Received: 30 January 2021 | Revised: 27 February 2021 | Accepted: 2 March 2021

DOI: 10.1111/anec.12846

ORIGINAL ARTICLE

WILEY

The impact of hydroxychloroquine–azithromycin combination on Tpeak-to-end and Tpeak-to-end/QT ratio during a short treatment course

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Abstract

Background: Since there was no proven treatment of coronavirus disease 2019 (COVID-19), hydroxychloroquine–azithromycin (HCQ-AZM) combination is being used in different countries as a treatment option. Many controversies exist related to the safety and effectiveness of this combination, and questions about how HCQ-AZM combination affects the ventricular repolarization are still unknown.

Objective: The aim of the study was to show whether the hydroxychloroquine–azithromycin (HCQ-AZM) combination prolonged Tpeak-to-end (TpTe) duration and TpTe/QT interval ratio or not.

Methods: One hundred and twenty-six consequent COVID-19(+) patients meeting the study criteria were enrolled in this study. Baseline ECGs were obtained immediately after hospitalization and before commencing the HCQ-AZM combination. On-treatment ECG was obtained 24–48 hr after the loading dose of HCQ/AZM. ECG parameters including PR interval, QRS duration, QT interval, QTc interval, TpTe duration, and TpTe/QT interval ratio were assessed. Demographic and laboratory findings were collected from an electronic recording system.

Results: ECGs of 126 COVID-19(+) patients who received HCQ-AZM combination were assessed. Mean baseline QTc (by Fridericia formula), TpTe, and TpTe/QT ratio were 420.0 ± 26.5 ms, 82.43 ± 9.77 ms, and 0.22 ± 0.02, respectively. On-treatment QTc, TpTe and TpTe/QT ratio were 425.7 ± 27.18 ms, 85.17 ± 11.17 ms, and 0.22 ± 0.03, respectively. No statistically significant acute impacts of HCQ-AZM combination on TpTe duration and TpTe/QT interval ratio were observed compared with baseline values. No ventricular tachycardia/fibrillation and the significant conduction delays were seen during in-hospital follow-up.

Conclusion: HCQ-AZM combination increased TpTe duration. However, no significant impact on TpTe/QT interval ratio was observed.

KEYWORDS
azithromycin, cardiac death, coronavirus disease 2019, electrocardiography, hydroxychloroquine, Tpeak-to-end

1 | INTRODUCTION

Hydroxychloroquine (HCQ) has been used as an antimalarial and antirheumatic drug for decades. It possesses low adverse effects profile compared with chloroquine (Saha et al., 2020). Since the antiviral effects of HCQ have been demonstrated, it entered the anti-COVID-19 protocols alone or in combination with AZM in some countries. Despite the controversial results exist regarding effectiveness in COVID-19(+) patients, HCQ with or without AZM is still used widely in some countries. Moreover, there are many concerns about the cardiac safety of HCQ alone or in combination with AZM (Saha et al., 2020). HCQ may activate potassium channels in the myocardium, and this may lead to QT prolongation and torsade de pointes in some cases (Pruchnicki et al., 1996).

QT interval is a sign of ventricular repolarization (Yan and Antzelevitch, 1998). The prolongation in QT interval leads to prolongation in ventricular repolarization. This causes a unidirectional block that may establish reentry in the ventricular myocardium (Yap & Camm, 2003). Therefore, it is critical to determine anomalies in repolarization that can prevent fatal arrhythmias.

In the last two decades, some new parameters related to ventricular repolarization such as TpTe, corrected TpTe (cTpTe), and TpTe/QT ratio have emerged and it was demonstrated that these parameters were associated with ventricular repolarization independent of QT interval (Tse and Yan, 2017). A number of articles exist to prove the connection between these new parameters and ventricular arrhythmia and/or sudden cardiac death. TpTe/QT ratio is associated with dispersion in repolarization and maybe the better predictor of arrhythmogenesis. This eliminates the confounding effects of heart rate variability and interpersonal variability of QT interval. Therefore, this parameter may provide valuable information regarding the prediction of arrhythmogenesis (Gupta et al., 2008). In a Finnish population-based study, TpTe was not associated with sudden cardiac death (Porthan et al., 2013). However, it was demonstrated that TpTe duration could predict SCD, ventricular fibrillation, ICD shock in patients with congenital and acquired QT prolongation, hypertrophic cardiomyopathy, systolic heart failure, and ST-elevation myocardial infarction (Çağdaş et al., 2018; Castro-Torres et al., 2017; Demidova et al., 2019; Rosenthal et al., 2015; Tse et al., 2018a, 2018b, 2018c). Although it is generally accepted that the TpTe duration indicates the dispersion in repolarization, there are conflicting publications regarding whether it is a transmural, global, or mix dispersion (Gupta et al., 2008; Kors et al., 2008; Opthof et al., 2007).

