Short Communication

QTc Interval of Healthcare Workers from India: Baseline and Effect of Hydroxychloroquine Prophylaxis during the COVID-19 Pandemic

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Abstract

Background: The aim of this study was to access the incidence of prolonged QTc interval and changes, if any, among Indian healthcare workers (HCWs) taking hydroxychloroquine (HCQ) prophylaxis while managing coronavirus disease 2019 (COVID-19) cases. **Methods:** At the beginning of the COVID-19 pandemic, as per the Indian Council of Medical Research (ICMR) policy, HCWs were advised to take HCQ as prophylaxis after getting an electrocardiogram (ECG) while being posted to look after COVID-19 patients. A follow-up ECG was repeated for those who took HCQ. The normal upper limit for QTc interval of 460 milliseconds (ms) for females and 450 ms for males was considered. **Results:** A baseline ECG was analyzed for 250 HCWs with a median age of 35 (30–43) years. The median QTc was 410 (395–421) ms with the prevalence of prolonged QTc of 1.8% in females and 0% in males. A follow-up ECG after HCQ intake for 43 HCWs was further analyzed. They had a median age of 35 (31–39) years and took an average dose of HCQ of 2372 ± 839 mg. Pre- and post-HCQ chemoprophylaxis QTc interval (ms) was as follows: 408 (386–419) and 405 (387–417), with $P = 0.434$, respectively. **Conclusion:** Among Indian HCWs, the prevalence of prolonged QTc is 1.8% and 0% in females and males, respectively. HCQ intake as chemoprophylaxis for COVID-19 did not affect their QTc interval.

Keywords: Electrocardiogram, healthcare workers, hydroxychloroquine, QTc, SARS-CoV-2 infection

Introduction

During the recent coronavirus disease 2019 (COVID-19) pandemic, before the availability of vaccine in the year 2020 itself, the National Task Force by the Indian Council of Medical Research (ICMR) recommended the use of hydroxychloroquine (HCQ) as chemoprophylaxis for asymptomatic healthcare workers (HCWs) involved in the care of suspected or confirmed cases of COVID-19 and asymptomatic household contacts of laboratory-confirmed cases.[1] Their recommendation was based on *in vitro* studies, which found that HCQ is effective against COVID-19.[2,3] In view of ICMR recommendations, the Indian Heart Rhythm Society (IHRS) proposed a scientific statement for the use of HCQ and strongly discouraged its use for the general public without medical supervision and prescription.[4]

As there is a scarcity of known prevalence of QT interval prolongation in nonhospitalized population in general, and none in specific population such as HCWs from India, we conducted this study to assess the baseline-corrected QT (QTc) interval, the incidence of prolonged QTc interval, and changes, if any, among HCWs taking HCQ prophylaxis while managing COVID-19-confirmed or COVID-19-suspected cases.

Methods

This was a prospective observational study conducted at a tertiary care university hospital in North India, after approval from the

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Institutional Ethics Committee (IEC code 2020-124-IP-EXP-18) and registered with the Clinical Trial Registry of India (CTRI/2020/05/025089). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines have been followed for the study [Supplement file 1].

Study participants' inclusion

During the study period (May–September 2020) at the beginning of COVID-19, our hospital followed ICMR recommendations to advise all HCWs to take HCQ as chemoprophylaxis during their posting to manage COVID-19-confirmed or COVID-19-suspected patients. As a part of good clinical practice, HCWs were also suggested to get an electrocardiogram (ECG) done before starting HCQ intake. Investigators routinely received the ECG of HCWs for review and advice for safety to take HCQ. These HCWs were further followed if they took HCQ as chemoprophylaxis, to get their follow-up ECG.

Data collection

For all included participants, we collected information on age and gender. We collected more variables for whom we had follow-up ECG after HCQ intake, which includes the presence of comorbidities, use of concurrent medication, dose of HCQ, and adverse effect of HCQ, if any.

