Effect of triple antimicrobial therapy on electrocardiography parameters in patients with mild-to-moderate coronavirus disease 2019

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Abstract

Objective: The effects of treatment of coronavirus disease 2019 (COVID-19) with a triple combination composed of hydroxychloroquine, an antiviral, and an antibiotic on electrocardiography (ECG) parameters in patients with mild-to-moderate symptoms are not wholly understood. We aimed to explore the changes in ECG parameters after treatment with triple combination therapy in patients with mild-to-moderate symptomatic COVID-19.

Methods: This retrospective, single-center case series analyzed 91 patients with mild-to-moderate symptomatic COVID-19 at Ankara Gazi Mustafa Kemal State Hospital of Ankara City, Turkey, from April 1, 2020, to April 30, 2020. Forty-three patients were treated with hydroxychloroquine+oseltamivir+azithromycin (Group 1) and 48 patients were treated with hydroxychloroquine+oseltamivir+levofloxacin (Group 2). Heart rate, P wave duration, P wave dispersion, PR interval, QRS duration, corrected QT interval (QTc), QTc dispersion (QTD), delta QTc, Tp-e, Tp-e dispersion, and Tp-e/QTc ratio were all calculated from the baseline and posttreatment 12-lead ECG recordings.

Results: The QTc, QRS duration, Tp-e, PR interval, and P wave duration were significantly increased after treatment ($p<0.001$; $p<0.001$; $p<0.001$; $p=0.001$; $p=0.001$). The posttreatment C-reactive protein level was significantly lower than at baseline in Group 1 ($p=0.014$). At admission, 30% of patients had QT prolongation, and 4.3% of them had a QT duration >500 ms. Both Group 1 and Group 2 showed significant prolongation of the QTc interval (Group 1; $p<0.001$ vs. Group 2; $p<0.001$), QRS duration (Group 1; $p=0.006$ vs. Group 2; $p=0.014$), Tp-e (Group 1; $p=0.036$ vs. Group 2; $p<0.001$), and PR interval (Group 1; $p=0.002$ vs. Group2; $p=0.05$). The QTD was significantly decreased in Group 1 ($p<0.001$). None of the patients experienced any overt ventricular arrhythmia.

Conclusion: To the best of our knowledge, this study is the first to investigate QT prolongation in a population of COVID-19 patients treated with triple combination therapy. We found that there was a significant decrease in the QTD after the treatment in patients who were taking triple therapy including azithromycin.

Keywords: COVID-19, SARS-CoV-2, coronavirus, antimicrobial therapy, ECG

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Introduction

In January 2020, a new infectious disease called coronavirus disease 2019 (COVID-19) spread from Wuhan, China, to the entire world to become a pandemic. There has been no proven agent for the treatment of this viral infection to date, but treatments based on chloroquine/hydroxychloroquine and an antiviral/antibiotic are suggested to be promising (1, 2). However, there is still no evidence regarding monotherapy or combination therapy, what the optimal combination would be, what the optimal dosage would be, and when the drug therapy should be initiated; therefore, many different treatment protocols have been suggested from all around the world (3). Different protocols and different dosages and combinations add to the safety concerns about drug-related side effects, especially concerning QT prolongation and the risk for torsades de pointes (TdP). In this con-

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HIGHLIGHTS

- In general, ECG is recommended for measurement of QTc interval in all hospitalized COVID-19 patients, before starting HCQ.
- Patients with a resting QTc ≥ 500 ms, it is important to assess the presence of QTc prolonging electrolyte abnormalities such as hypokalemia and QTc prolonging drugs.
- QTD helps identify patients at increased risk of ventricular arrhythmias as QTc interval.

text, the reports about the effects on electrocardiography (ECG) results of different agents used in COVID-19 treatment are growing (4, 5).

In the absence of a vaccine or any proven therapeutic agent, hydroxychloroquine and azithromycin, often used in combination, have emerged as a potential therapy on the basis of extremely limited clinical evidence. Hydroxychloroquine is an antimalarial drug that has also been used to treat arthritis and systemic lupus erythematosus. Noteworthy, respiratory fluoroquinolones, levofloxacin and moxifloxacin, constitute fist line therapeutic agents for the management of severe community-acquired pneumonia. They are characterized by advantageous pharmacokinetic properties; higher concentrations in the lungs; and an excellent safety profile comparable to other antibiotics used to treat respiratory infections. Macrolides are indicated for different respiratory infectious diseases, and so azithromycin may be beneficial in fighting COVID-19 with its therapeutic value (e.g., antiviral effect). Azithromycin is a macrolide antibiotic used to treat a wide variety of bacterial infections. Although these medications have an adequate safety profile in diverse clinical situations, both of them block the hERG potassium channel, which can prolong ventricular repolarization and cause torsades de pointes. Currently, there is limited evidence for effective therapeutic strategies and the comprehensive data on clinical randomized trials are lacking. The physicians may indicate a medication or a combination of medications as clinical practice and based on their responsibility.

The various governments have so far adopted different policies for handling the pandemic; some of them involve quarantine and strict social limitations and some involve herd immunity. Turkey has been affected by the pandemic, but the mortality rate is considerably lower when compared to those of many other countries (6). In addition to having a relatively young population, a comprehensive contact tracing and an early detection and early treatment policy may be some of the keys to this success. Largely thanks to this policy, a patient population with mild-to-moderate symptoms who were diagnosed early and treated early with combination therapy has been observed in Turkey. Although this early treatment policy may have beneficial effects for prognosis and preventing the spread of the pandemic, this relatively low-risk patient group is faced with the potential side effects of one or more QT-prolonging agents. The full effects of COVID-19 treatment with a triple combination composed of hydroxychloroquine, an antiviral, and an antibiotic on ECG parameters in mild-to-moderate symptomatic patients are not wholly understood; therefore, in this study, we aimed to explore the changes in ECG parameters after triple combination therapy for patients with mild-to-moderate symptomatic COVID-19.

Methods

Patient group and study protocol

This single-center, retrospective, observational study was conducted at the Ankara Gazi Mustafa Kemal Hospital, Ankara, Turkey. We retrospectively analyzed 91 patients with mild-to-moderate symptomatic COVID-19 who were admitted between April 1 and April 30, 2020. All of the patients were diagnosed according to the interim guidance of the World Health Organization. Clinical information was collected on admission and during hospitalization by the attending physicians. Critically ill patients who needed intensive care unit follow-up because of sepsis or acute respiratory distress syndrome (ARDS) and patients with cardiovascular manifestations such as myocardial infarction, myocardial injury, and myocarditis were excluded from the study.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Ankara Gazi Mustafa Kemal Hospital (E1-20-749).

Data collection

The electronic medical records of the patients were reviewed by a trained team of physicians who worked in Ankara Gazi Mustafa Kemal Hospital during the epidemic period. Patient data including demographics, medical history, laboratory examination results, comorbidities, treatment measures (antiviral and antibiotic therapy), admittance, and fifth day ECGs were collected. Triple combination therapy with oseltamivir (75 mg twice a day) plus hydroxychloroquine (loading dose 800 mg/day, maintenance dose 400 mg/day) plus an antibacterial (levofloxacin, 0.5 g/day or azithromycin, loading dose 0.5 g/day, maintenance dose 0.25 g/day) was the main treatment approach for all of the patients. The difference in the antibacterial choice divided our population into two groups; Group 1: hydroxychloroquine+oselt amivir+azithromycin and Group 2: hydroxychloroquine+oseltam ivir+levofloxacin. None of the patients received any additional medication during their follow-up beyond their regular medications and triple antimicrobial therapy.

Baseline ECG parameters, fifth day ECG parameters, baseline and predischarge C-reactive protein (CRP) and highly-sensitive troponin T, and baseline D-dimer, procalcitonin, creatinine, sodium, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hemogram were extracted from the patients' files.

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Electrocardiography

The 12-lead ECG recordings were obtained with a paper speed of 25 mm/s and voltage of 10 mm/mV using standard ECG equipment while the patient was in the supine position. Heart rate, P wave duration, P wave dispersion, PR interval, QRS duration, corrected QT interval (QTc), QTc dispersion (QTD), T wave peak-to-end interval (Tp-e), Tp-e dispersion, and Tp-e/QTc ratio were all determined manually with a magnifying glass and recorded. The onset of the P wave was defined as the point of the first visible upward departure from the baseline and the end of the P wave was defined as the point of the return to the baseline. The maximum P wave and minimum P wave duration were calculated from the D2 and V5 derivations. P wave dispersion was measured as the difference between the maximum P wave duration minus the minimum P wave duration. The QT interval was defined as the time from the onset of the QRS complex to the point at which the T wave returned to baseline. The QTc interval was calculated using Bazett's formula. A QTc value >450 ms for men and >460 msec for women was accepted as a prolonged QTc (7). The change in the QTc interval (delta QTc) was calculated by subtracting the pretreatment QTc from the posttreatment QTc. The T wave variables were measured in leads V5 and D2. We analyzed all 12 lead electrodes, but usually evaluated leads V5 and D2 (8, 9). The Tp-e interval was measured from the peak of the T wave to the end of the T wave. The end of the T wave was defined as the intersection of the tangent to the downslope of the T wave and the isoelectric line. When a U wave was present, the end of the T wave was defined as the nadir between the T wave and the U wave. In the case of complex T waves (biphasic, triphasic, etc.), the interval from the nadir of the first component of the T wave to the end of the T wave was measured. All measurements were evaluated by two independent cardiologists who were blinded to the patients' other clinical information. The mean values of the measurements were used in the analysis.

Outcome

The primary endpoint was the presence of prolonged QTc after five days of taking the medications. The secondary endpoint was prolongation of the QTc to >500 ms on the fifth day of treatment.

Statistical analysis

The SPSS 22.0 software for Windows was used for analysis of the data. For continuous variables, the normality of the distribution was tested using the Kolmogorov–Smirnov test. The results were presented as the mean ± standard deviation for variables with normal distribution and as the median (interquartile range 25–75) for variables with abnormal distribution. The statistical comparisons of continuous variables were performed using independent samples t test or Mann–Whitney U test regarding the distribution patterns when analyzing the differences between Groups 1 and 2. Categorical variables were compared using chi-square test or Fisher's exact test between Groups 1 and 2. To compare the ECG parameters derived from baseline recordings and posttreatment recordings, paired samples t test or Wilcoxon test were used according to the distribution pattern of the variables. The change in the presence of long QTc before and after the treatment in the patient population was compared using the McNemar test. A p value <0.05 was considered statistically significant.

Table 1. Clinical characteristics of patients with COVID-19

Age, years	41.1±15.4 (16-74)
Female sex, n (%)	45 (49.5)
Diabetes mellitus, n (%)	9 (9.9)
Hypertension, n (%)	11 (12.1)
CHD, n (%)	3 (3.3)
Any medication use, n (%)	24 (26.2)
Antihypertensive	11 (12.1)
Oral antidiabetics	9 (9.9)
Antiplatelets/Anticoagulants	5 (5.5)
Antiepileptic	3 (3.3)
Others	4 (4.4)
Admission hs-cTnT, ng/L, median (IQR)	2.5 (2.5-3.86)
Discharge hs-cTnT, ng/L, median (IQR)	2.5 (2.5-2.70)
Creatinine, mg/dL	0.73±0.20 (0.38-1.56)
ALT, IU/L	28±25 (7-178)
AST, IU/L	26±15 (10-97)
Sodium, mEq/L	136±2.8 (126-144)
Potassium, mEq/L	4.07±0.49 (2.8-6.4)
WBC, $\times 10^9$/L	5.9±3.1 (0.11-25.6)
Hemoglobin, g/L	14.2±1.7 (9.2-18.6)
Platelet count, $\times 10^9$/L	200±57 (76-392)
Neutrophil count, $\times 10^9$/L	62.1±12.3 (6.8-87.6)
Lymphocyte count, $\times 10^9$/L	26.1±10.4 (5.5-58.7)
Monocyte count, $\times 10^9$/L	9.7±4.0 (0.5-30.5)
NLR	3.2±2.5 (0.15-15.93)

ALT - alanine aminotransferase; AST - aspartate aminotransferase; CHD - coronary heart disease; hs-cTnT - highly-sensitivity troponin T; IQR - interquartile range, NLR - neutrophil-to-lymphocyte ratio; WBC - white blood cell count

Results

Ninety-one patients with mild-to-moderate symptoms of COVID-19 were recruited during the study period. The baseline clinical characteristics and biochemical parameters of the study population are summarized in Table 1. On admission, none of the patients had a history of chronic pulmonary disease, chronic liver disease, chronic kidney disease, or rheumatism and none of them showed signs of sepsis, ARDS, acute myocardial infarction, myocarditis, or myocardial injury.

Forty-three patients were treated with hydroxychloroqui ne+oseltamivir+azithromycin (Group 1) and 48 patients were

Table 2. Clinical characteristics and ECG parameters of Groups 1 and 2

	Group 1	Group 2	*P*
Age, years	35±14	46±15	0.001
Female sex, n (%)	21 (48.8)	24 (50)	0.912
Hypertension, n (%)	2 (4.7)	9 (18.8)	0.039
Diabetes mellitus, n (%)	5 (11.6)	4 (8.3)	0.730
CHD, n (%)	0	3 (6.2)	NA
Baseline heart rate, bpm, mean±SD	79±16	83±13	0.147
Baseline QTc, ms, mean±SD	446±30	434±40	0.139
Baseline QTD, ms, median (IQR)	20 (15-28)	20 (14-34)	0.593
Baseline QRS duration, ms, mean±SD	107±19	105±20	0.673
Baseline Tp-e, ms, mean±SD	102±16	86±18	<0.001
Baseline Tp-e Dispersion, ms, median (IQR)	12 (8-18)	9 (6-15)	0.095
Baseline Tp-e/QTc ratio, mean±SD	0.23±0.04	0.20±0.04	<0.001
Baseline PR interval, ms, median (IQR)	150 (134-164)	148 (129-176)	0.707
Baseline P wave duration, ms, mean±SD	113±17	106±19	0.105
Baseline P wave dispersion, ms, median (IQR)	9 (5-15)	6 (4-11)	0.101
PT Heart rate, bpm, median (IQR)	72 (66-78)	76 (69-86)	0.045
PT QTc, ms, mean±SD	456±28	455±38	0.960
PT QTD, ms, median (IQR)	15 (13-21)	20 (13-27)	0.099
PT QRS duration, ms, median (IQR)	112 (95-120)	106 (98-126)	0.683
PT TP-e, ms, mean±SD	104±14	95±15	0.007
PT Tp-e dispersion, ms, median (IQR)	10 (6-15)	10 (6-14)	0.758
PT Tp-e/QTc ratio, mean±SD	0.23±0.03	0.21±0.03	0.005
PT PR interval, ms, mean±SD	160±24	163±35	0.582
PT P wave duration, ms, mean±SD	115±17	115±121	0.896
PT P wave dispersion, ms, median (IQR)	9 (6-13)	8 (6-13)	0.583
Delta QTc	12 (4-18)	20.5 (10.5-35)	0.008
PT CRP, mg/L, median(IQR)	2.01 (0.57–5.12)	4.38 (1.34–19.79)	0.014

Group 1: hydroxychloroquine+oseltamivir+azithromycin, Group 2: hydroxychloroquine+oseltamivir+levofloxacin.
CHD - coronary heart disease; CRP - C-reactive protein; ECG - electrocardiography; IQR - interquartile range; PT - posttreatment; QTc - corrected QT interval; QTD - QTc dispersion; SD - standard deviation; Tp-e - T wave peak-to-end interval

treated with hydroxychloroquine+oseltamivir+levofloxacin (Group 2). There were no statistically significant differences between Group 1 and Group 2 regarding sex, presence of diabetes, and all ECG parameters apart from baseline and posttreatment Tp-e (102±16 vs. 86±18 ms, p<0.001 and 104±14 vs. 95±15 ms, p=0.007, respectively) and delta QTc [12 (4–18) vs. 20.5 (10.5–35) ms, p=0.008] (Table 2). The frequency of hypertension [2 (4.7) vs. 9 (18.8), p=0.039) and the mean age (35±14 vs. 46±15 years, p<0.001] were lower in Group 1 than in Group 2. Baseline heart rates were not significantly different between Group 1 and Group 2, but posttreatment heart rates were significantly lower in Group 1 [72 (66–78) vs. 76 (69–86) bpm, p<0.045]. Admission mean serum creatinine was 0.67±0.14 mg/dL in Group 1 and 0.78±0.22 mg/dL in Group 2 (p=0.010). We also found that posttreatment CRP was significantly lower in Group 1 compared to Group 2 [2.01 (0.57–5.12) mg/L vs. 4.38 (1.34–19.79) mg/L, p=0.014]. All other blood parameters were similar between the two groups.

Table 3 shows the baseline and posttreatment ECG parameters of the patients. Resting heart rate (81±14 vs. 74±14 bpm, p<0.001) and QTD (24±15 vs. 20±10 ms, p=0.004) were significantly decreased after treatment compared to baseline values. The QTc interval, QRS duration, Tp-e, PR interval, and P wave duration were significantly increased after the treatment (p<0.001 for all values). No statistically significant differences were observed for Tp-e dispersion and P wave dispersion (p>0.05 for all values).

Table 4 shows the ECG parameter changes in Group 1 and Group 2 separately. The QTc interval (p<0.001 vs. p<0.001), QRS duration (p=0.006 vs. p=0.014), Tp-e (p=0.036 vs. p<0.001), and PR interval (p=0.002 vs. p=0.05) were significantly prolonged in both those receiving azithromycin (Group 1) and those receiving levofloxacin (Group 2). Heart rates significantly decreased in both Group 1 and Group 2 after medical therapy (p<0.001 vs. p=0.007). The QTD was significantly decreased in Group 1 (p<0.001) but was not significantly changed in Group 2 (p=0.381). The P wave duration showed no significant difference in patients treated with

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Table 3. Characteristics of the patient ECG parameters before and after treatment

	Baseline		After treatment		*P*
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
Heart rate, bpm	81±14	82 (70-91)	74±14	74 (68-81)	<0.001
QTc, ms	440±35	442 (418-462)	455±34	453 (432-479)	<0.001
QTD, ms	24±15	20 (15-30)	20±10	18 (13-24)	0.004
QRS duration, ms	106±19	104 (93-120)	112±23	112 (96-124)	<0.001
Tp-e, ms	94±19	94 (80-105)	99±15	98 (88-111)	<0.001
Tp-e dispersion, ms	12±7	10 (7-16)	11±6	10 (6-14)	0.195
Tp-e/QTc ratio	0.21±0.04	0.21 (0.19-0.24)	0.22±0.03	0.22 (0.20-0.24)	0.154
PR interval, ms	153±29	150 (132-165)	161±30	162 (139-176)	0.001
P wave duration, ms	110±18	112 (96-122)	115±19	115 (103-128)	0.001
P wave dispersion, ms	9±6	8 (4-12)	10±5	8 (6-13)	0.277

ECG - electrocardiography; IQR - interquartile range; QTc - corrected QT interval; QTD - QTc dispersion; SD - standard deviation; Tp-e - T wave peak-to-end interval

Table 4. Characteristics of the ECG parameters before and after treatment in the patients who did and did not receive azithromycin treatment

Variables	Group 1					Group 2				
	Baseline		Post treatment			Baseline		Post treatment		
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	*P*	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	*P*
Heart rate, bpm	79±16	77 (69-90)	72±10	72 (66-78)	<0.001	83±13	86 (72-92)	76±17	76 (69–86)	0.007
QTc, ms	446±30	447 (425-464)	456±28	455 (440-473)	<0.001	434±40	434 (402-458)	455±38	453 (426–489)	<0.001
QTD, ms	21±9	20 (15-28)	18±9	15 (13-21)	0.001	27±19	20 (14-34)	21±11	20 (13–27)	0.381
QRS duration	107±19	105 (95-120)	110±21	112 (95-120)	0.006	105±20	101 (92-120)	114±26	106 (98–126)	0.014
Tp-e, ms	102±16	100 (89-110)	104±14	102 (94-114)	0.036	86±18	86 (76-98)	95±15	94 (85–106)	<0.001
Tp-e dispersion, ms	13±6	12 (8-18)	11±6	10 (6-15)	0.156	11±8	9 (6-15)	10±6	10 (6–14)	0.635
Tp-e/QTc ratio	0.23±0.04	0.23 (0.20-0.25)	0.23±0.03	0.24 (0.20-.025)	0.858	0.20±0.04	0.20 (0.18-0.23)	0.21±0.03	0.21 (0.19–0.23)	0.073
PR interval, ms	153±25	150 (134-164)	160±24	162 (139-172)	0.002	153±33	148 (129-176)	163±35	160 (139–183)	0.050
P wave duration, ms	113±17	114 (97-124)	115±17	120 (104-129)	0.075	106±19	106 (93-119)	115±121	112 (103–128)	0.007
P wave, dispersion, ms	10±7	9 (5-15)	10±5	9 (6-13)	0.535	8±6	6 (4-11)	9±5	8 (6–13)	0.055

Group 1: hydroxychloroquine+oseltamivir+azithromycin, