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Temporal change of ventricular repolarization indices and index of cardioelectrophysiological balance (iCEB) during COVID-19 treatment including hydroxychloroquine at a tertiary referral hospital

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ABSTRACT

Aim: Hydroxychloroquine (HCQ) is widely administered to patients with confirmed or suspected COVID-19. It may increase the risk of cardiac arrhythmias associated with QT and QTc prolongation. This study aimed to assess the change in iCEB, a new marker of drug-induced arrhythmia, and other repolarization parameters in suspected COVID-19 patients treated with short-course HCQ.

Material and Method: This was a retrospective cross-sectional study including 40 patients hospitalized with suspected COVID-19 according to the CT findings and treated with HCQ. Serial assessments of the QT and QTc intervals and the calculation of the index of cardio-electrophysiological balance (iCEB) were performed using standard 12 lead electrocardiogram before hydroxychloroquine treatment, on the second day of HCQ treatment, and after the day of the last administered dose.

Results: QT, QTcB, QTcF, iCEB, iCEBcB significantly increased on the second day of HCQ treatment compared to baseline (p=0.009, p=0.001, p=0.002, p=0.047, p=0.05, respectively). Similarly, QT, QTcB, QTcF, iCEBcB and iCEBcF were significantly higher on the fifth day compared to baseline (p=0.011, p=0.005, p=0.005, p=0.013, p=0.028, p=0.024 respectively). However, there were no differences between the second and the fifth days of treatment for any of the studied parameters.

Conclusions: QT, QTc, and iCEB significantly increased compared to baseline on the second day, and remained increased on the fifth day of treatment. The differences were attributed to the amount of loading dose and the duration of HCQ treatment. Our study suggests that, along with other ECG markers, iCEB can be used in COVID-19 patients treated with HCQ.

Keywords: Hydroxychloroquine, COVID-19, QTc, iCEB, repolarization

INTRODUCTION

The new type of Coronavirus (SARS-Cov-2) has spread from China to the whole world and caused a pandemic that has caused serious medical, social, and economic problems worldwide. The disease termed as COVID-19 infection caused by the SARS-Cov-2 virus results in a wide range of clinical presentations ranging from asymptomatic course to mild flu-like clinics to severe pneumonia and hyperinflammatory response, with the latter potentially requiring intensive care and even causing death. In the case of serious disease, COVID-19 is a systemic disease with hyperinflammation, cytokine storm, and elevated cardiac enzymes (1). The risk classification for sudden cardiac death is still challenging due to drug-induced arrhythmias, acquired heart disease, or congenital heart disease. There are a few but commonly used risk markers to determine the risk of sudden cardiac death in patients with drug-induced arrhythmias. The QT interval is an ECG parameter reflecting action potential duration and one of the most widely used ECG risk markers for arrhythmias (2). Prolonged QT and QTc intervals are used as a common risk marker for torsades de pointes (TdP), polymorphic ventricular tachycardia (VT), and ventricular fibrillation (VF). However, additional biomarkers are needed for the patients who are at risk for the development of non-TdP-induced

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VT/VF since the risk can not be identified only by evaluating QT or QTc. It is known that although some drugs prolonging the QT interval are proarrhythmic, the absence of QT prolongation does not mean freedom of arrhythmia risk. Therefore, there is a need for identifying better risk markers for drug-induced arrhythmias (3). Index of cardio-electrophysiological balance (iCEB), a new non-invasive ECG marker, compares the balance of depolarization and repolarization duration of the myocardial action potential and has been recently identified as a potential risk marker for drug-induced arrhythmia in an animal-based experimental study (4). Defined as a new marker for drug-induced arrhythmias, iCEB is calculated by dividing the QT interval by the QRS duration. It is assumed that iCEB is equivalent to cardiac wavelength λ (λ = effective refractory period (ERP) x conduction velocity), with an increased or decreased iCEB value would potentially predict increased sensitivity to TdP or non-TdP-mediated VT/VF (5). In a previous study in humans, iCEB was found lower in patients with Brugada syndrome and those who were administered arrhythmogenic drugs. It was stated that iCEB was a useful tool to detect an increased risk of both TdP and non-TdP-mediated VT/VF; hence, iCEB can arguably be a universal marker for ventricular arrhythmias (6).

