other supporting staff | 68.9% (189) |
| 4.   | Comorbidities |       |
|      | Hypertension | 1.09% (3)    |
|      | Diabetes   | 0.73% (2)      |
|      | Smoking    | 5.84% (16)     |
| 5.   | High risk zone posting | 5.83% (16) |
| 6.   | Covid test done | 41.9% (115) |
| 7.   | Prophylaxis |             |
|      | Hydroxychloroquine (HCq) | 79.56% (218) |
|      | HCq + Chlороquine (CQ) | 2.5% (7)    |
|      | HCq + Azithromycin | 0.7% (2)    |

Table 2

| S.No | Participant ID | Baseline QTc | Follow-up QTc |
|------|---------------|--------------|---------------|
| 1.   | MCoV001       | 388          | 394           |
| 2.   | MCoV009       | 399          | 408           |
| 3.   | MCoV012       | 348          | 352           |
| 4.   | MCoV013       | 388          | 401           |
| 5.   | MCoV022       | 409          | 410           |
| 6.   | MCoV033       | 335          | 340           |
| 7.   | MCoV040       | 376          | 381           |
| 8.   | MCoV044       | 399          | 406           |
| 9.   | MCoV059       | 323          | 354           |
| 10.  | MCoV066       | 390          | 416           |
| 11.  | MCoV072       | 341          | 334           |
| 12.  | MCoV105       | 387          | 396           |
| 13.  | MCoV117       | 410          | 416           |
| 14.  | MCoV126       | 380          | 394           |
| 15.  | MCoV158       | 358          | 384           |
| 16.  | MCoV139       | 408          | 403           |
| 17.  | MCoV176       | 398          | 398           |
| 18.  | MCoV150       | 348          | 353           |
| 19.  | MCoV152       | 392          | 397           |
| 20.  | MCoV156       | 330          | 348           |
| 21.  | MCoV157       | 392          | 395           |
| 22.  | MCoV169       | 375          | 389           |
| 23.  | MCoV184       | 367          | 371           |
| 24.  | MCoV186       | 343          | 351           |
| 25.  | MCoV187       | 355          | 361           |
| 26.  | MCoV214       | 355          | 361           |
| 27.  | MCoV224       | 405          | 386           |
| 28.  | MCoV233       | 348          | 359           |
| 29.  | MCoV237       | 388          | 390           |
| 30.  | MCoV247       | 354          | 362           |
| 31.  | MCoV253       | 372          | 383           |
| 32.  | MCoV255       | 386          | 390           |
| 33.  | MCoV273       | 399          | 400           |

Fig. 1. Percentage of patients falling into different QTc ranges.
At one-month follow-up, median cumulative dose of HCQ taken by 33 participants was 2000 mg and the median QTc was 389 ms. Baseline and follow-up QTc values are shown in Table 2. Age-matched comparison of QTc among the participants taking HCQ and those not taking HCQ is presented in Table 3. There was no statistically significant difference observed in the QTc of the two groups.

4. Discussion

The present study was aimed to find any effect of HCQ prophylaxis on QTc prolongation amongst the HCWs. We found that majority of the HCWs were young (32.19 ± 9.29 years) and had no co-morbidities. At the time of this study, the cumulative dose taken by most of the participants was 1600 mg over 3 weeks' time. We did not observe any QTc prolongation in any of the participants. As the pandemic and its prophylaxis continued, we followed-up 33 participants with ECG and found the cumulative dose of 2000 mg as the median. Interestingly, there was no QTc prolongation at this dose also.

Ever since the ICMR recommendations for HCQ use as prophylaxis for asymptomatic HCWs has come, many concerns regarding its association with QTc prolongation have been raised. However, we did not come across any such findings. Some studies done by ICMR15 and Closon et al16 concluded that in this era of Sars-Cov-19, HCQ provided significant advantage as a part of treatment/prophylaxis for the same, even though there would be more studies required with larger number of subjects to come to a definite conclusion.17

This is the first study on prophylaxis and QTc prolongation, in contrast to a study in Nature Medicine showing QTc prolongation in 9 patients who were on treatment (HCQ + Azithromycin).18

With this study, our purpose was neither to recommend nor discourage the use of HCQ as a prophylaxis.

5. Conclusion

Ours is a first study in the middle of the pandemic which showed that HCQ prophylaxis in young HCWs without comorbidities did not show any QTc prolongation. However large population based studies would further validate our results. Randomized control studies are being conducted worldwide to determine the safety and efficacy of HCQ as prophylaxis in COVID-19.

6. Limitations

The sample size was small, however it was well representative of the HCWs population. The follow up of the patients need to be done further up to at least 7 weeks.

Declaration of competing interest

There are no conflicts of interest involved in this study.

References

1. Savarino A, Trani LD, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. Lancet Infect Dis. 2006;6(2):67–69.
2. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71(15):732–739.
3. Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents. 2020;55(5):105938.
4. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;105949.
5. Tourret F, Laballiere XD. Of chloroquine and COVID-19. Antivir Res. 2020;177:104762.
6. Gualtelaegname M, Vallone A. Could chloroquine/hydroxychloroquine be harmful in coronavirus disease 2019 (COVID-19) treatment? Clin Infect Dis. 2020;71(15):888–889.
7. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with covid-19. N Engl J Med. 2020;382(25):2411–2418.
8. Advisory on the Use of Hydroxy-Chloroquine as Prophylaxis for SARS-CoV-2 Infection. MOHFW; 2020. Available from: https://www.mohfw.gov.in/pdf/AdvisoryontheuseofhydroxychloroquineprophylaxisforSARS-CoV2Infection.pdf.
9. Teitt SE, Cutler DJ, Day RO, Brown XF. Bioavailability of hydroxychloroquine tablets in healthy volunteers. Br J Clin Pharmacol. 1989 Jun;27(6):771–779.
10. Sanders JM, Monogue ML, Jodlowski TZ, Cattrell JB. Pharmacologic treatments on COVID-19. JAMA. 2020;323(18):1824–1836.
11. Sinha N, BalaGya G. Hydroxychloroquine and covid-19. Postgrad Med J. 2020;95:550–555.
12. https://www.uptodate.com/contents/image?imageKey=CARD%2F57431&topicKey=RHEUM%2F7964&source=see_link. Assessed on: 01-07-2020.
13. https://www.uptodate.com/contents/acquired-long-qt-syndrome-causes-and-pathophysiology?cissi=6139821-e8cc-40a4-b82a-d512d958b64&source=contentShare. Assessed on: 01-07-2020.
14. Jha S, Soni A, Siddiqui S, et al. Prevalence of flu-like symptoms and COVID-19 in healthcare workers from India. J Assoc Phys India. 2020;68(7).
15. National Taskforce for COVID-19. Advisory on the Use of Hydroxy-Chloroquine as Prophylaxis for SARS-CoV-2 Infection; 2020. https://www.mohfw.gov.in/pdf/Advisory on the use of HydroxychloroquinaprophylaxisforSARS-CoV2Infec tion.pdf. Accessed March 23, 2020.
16. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020;55(5):105932.
17. Shah S, Das S, Jain A, et al. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). Int J Rheum Dis. 2020;23(5):613–619. https://doi.org/10.1111/1756-185X.13842.
18. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. Nat Med. 2020;26(6):808–809.

Table 3

| Age categories (years) | Median QTc (Participants taking HCQ) | Median QTc (Participants not taking HCQ) |
|-----------------------|-------------------------------------|----------------------------------------|
| 18–30 (n = 157)       | 390 (n = 129)                       | 391 (n = 28)                           |
| 31–40 (n = 67)        | 390 (n = 53)                        | 390 (n = 14)                           |
| 41–50 (n = 38)        | 390 (n = 29)                        | 391 (n = 9)                            |
| >50 (n = 12)          | 389 (n = 7)                         | 390 (n = 5)                            |
| Age-matched QTc values.

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