TpTe duration was better associated with dispersion in cardiac repolarization in a previous study (Zabel et al., 1995). A study published recently demonstrated prolongation in TpTe and TpTe/QT ratio in patients with COVID-19 compared with healthy controls (Yenerçağ et al., 2020). In the present study, we aimed to assess the impact of short duration HCQ/AZM combination on the parameters of cardiac repolarization in nonsevere COVID-19 patients.

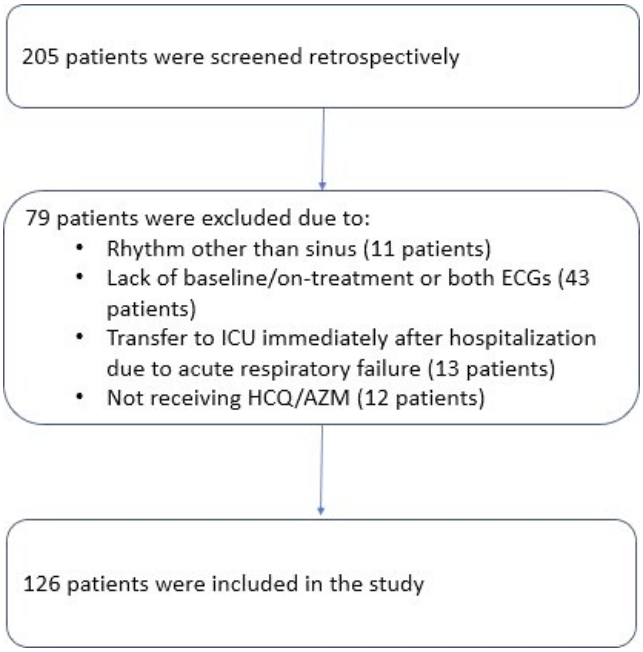

FIGURE 1 Study population flow chart

2 | PATIENTS

The study was designed as a retrospective observational. Consecutive patients who received the short course (5 days) of HCQ-AZM combination between April 1, 2020, and May 1 2020, were enrolled in the study (Figure 1). The indication of HCQ-AZM therapy was COVID-19 in all patients. Only noncritical patients (who did not need noninvasive or invasive mechanical ventilation or circulatory support devices) were screened for the study. The exclusion criteria were as follows: (a) patients without both baseline (before the starting of HCQ-AZM) and on-treatment (after the loading dose of HCQ-AZM) ECGs and (b) patients had abnormal T-wave configurations (such as, flattened, notched) which increased the uncertainty of TpTe measurement on the baseline ECGs.

Baseline ECGs were obtained before the commencing of HCQ-AZM. ECGs obtained 24–48 hr after the loading dose of HCQ-AZM were defined as control ECGs. PR interval, QT and QTc (according to Fridericia formula) intervals, and TpTe interval were assessed. Baseline and control ECG findings were compared. Demographic findings and laboratory results were recorded.

2.1 | Treatment protocol

The treatment protocol was adapted according to the national health system. According to this protocol, on the first day HCQ was loaded orally with 800 mg following 400 mg for 4 days. After 500 mg loading dose on the first day, AZM was continued with 250 mg od for following 4 days. Until influenza was excluded, oseltamivir 75 mg bid was added to the treatment protocol. Hydroxychloroquine and azithromycin combination was given

for 5 days if not any contraindications. The contraindications for HCQ/AZM combination were as follows: (a) QTc > 500 msn (or >550 msn in bundle branch block) on the baseline ECG and (b) hypersensitivity.