In patients with COVID-19, blood pressure abnormalities and different arrhythmias such as tachycardia, bradycardia, or asystole are observed at a higher rate in critically ill patients (7,8). Arrhythmias in this population can occur secondary to hypoxemia, metabolic disorders, systemic inflammation, or myocarditis. In some publications published during the COVID-19 pandemic, it has been stated that treatment with hydroxychloroquine (HCQ) and/or azithromycin caused prolonged QT and QTc, at times resulting in TdP. However, it has been recently stated that the concomitant use of high dose HCQ with azithromycin rather than the standalone use of either agent in COVID-19 leads to QT and QTc prolongation and may result in TdP (9-11). Although it is suggested that the main cause of TdP in COVID-19 patients treated with HCQ is the combination of COVID-19's cardiac involvement, coexisting conditions such as severe kidney disease, older age, severe liver disease, and high dose HCQ and/or azithromycin use, it is still unclear whether ventricular arrhythmias occur due to the critical QT prolongation by HCQ independently of the COVID-19 disease (9). Although the benefit of HCQ in COVID-19 is controversial, it is still used as a treatment option in some countries including Turkey. In this paper, we aimed to investigate the temporal changes in ventricular repolarization indices and iCEB in patients with suspected COVID-19 treated with short-term HCQ.

MATERIAL AND METHOD

This study was approved by Başkent University Non-Interventional Clinical Research Ethics Committee (Date: 2021, Project No: KA20/227, Decision No: 21/127). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between April 2020-July 2020, we retrospectively reviewed the medical records of 116 patients with suspected COVID-19, of whom we enrolled 38 eligible patients. The patients with electrolyte abnormalities, chronic inflammatory disease, moderate to end-stage renal disease (GFR<30 ml/min), bundle branch block, atrial fibrillation, preexcitation syndromes, or use of any drug affecting QT duration were excluded. The patients treated with HCQ and other antibiotic regimens such as azithromycin were also excluded. The inclusion criterion was having typical COVID-19 symptoms combined with pulmonary ground-glass opacities on thoracic computed tomography (CT). All patients received HCQ treatment for 5 days according to our hospital treatment policy protocol for COVID-19. All patients' PCR results taken at the time of hospitalization and in the follow-ups were negative. Even though the patients had PCR negative test results, they were still treated with HCQ due to the clinical and CT findings during their hospitalization and discharged after having two consecutive negative PCR tests. On the first day, the patients were administered 400 mg PO HCQ twice a day followed by 200 mg PO HCQ twice a day for at least 4 days. HCQ was stopped after the fifth day of the treatment. The patients' demographic and clinical characteristics, as well as baseline laboratory findings (serum creatinine, potassium, magnesium, white blood cell count, platelet count, neutrophil/lymphocyte ratio, CRP, and troponın I), were recorded on admission. A 12-lead surface electrocardiogram (ECGs) was obtained from each patient using GE Healthcare MAC 2000 (General Electric, Milwaukee, USA) ECG recorder with a paper speed of 25 mm/s and voltage of 10 mm/mV. The ECGs were taken before the start of HCQ treatment on the second day of HCQ treatment (which corresponded to after 800 mg loading dose of HCQ and after the last dose of HCQ regimen. Electrocardiographic parameters including heart rate, QRS duration, and QT, interval were measured manually. All ECG measurements were calculated and analyzed by the same cardiologist. QTc interval was calculated manually by using Bazett's and Fridericia's formulas. Index of Cardio-Electrophysiological Balance (iCEB) was calculated manually by dividing the QT interval by the QRS duration. We also calculated corrected iCEB durations (iCEBcB and iCEBcF), by

dividing the QTc interval calculated by using Bazett's and Fridericia's formulas, respectively, by the QRS duration. Prolonged QTc was defined as ≥450 ms for adult males and ≥460 ms for adult females; based on the literature data, the QTc cut-off value for an increased TdP risk was accepted as 500 ms.

Statistical Analysis

IBM SPSS Statistics volume 25.0 (SPSS Inc, IBM, USA) was used for the statistical analyses. Descriptive statistics included median (interquartile range, min-max (IQR)) for non-parametric quantitative variables and number and percentage for categorical variables. Quantitative variables were tested for normality of distribution using the Shapiro-Wilk test. The Friedman test was used to make the paired comparison of the ECG parameters of the patients at three different times. A p-value of less than 0.05 was considered statistically significant.

RESULTS

This study included 40 eligible patients who were hospitalized with suspected COVID-19 and received a short course of HCQ regimen. Two patients died at the hospital due to non-arrhythmic causes (one from myocardial infarction and the other from hospital infection) after the start of the HCQ treatment. Of the 40 patients, 24 were male (60%) and 16 were female (40%). The median age was 61.5 (Interquartile range (IQR) 39-89) years. Their demographic data and clinical characteristics are given in **Table 1**. The comparison of ECG parameters between baseline and the second day of HCQ treatment, between the second day and after the fifth day of HCQ treatment, and between baseline and after the fifth day of HCQ treatment are given in **Table 2**. The proportions of patients with prolonged baseline QTcB, second-day QTcB, fifth-day QTcB and prolonged baseline QTcF, second-day QTcF, fifth-day QTcF values were 13.1% (n=5, 3 male and 2 female patient), 36.8% (n=14, 8 male and 6 female patients) 36.8% (n=14, 10 male and 4 female patients) and 2.6% (n=1, one male patient), 5.2% (n=2, 2 male patients) and 15.8% (n=6, 4 male and 2 female patients) respectively. Besides, the temporal changes of QT, QTcB, QTcF, iCEB, iCEBcB and iCEBcF are shown in **Figure 1**. When the baseline and the second day ECG parameters were compared QT interval, QTcB, QTcF, iCEB, iCEBcB were significantly greater on the second day than the baseline values (p=0.009, p=0.001, p=0.002, p=0.047, p=0.05, respectively); there was a trend for statistical significance for iCEBcF between the second day and baseline values (p=0.056). There was no significant difference between heart rate and QRS duration of baseline and the second day (p=0.361 and p=0.659). QT, QTcB, QTcF, iCEBcB, and iCEBcF were significantly greater on the fifth day compared to baseline (p=0.011, p=0.005, p=0.005, p=0.013, p=0.028, p=0.024, respectively). However, there was no significant difference between QRS duration and heart rate values of the fifth day and baseline (p=0.361 and p=0.659). Finally, no significant difference was observed between the second day and the 5th day concerning any of the ECG parameters (p=0.824 for QT, p=0.876 for QTcB, p=0.719 for QTcF, p=0.235, p=0.296 for iCEB, p=0.401 for iCEBcB, p=0.300 for iCEBcF, p=0.887 for QRS).

Table 1. Demographic and clinical characteristics of the patients treated with HCQ

Variable	Patients treated with hydroxychloroquine
Age (years)	61 (39-89)
Sex (male)	24 (60%)
Smoking	12 (31.5%)
Hypertension	17 (44%)
Diabetes mellitus	6 (15.7%)
Coronary atherosclerotic disease	8 (21%)
Ischemic cerebrovascular disease	4 (10.5%)
Pulmonary disease	6 (15.7%)
Creatinine (mg/dL)	0.84 (0.54-2.15)
K (mmol/L)	4.2 (3.5-4.7)
Mg (mg/dL)	2.04 (1.8-2.4)
WBC (10^3/μL)	7.62 (3.7-16.45)
Lymphocyte (10^3/μL)	1.62 (0.15-6.12)
Platelet (K/μL)	248 (58-390)
Neutrophil/lymphocyte ratio	3.32 (0.71-23.4)
CRP (mg/L)	56.9 (0.5-254.5)
Troponin (ng/mL)	0.005 (0-7.085)
Diuretics use	6 (15.7%)
Hospitality (days)	6 (5-30)
CT findings	40 (100%)
Unilateral ground-glass opacity	26 (63.1%)
Bilateral ground-glass opacity	14 (36.9%)

Table 2. Comparison of the baseline, second day, and fifth day ECG parameters of the suspected COVID-19 patients treated with HCQ

Variable	Baseline (IQR)	2nd day (IQR)	5th day (IQR)
QT (msec)	365.57 (69)	386.5 (66)*	381 (54)**
QTcB (msec)	425.5 (28)	441.5 (45)#	442 (42)##
QTcF (msec)	406.5 (31.75)	420 (40.5)†	417 (24)††
iCEB	3.95 (0.94)	4.11 (1.04)‡	4.26 (1.17)‡‡
iCEBcB	4.50 (1.23)	4.58 (1.02)§	4.83 (1.17)§§
iCEBcF	4.23 (1.14)	4.36 (1.05)Ψ	4.62 (0.99)ΨΨ
Heart rate (/min)	84.5 (31)	82 (19)	80.5 (23)
QRS (msec)	91 (20)	93.5 (18)	91.5 (18)

*= P=0.009 versus baseline, **= P=0.011 versus baseline, #= P=0.001 versus baseline, ##= P=0.005 versus baseline, †= P=0.002 versus baseline, ††= P=0.005 versus baselinei, ‡= P=0.047 versus baseline, ‡‡=P=0.017 versus baseline, §= P=0.050 versus baseline, §§= P=0.028 versus baseline, Ψ= P= 0.056 versus baseline,ΨΨ= P= 0.024 versus baseline