QTc interval measurement

A 12-lead ECG was used to measure the QT interval (and standard correction for heart rate (HR) by Bazett's formula) to calculate the corrected QT for HR (QTc). Data acquisition and ECGs were read by a single independent observer and confirmed by a certified cardiologist led to a reduction in bias. The normal upper limit for QTc interval is considered 460 ms for females, 450 ms for males, and delta QTc (absolute increase in QTc post-HCQ) by 60 ms.[5]

Sample size

For the calculation of sample size to determine the effect of HCQ on the QTc interval, the effect size (Cohen's d) range between 0.2 and 0.49 was considered a small effect size when estimated between two paired means.[6] Assuming a small change (effect size = 0.49) to be detected in the QTc interval between pre- and post-observations, at a two-sided 95% confidence interval and 90% power of the study, the estimated sample size for paired observations came out to be 46. The sample size was estimated using software G Power version 3.1.9.2 (Düsseldorf University, Germany).

Statistical analysis

Descriptive statistics of the continuous variables were presented as mean ± standard deviation/median (interquartile range (IQR)), whereas categorical data were presented in frequency (%). A paired-samples t-test was used to calculate the significance level as appropriate. A P value <0.05 was considered statistically significant. Statistical Package for Social Sciences version 23 (SPSS 23, IBM, Chicago, USA) software was used for data analysis.

Results

Of the 294 ECGs collected over 6 months, 250 were analyzed (44 ECGs excluded due to artifacts and fainting of ink). Baseline ECG was analyzed for 250 HCWs with a median age of 35 (30–43) years. The median QTc was 410 (395–421) with the prevalence of prolonged QTc in females (n = 107) and males (n = 143) being 1.8% and 0%, respectively [Supplementary Figure 1].

In follow-up, there were 43 HCWs who took HCQ and had a second ECG. They were included for further analysis to determine the effect of HCQ on QTc interval, with a median age of 35 (31–39) years and body mass index (BMI) of 24 (23–27.5), and 19% were female. None of the participants were taking any known medication that causes prolongation of QTc. Five had comorbidities (diabetes mellitus with hypertension: 1 (2.3%), asthma: 1 (2.3%), hypothyroidism: 1 (2.3%), and arthritis: 2 (4.7%)), with median QTc of 421 (412.5–427.5) [Table 1]. The average dose of HCQ taken by HCW was 2372 ± 839 mg (1200–4000 mg).

Pre- and post-HCQ chemoprophylaxis HR per minute was as follows: 76 (67–83) and 75 (68–84), with P = 0.520; QT interval (ms): 360 (340–390) and 358 (340–382), with P = 0.388; and QTc interval (ms): 408 (386–419) and 405 (387–417), with P = 0.434, respectively [Figure 1 and Supplementary Figure 2]. The linear coefficient of correlation

Table 1: Demographics, HCQ dose, and ECG variables among HCW (n=43) follow-up

Demographic, HCQ dose, and ECG variables	Mwedian (IQR)/*n* (%)
Demographic	
Age, median in years	35 (31,39)
Female sex (n (%))	8 (18.6%)
BMI	24 (23.0, 27.5)
Comorbidities (*n* (%))	
Diabetes mellitus/hypertension	1 (2.3%)
Asthma	1 (2.3%)
Hypothyroidism	1 (2.3%)
Arthritis	2 (4.7%)
HCQ dose	
Average dose of HCQ (mean (in mg))	2372±839
ECG variables at baseline	
Heart rate (beats/min)	76 (67–83)
QT interval (ms)	360 (340–390)
QTc interval (ms)	408 (386–419)
Changes (Δ) in ECG variables in follow-up	
Δ HR (beats/min)	2 (-6 to 7)
Δ QT interval (ms)	-6.0 (-16 to 10)
ΔQTc interval (ms)	-2.0 (-20 to 7)
Adverse effects of HCQ (*n* (%))	
Headache	1 (2.3%)
Anxiety	1 (2.3%)
Palpitation	1 (2.3%)
Loose motion	3 (6.9%)
Gastritis	2 (4.7%)

between dose of HCQ and delta QTc is very weakly positive (R^2 = 0.007) [Supplementary Figure 3]. Post-HCQ median delta (Δ) changes were as follows: HR of 2 (IQR: -6 to 7) per minute; QT interval of -6 (IQR: -16 to 10) ms; and QTc interval of -2 (IQR: -20 to 7) ms [Table 1].