2.2 | ECG recordings and analysis

ECGs were obtained in a supine position by using Mortara ELI 250 device (Welch Allyn, Inc.; standard 12-lead resting ECG, paper speed of 25 mm/s, amplitude of 10 mm/V, and a sampling rate of 250 Hz) and transferred to EP calipers software (EP Studios, Inc., version 3.1). Both baseline and control ECGs were assessed in terms of PR interval, QT and QTc intervals, TpTe duration, and TpTe/QT interval ratio. Leads II, V_5, and V_6 were used for measurements. QT interval and TpTe duration were measured in the same derivation in both baseline and during the treatment period to increase the accuracy of comparison. The QRS duration was the interval between the first deflection of the QRS complex and the returning point to the baseline. The QT interval was measured from the onset of the first deflection of QRS complex to the end of T wave. The end of the T wave was determined by the tangent method. QT measurement was performed according to the guideline proposed by expert panel (Anderson et al. (2002)). The corrected QT (QTc) interval was calculated according to Fridericia's formula. TpTe duration was measured according to "tangent" method (Rosenthal et al., 2018). The T peak was defined as the maximum absolute T-wave deflection from the isoelectric line. The T-end was accepted the intersection of the tangent to the downslope of the T wave and the isoelectric line.

ECG measurements were performed blindly by two cardiologists (NB and RO). To evaluate intra-observer variability, the first thirty ECGs were assessed seven days apart by the same cardiologist. Intra-observer variability for both cardiologists and interobserver variability were under 5%.

All measurements were performed manually using EP calipers software (EP Studios, Inc., version 3.1).

2.3 | Statistical analysis

SPSS version 20.0 was used for statistical analysis. Normally distributed continuous variables were expressed as mean ± standard deviation (*SD*), non-normally distributed variables were expressed as median with interquartile range (IQR), and categorical variables were expressed as percentage. Continuous variables were checked for the normal distribution assumption using the Kolmogorov–Smirnov statistics and visual inspection of histograms. Baseline and control ECG parameters were compared by using paired *t* test or Wilcoxon signed-rank test where appropriate. Cohen's kappa test was applied to determine inter- and intra-observer agreement for ECG measurements. Statistical significance was accepted for 2-sided $p < .05$.

TABLE 1 Baseline characteristics of the study population

Variables	Values (*n* = 126)
Gender, Male, *n* (%)	56 (44)
Age, years, mean ± *SD*	58 ± 14
Tisdale score, *n* (%)	
Low (≤6)	110 (87.3)
Moderate (7–10)	13 (10.4)
High (≥11)	3 (2.4)
Comorbidities, *n* (%)	
Arterial hypertension	53 (42)
Diabetes mellitus	38 (30)
HFrEF or HFpEF	9 (7)
CAD	26 (21)
COPD	24 (19)
Medications, *n* (%)	
Beta-blockers	15 (12)
Calcium channel blocker	25 (20)
ACEI/ARB/ARNI	31 (25)
Ranolazine/Ivabradine	0 (0)
Amiodarone	1 (0.8)
Oseltamivir	85 (68)
Favipiravir	35 (28)
Diuretics	24 (19)
SSRI	9 (7)

Abbreviations: ACEI, angiotensin converting enzyme inhibitory; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SSRI, selective serotonin receptor inhibitor.

3 | RESULTS

A total of 126 patients were included in the study. Tisdale score was low in most of the study population. CAD was observed in 26 (21%) and heart failure was observed in 9 (7%) patients. Eighty-five (68%) patients received oseltamivir, and 35 (28%) patients received favipiravir concomitantly with HCQ/AZM combination. SSRI use was low among patients (9 [7%] patients). Detailed baseline characteristics are summarized in Table 1. Baseline laboratory findings are demonstrated in Table 2. There was no significant change in baseline and on-treatment serum potassium, calcium, and magnesium levels (Table 3). Baseline mean QRS duration was 92.8 ± 14.6 ms. We did not notice significant changes in QRS duration compared with the baseline values. Electrocardiographic data are summarized in Table 4. Mean baseline QT, QTc (by Fridericia formula), TpTe, and TpTe/QT ratio were 371.0 ± 37.5 ms, 420.0 ± 26.5 ms, 82.43 ± 9.77 ms, and 0.22 ± 0.03, respectively. On-treatment QT, QTc, TpTe, and TpTe/QT ratio were 387.3 ± 39.8 ms, 425.7 ± 27.2 ms, 85.17 ± 11.17 ms, and 0.22 ± 0.03, respectively. There were no statistically significant

differences between baseline and on-treatment QTc intervals. Baseline mean heart rate was higher than on-treatment. TpTe duration increased 2.74 ± 10.39 ms on on-treatment ECG (p = .004). There was no statistical difference between the baseline and on-treatment TpTe/QT ratio (p = .44).

4 | DISCUSSION

Although there was a significant difference between baseline and on-treatment TpTe duration, we did not find significant changes in TpTe/QT ratio during the treatment period. We attributed this discrepancy to the difference between baseline and on-treatment heart rates. Baseline heart rate was significantly higher than on-treatment value. Since baseline ECGs were obtained mostly immediately after hospital admission, anxiety may have led to higher heart rates. Other explanation was that the rate-lowering effect of HCQ/AZM combination was responsible for a slower heart rate. In a previous study, we observed similar trends in heart rate and this remained relatively stable throughout treatment period (Bakhshaliyev et al., 2020). Significant QT prolongation was not observed during the follow-up period compared with the baseline values in the present study. No ventricular arrhythmias, second and third-degree heart blocks, or severe pauses were recorded during the treatment period.

No significant difference was observed between baseline and on-treatment serum sodium, potassium, magnesium, and calcium levels. However, we could not interpret the effect of HCQ/AZM combination on serum potassium level because in some patients especially whose baseline serum potassium levels were less than 4.0 mmol/L, additional potassium supplementation was ordered attending physician.

TpTe and TpTe/QT ratio have emerged as a new indicator of dispersion in ventricular repolarization (Antzelevitch et al., 2017). TpTe duration was defined as the duration from the peak of the T wave to the end of the T wave (Kors et al., 2008). In contrast to QT interval, no generally accepted cutoff points exist for TpTe and TpTe/QR ratio. Cutoff point for increased ventricular arrhythmia and/or SCD was 113.6 ms for the general population. Interestingly, cutoff point for ischemic heart disease was close to the general population and was 109.6 ms. Cutoff points for TpTe duration were much lower for heart failure and Brugada syndrome (106.3 and 95.8 ms, respectively). In this study, only in 7 (5.6%) patients we noticed the increase TpTe above 105 ms. No ventricular arrhythmias or SCD was observed during the treatment period (Tse et al., 2017).

In a meta-analysis, TpTe was associated with a 1.14-fold increased risk for ventricular arrhythmia, cardiovascular, and all-cause mortality (Tse et al., 2017). However, subgroup analysis demonstrated various increased risks in different scenarios: The risk of ventricular arrhythmia or SCD in Brugada syndrome was 5.6-fold, and in hypertension was 1.5-fold increase (Tse et al., 2017).

HCQ/AZM serum concentration may affect the QT interval. Although we did not measure serum concentration, several studies provide the data regarding serum concentration of these medications. Munster et al. demonstrated that mean serum concentration of HCQ was ~1,000 ng/ml after taking daily 400 mg oral tablet (Munster et al., 2002). Mean serum concentration of AZM was reported ~500 ng/ml on daily 500 mg oral tablet (Matzneller et al., 2013).

Despite lacking data regarding the effect of HCQ or HCQ/AZM combination on TpTe and TpTe/QT ratio, studies investigating the impact of HCQ or HCQ/AZM combination on QT interval have been reported recently. In the study published by Bernardini et al., HCQ/AZM combination or HCQ-alone groups were compared with patients not taking these both medications (Bernardini et al., 2020). Death was observed in 18% of the patients during the follow-up. While QT prolongation was observed in 67% of patients receiving

TABLE 2 Baseline laboratory findings of the study population

Variables	Values (n = 126)
Hemoglobin, g/dl, mean ± *SD*	13.07 ± 1.76
Serum creatinine, mg/dl, median (IQR)	0.81 (0.73–0.99)
BUN, mg/dl, median (IQR)	13.08 (10.75–19.63)
eGFR, ml/min, median (IQR)	88 (69–100)
C reactive protein, g/dl, median (IQR)	34.2 (10.9–79.5)
Serum ferritin, mg/dl, median (IQR)	216 (79–458)
ESR, mm/hr, median (IQR)	30 (18–47)
Procalcitonin, median (IQR)	0.210 (0.900–0.350)
Serum albumin, g/dl, mean ± *SD*	3.8 ± 0.5
Serum sodium, mg/dl, mean ± *SD*	137 ± 3
Troponin I, median (IQR)	3.9 (2.15–8.70)
Creatine kinase MB, median (IQR)	0.8 (04–1.6)
D-dimer, median (IQR)	256 (181–361)

Abbreviations: BUN, blood urine nitrogen; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; IQR, interquartile range; *SD*, standard deviation.

TABLE 3 Changes in electrolytes levels during treatment

Variables Mean ± *SD*	Baseline value	ΔOn-treatment versus baseline	p-Value
Serum potassium, mmol/L, n = 126	4.10 ± 0.39	−0.06 ± 0.40	.11
Serum calcium, mg/dl, n = 119	8.90 ± 0.76	−0.09 ± 1.12	.47
Serum magnesium, mg/dl, n = 99	1.90 ± 0.31	0.07 ± 0.20	.30
Serum natrium, mmol/L, N = 126	137 ± 3	1 ± 3	<.001

TABLE 4 Changes in electrocardiographic parameters during treatment

Variables	Baseline value *N* = 126	On-treatment *N* = 126	ΔOn-treatment versus baseline	*p*-Value
TpTe duration, ms, mean ± *SD*	82.43 ± 9.77	85.17 ± 11.17	2.74 ± 10.39	**.004**
QT interval, ms, mean ± *SD*	371.0 ± 37.5	387.3 ± 39.8	16.0 ± 39.2	**<.001**
QTc interval, ms, mean ± *SD*	420.0 ± 26.5	425.73 ± 27.2	5.7 ± 20.5	.12
TpTe/QT ratio, mean ± *SD*	0.22 ± 0.02	0.22 ± 0.03	0.003 ± 0.036	.44
QRS duration, ms, mean ± *SD*	92.8 ± 14.6	93.4 ± 16.0	0.6 ± 11.1	.53
Mean heart rate, bpm, mean ± *SD*	87 ± 15	82 ± 14	−5 ± 11	**<.001**

Note: Bold indicates statistically significant value.

Negative value indicates that on-treatment value is less than baseline value.

HCQ alone or in combination with AZM, QTc prolongation >500 ms was seen only in 4% of patients. TpTe duration was reported in this study along with QT interval. TpTe was 94.5 ± 23.2 msn in the whole study population. TpTe duration was not statistically significant between groups (p = .21). TpTe durations were 86.5 ± 23.9, 95.5 ± 25.1, and 94.5 ± 23.3 ms in patients taking no HCQ, HCQ, and HCQ/AZM, respectively. Cardiac arrest and fatal cardiac arrhythmias were not documented in any of the patients in the study. However, since the control ECG recording time was not specified in the study, it becomes difficult to comment on the course of the QTc interval during follow-up. In the study conducted by our team, the effect of HCQ / AZM combination on QT interval was more severe than the QTc interval in ECGs taken after 36–72 hr after loading dose, suggesting that it was a dose dependent rather than a cumulative effect (Bakhshaliyev et al., 2020). In another study involving 40 patients reported by Bessiere et al., the significant QTc prolongation (QTc 500 ms or QTc ≥ 60 ms) was observed in 14 patients (36%) receiving HCQ or HCQ/AZM combination (Bessière et al., 2020). Approximately one-third of the study patients consisted of critically ill patients requiring intensive care follow-up (75% patients required invasive mechanical ventilation, 63% required vasoactive drugs, 8% patients required renal replacement therapy). Vasoactive drugs were used in 86% of patients with severe QT prolongation (p = .04). In another study reported by Mercuro and his team, the effect of HCQ in combination with AZM and alone on QT interval was investigated (Mercuro et al., 2020). Approximately one-third of the study patients needed an intensive care unit, and one-quarter needed mechanical ventilation. In one patient, HCQ was discontinued due to the QTc was 499 ms, and 3 days after discontinuation, torsade de pointes developed which was treated by lidocaine. However, no information was given about the electrolyte level, left ventricular ejection fraction, or other confounding factors when arrhythmia developed.

There are some limitations of our study. First, this study is a retrospective observational study and we could not exclude possible bias completely because of the study design. Second, the population of our study represented noncritical COVID-19(+) patients and the results of the present study should not be generalized to all COVID-19(+) patients. Third, we could not assess the impact of COVID-19 alone on ECG independent of treatment medications. Finally, the number of study population is relatively low. To minimize the type II error and to confirm our result, it would be better to design larger trials.

In conclusion, we observed significant increase in TpTe duration and nonsignificant changes in TpTe/QT ratio in the short term using of HCQ/AZM combination in nonsevere COVID-19(+) patients.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

Nijad Bakhshaliyev: conception/design, acquisition of data, and initial analysis, drafting manuscript ; Ramazan Özdemir: analysis, interpretation of data, critical review and supervision.

ETHICAL APPROVAL

This study was approved by the local institutional Ethics committee.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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How to cite this article: Bakhshaliyev N, Özdemir R. The impact of hydroxychloroquine–azithromycin combination on Tpeak-to-end and Tpeak-to-end/QT ratio during a short treatment course. *Ann Noninvasive Electrocardiol*. 2021;26:e12846. https://doi.org/10.1111/anec.12846