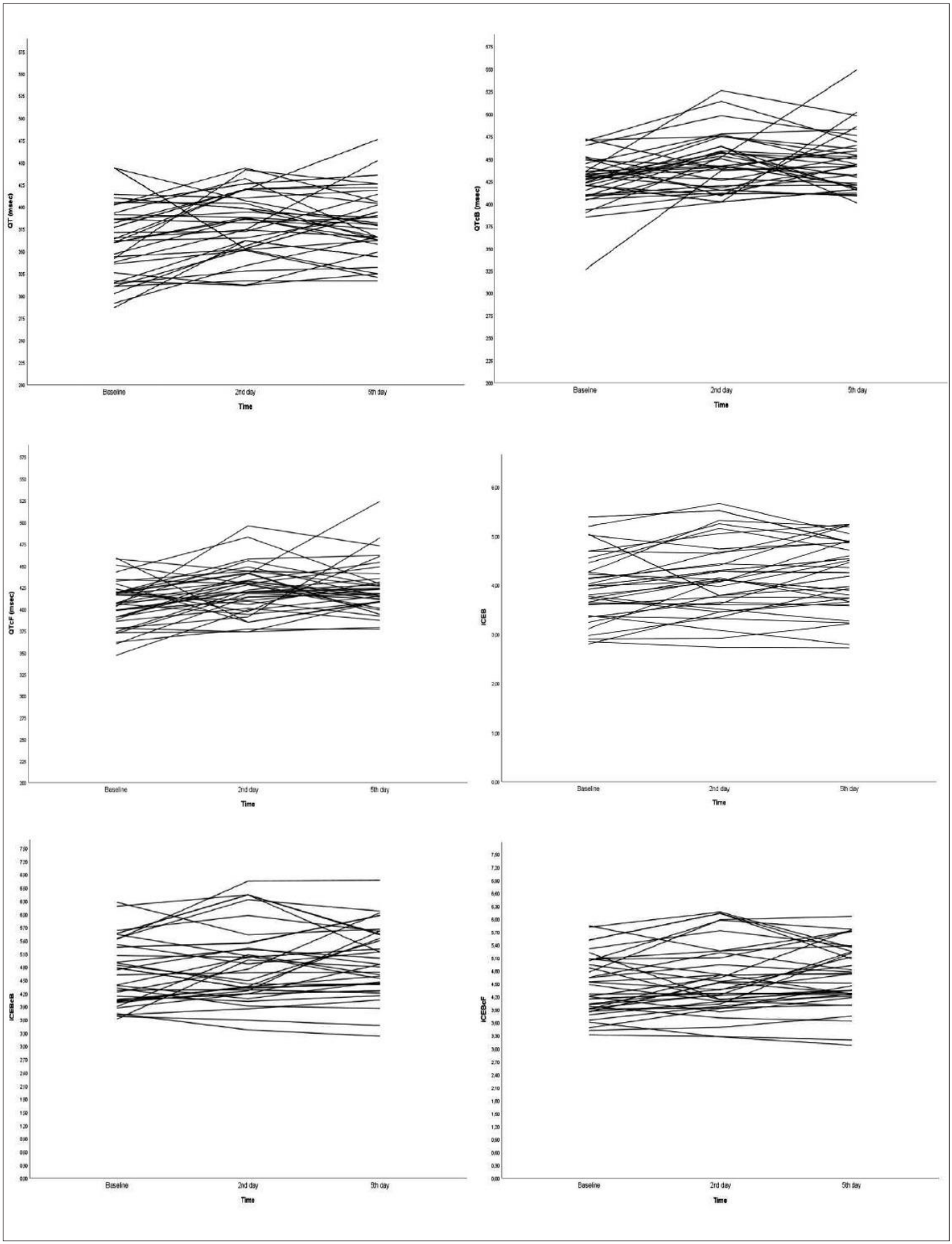

Figure 1. Multilinear graphical representation of the change of baseline, second day, and fifth-day values of ECG parameters of each patient. When the 2nd day values were compared with the baseline values, a statistically significant increase was observed for QT, QTc, iCEB, iCEBcB. However, there was an insignificant increase when 2nd day iCEBcF compared to the baseline values (p=0.056). QT, QTcB, QTcF, iCEBcB, and iCEBcF were significantly greater on the fifth day compared to baseline. When compared the second day and the 5th day values of QT, QTc, iCEB, iCEBcB, and iCEBcF, there was no significant difference between them.

DISCUSSION

COVID-19 infection, which may present as a novel microvascular thrombo-inflammatory syndrome leading to multiorgan failure and death. During the first wave of the epidemic, the disease has been treated intensively using certain drugs such as hydroxychloroquine (HCQ) and azithromycin, both of which portend a risk of QTc interval prolongation and ventricular arrhythmias. Clinically, acute myocardial damage, arrhythmias, and cardiogenic shock have been observed in the disease course in addition to the major respiratory manifestations of COVID-19. COVID-19 may also cause ECG abnormalities such as wide QRS complexes (>120 ms), prolonged QTc interval, lateral ST-T segment abnormalities, abnormal PR intervals with increased heart rate, and cardiac arrhythmias (12,13). A prolonged QTc interval has also been particularly reported in a variety of studies in COVID-19 as the predominant side effects of hydroxychloroquine/chloroquine and azithromycin (9). Although the use of HCQ with other antibiotics has been shown to prolong QTc, to affect ventricular depolarization, and, rarely, to cause TdP, only a few studies are examining the effect of isolated HCQ use in COVID-19 treatment on ventricular repolarization parameters in the literature; even more notably, no studies have ever investigated the effect of HCQ on iCEB (14,15). Thus, the present study aimed to investigate the changes of iCEB along with other ventricular repolarization parameters in patients treated with the HCQ alone. It found that after using high dose HCQ (800 mg/day), QT, QTcB, iCEB, iCEBcB, and iCEBcF significantly increased after the HCQ treatment compared to the baseline values. Although QTc calculated by Fridericia's formula is more accurate than that calculated by Bazett's formula, there was a non-significant difference between the baseline and 2nd-day iCEBcF values. The finding that there were only significant differences between the baseline values of iCEB, iCEBcB, QT, QTcB, and QTcF and the 2nd-day and 5th-day values may be explained that the increases in QT, QTc, iCEB, iCEBcB, and iCEBcF may have been linked to the higher loading doses of HCQ. However, we did not observe any TdP or other fatal ventricular arrhythmias during the hospitalization of the patients, and only two patients died from secondary problems (one died from myocardial infarction and the other one from hospital infection) after the start of the HCQ treatment. We could not make any comparison between the deceased patients and the survivors regarding the repolarization parameters due to the low number of the former. However, iCEB remarkably increased after HCQ use and we still believe that it may be a useful novel marker of ventricular repolarization and ventricular arrhythmias apart from QT/QTc, particularly after high doses of HCQ.

In recent studies, adverse events were found more frequent in HCQ-treated patients than in non-HCQ-treated ones (16,17). Recently there has been a plethora of retrospective and prospective studies about HCQ's effect on QT and QTc intervals and the risk of ventricular arrhythmias. Some of these studies have pointed that HCQ had no significant effect on QT and QTc intervals and no effect on the occurrence of ventricular arrhythmias while some others have reported significant QT and QTc prolongation but the rare occurrence of fatal ventricular arrhythmias or death (12-15,17-19). It has been argued that, besides QTc prolongation, other factors including transmural heterogeneity of myocardial repolarization also play a role in the genesis of TdP. A meta-analysis indicated that the chance of developing TdP is substantially low, and there is an inconsistent relationship between QT prolongation and TdP (19). Therefore it can be emphasized that there is an incomplete and complex relationship between prolongation of the QTc interval and the risk of developing TdP. In support of this complex interaction, a recent study found that TdP occurred even in COVID-19 patients with a QTc<500 ms (20). Also, regarding the iCEB we investigated in our study, we found a significant iCEB increase in addition to significant QT and QTc prolongation without any ventricular arrhythmias in a short-term HCQ treatment. It is plausible that although HCQ has the potential to significantly prolong repolarization parameters in ECG, it may be rarely leading to the occurrence of TdP. Since it is known that TdP has some established factors such as structural heart disease, female sex, advanced age congenital QT prolongation, electrolyte disorders, and baseline QTc prolongation, we believe that HCQ should be used more carefully with these conditions or using other QT-prolonging agents such as macrolide antibiotics (21,22).

Limitations

There are several limitations to our study. Firstly, this was a retrospective study and the sample size was relatively small, especially regarding the prognostic value of the studied parameters. Secondly, it lacked Holter monitoring or telecardiography to more accurately detect ventricular arrhythmias. Thirdly, a single researcher evaluated the ECG parameters manually using a magnifying glass; thus, intraobserver variability was not evaluated for QTc and iCEB. Also, using an automated ECG measurement method might have been more effective in reducing measurement errors. Fourthly, only suspected COVID-19 patients were enrolled and the HCQ treatment duration was short. And lastly, there was no data regarding the long-term mortality and morbidity effects of HCQ treatment.

CONCLUSION

HCQ causes an increase in iCEB, QT, and QTc in ECG, most notably after the loading dose. It can be suggested that it appears safe for a short time in those without myocardial substrates or other risk factors for ventricular arrhythmias related to QT and/or QTc prolongation. iCEB may be a useful parameter for evaluating the TdP risk for those treated with HCQ and should be further studied in prospective randomized controlled studies

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by Başkent University Non-Interventional Clinical Research Ethics Committee (Date: 2021, Project No: KA20/227, Decision No: 21/127).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Siddiqi HK, Mehra MR. Covid-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant 2020; 39: 405-7.
2. Postema PG, Wilde AA. The measurement of the QT interval. Curr Cardiol Rev 2014; 10: 287-94.
3. Laverty H, Benson C, Cartwright E, et al. How can we improve our understanding of cardiovascular safety liabilities to develop safer medicines? Br J Pharmacol 2011; 163: 675-93.
4. Lu HR, Yan GX, Gallacher DJ. A new biomarker– index of cardiac electrophysiological balance (iCEB)–plays an important role in drug-induced cardiac arrhythmias: Beyond QT-prolongation and torsades de pointes (TdPs). J Pharmacol Toxicol Methods 2013; 68: 250-9.
5. Robert E, Aya AG, dela Coussaye JE, et al. Dispersion-based reentry: Mechanism of initiation of ventricular tachycardia in isolated rabbit hearts. Am J Physiol 1999; 276: H413-H423.
6. Robyns T, Lu HR, Gallacher DJ, et al. Evaluation of index of cardio-electrophysiological balance (iCEB) as a new biomarker for the identification of patients at increased arrhythmic risk. Ann Noninvasive Electrocardiol 2016; 21: 294-304.
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-9.
8. Liu K, Fang YY, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei province. Chin Med J (Engl) 2020; 133: 1025-31.
9. Jankelson L, Karam G, Becker ML, Chinitz LA, Tsai MC. QT prolongation, torsades de pointes and sudden death with short courses of chloroquine or hydroxychloroquine as used in COVID-19: a systematic review. Heart Rhythm 2020; 17: 1472-9.
10. Chorin E, Wadhwani L, Magnani S, et al. QT interval prolongation and torsades de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. Hearth Rhythm 2020; 17: 1425-33.
11. Saleh M, Gabriels J, Chang D, et al. The effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Circ Arrhytm Electrophysiol 2020; 13: e008662.
12. Santoro F, Monitillo F, Raimondo P, et al. QTc interval prolongation and life-threatening arrhythmias during hospitalization in patients with COVID-19. Results from a multi-center prospective registry. Clin Infect Dis 2020: ciaa1578.
13. Angeli F, Spanevello A, De Ponti R, et al. Electrocardiographic features of patients with COVID-19 pneumonia. Eur J Intern Med 2020; 78: 101-6.
14. 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: 808-9.
15. Mahévas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. BMJ 2020; 369: m1844.
16. Sarma P, Kaur H, Kumar H, et al. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: a systematic review and meta-analysis. J Med Virol 2020; 92: 776-85.
17. Bignardi PB, Vengrus CS, Aquino BM, Neto AC. Use of hydroxychloroquine and chloroquine in patients with COVID-19: a meta-analysis of randomized clinical trials. Pathog Glob Health 2021; 115: 139-50.
18. Abdulrahman A, Alsayed I, Almadhi M, et al. The efficacy and safety of hydroxychloroquine in patients with COVID-19: a multicenter national retrospective cohort. Infect Dis Ther 2021; 10: 439-55.
19. Agstam S, Yadav A, Kumar-M P, Gupta A. Hydroxychloroquine and QTc prolongation in patients with COVID-19: A systematic review and meta-analysis. Indian Pacing Electrophysiol J 2021; 21: 36-43.
20. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; 5: 1036-41.
21. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation 2010; 121: 1047-60.
22. Roden DM, Harrington RA, Poppas A, Russo AM. Consideration for drug interactions on QTc in exploratory COVID-19 (Coronavirus Disease 2019) treatment. Circulation 2020; 141: e906-7.