Adverse effects related to HCQ were nonserious and occurred in 18.6% (n = 43) of the HCWs (headache: 1 (2.3%), anxiety: 1 (2.3%), palpitation: 1 (2.3%), loose motion: 3 (6.9%), and gastritis: 2 (4.7%)) [Table 1].

Discussion

In our study, the prevalence of prolonged QTc interval is 1.8% and 0% in females and males, respectively, which is very low in comparison with other nonhospitalized studied populations in various countries, viz. Chinese population (70.6% and 29.3%),[7] Uganda population (14% and 9%),[8] and Italian population (10% and 5%).[9] We reviewed the demographic and clinical characteristics of populations in these studies and possibilities of other variables, which might influence the prevalence of prolonged QTc interval like the definition of prolonged QTc interval, age, comorbidities, and use of concurrent medications. First, varied prevalence might be due to differences in the definition of prolonged QTc (for males it is 440 ms in the Italian and Chinese population, while 450 ms for the Uganda population; also, for females it is 440 ms in the Italian and Chinese population, while 460 ms for Uganda population). Second, with aging, there is an increase in QTc interval seen by the median age of the Chinese population of 54 years versus our study of 35 years. Third, simultaneously with a growing population, there is a rise in comorbidities, as it is clearly demarcated in a Chinese population that hypertension, dyslipidemia, and obesity are associated with an increase in the prevalence of prolonged QTc while our study has not studied comorbidities in all HCWs. Lastly, as seen with the Chinese population, the prevalence of prolonged QTc is associated with 59.9% population using medications that cause prolonged QTc interval, which is not the case with ours. An Indian study in 366 healthy adult males showed a mean QTc of 372 ms, but the prevalence of prolonged QTc has not been calculated.[10]

In our cross-sectional study among 43 HCWs, the median age of the population was 35 years. The baseline characteristics of HCWs revealed that all were healthy with comorbidities only in five (11%) HCWs. By week 4, nearly 32.5% of HCWs had stopped HCQ, and we followed up participants with ECG and found a cumulative dose of 2372 mg (mean). All HCWs who took HCQ were aware of the side effects and investigated with ECG to rule out prolonged QT, QTc, and HR and reported no significant difference in the changes in QTc, change in QT, and HR. Our findings are also supported by Jha *et al*.[11] who reported 33 HCW's follow-up and found to have a median QTc of 389 ms and a cumulative dose of HCQ of 2000 mg. However, there is no meta-analysis that evaluated the HCQ effect in a healthy population, but studies were done in COVID-19 patients or other diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). A meta-analysis of 28 studies on HCQ use in severe acute respiratory syndrome (SARS)-COVID-19 patients did not show a significant incidence of prolonged QTc.[12] Another meta-analysis of 13 studies on HCQ or chloroquine use with or without azithromycin in SARS-COVID-19 patients produces a significant risk of QTc prolongation, but the data were heterogeneous.[13]

On further evaluation, our study showed that the median delta QTc of -2 (-20 to 7) ms is not significant (an absolute value of 60 ms is considered significant). A study of HCQ on 152 COVID-19-positive Turkish outpatients showed similar results on delta QTc of -7 (-10.5 to 23.5) ms.[14] In our study, none of the study participants had a delta QTc variation of more than 1%, which is similar to a study on 219 COVID-19 patients, which showed that the vast majority (75%) of patients had a variation of less than 5%.[15] In our study, delta QTc and variation of delta QTc were not significantly changed by HCQ, possibly because of relatively young and absence of comorbid population, and also, none were taking concurrent medication causing prolonged QTc.

Limitation and strength of the study

The limitation of our study is that being a single center and involving a small number of participants, the results cannot be generalized to a larger population due to the possibility of regional or ethnic predisposition. Also, we did not ascertain abstinence from caffeine, tobacco, and alcohol at least 24 hours before the ECG was recorded, which might have affected QTc interval. However, the strength is that our study is the first among HCWs so far to know the prevalence of prolonged QTc interval.

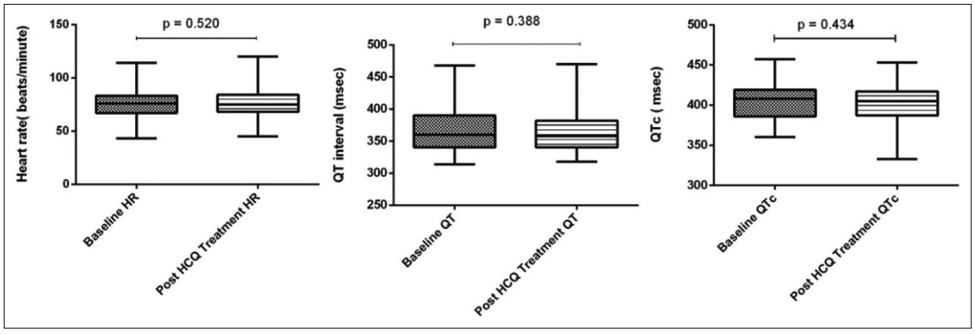

Figure 1: Pre- and post-intakes of total HCQ doses and changes in ECG variables

Conclusion

Among Indian HCWs, the prevalence of prolonged QTc is 1.8% and 0% in females and males, respectively. The short-term use of HCQ by HCWs as chemoprophylaxis for COVID-19 did not affect their QTc interval.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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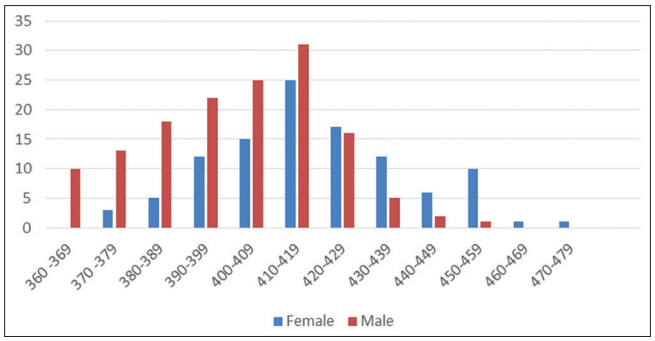
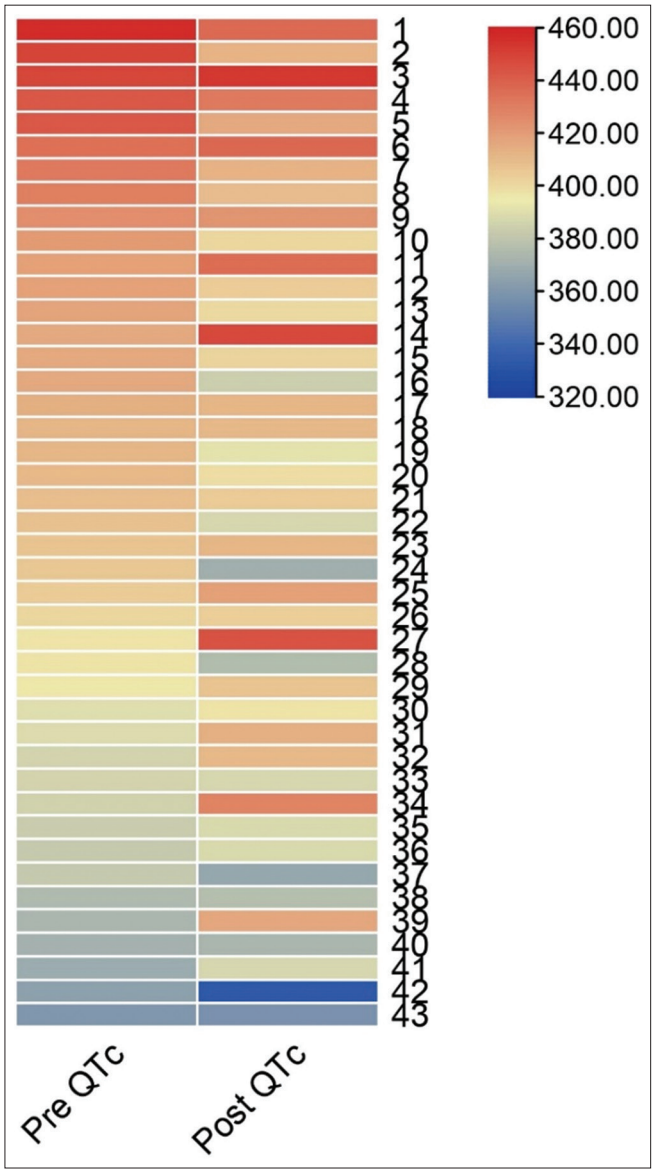
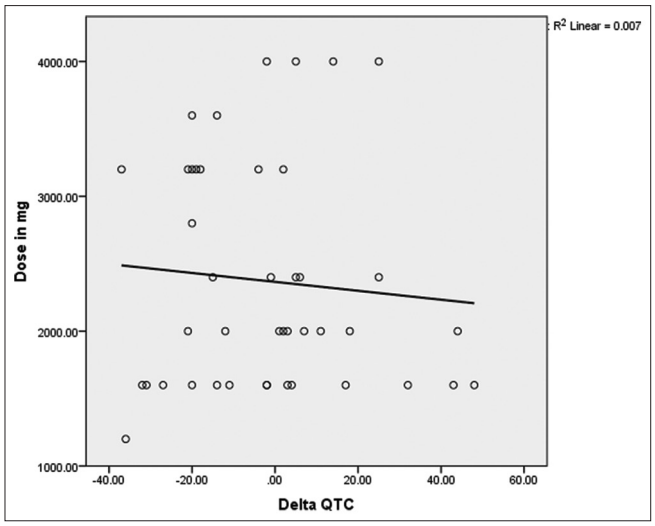


Supplementary Figure 1: Baseline QTc interval in milliseconds among 250 HCW's



Supplementary Figure 2: Heat map corresponding to pre-exposure and post-exposure of HCQ on QTc conditions for each case. The transverse axis of the heat map represents the leads of the pre-QTc and post-QTc, and the longitudinal axis represents the cases. Each lattice color represents different QTc, with blue representing QTc =320, red representing QTc =460, and blue-to-red lattice color changes representing the QTc = 440 to 340.



Supplementary Figure 3: Correlation between intakes of total HCQ doses (in milligram) with ΔQTc

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**01**	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**01-02**	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**03**	
Objectives	3	State specific objectives, including any prespecified hypotheses	**04**	
Methods				
Study design	4	Present key elements of study design early in the paper	**04**	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**04-05**	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**04-05**	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**04-05**	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**04**	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**04**	
Bias	9	Describe any efforts to address potential sources of bias	**05**	
Study size	10	Explain how the study size was arrived at	**05**	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**05**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**05**
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**05-06**
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**05-06**
		(b) Indicate number of participants with missing data for each variable of interest	**05-06**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	**05-06**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	**05-06**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **6-7**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **7,8,9**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **9**
Generalisability	21	Discuss the generalisability (external validity) of the study results **9**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **NIL**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.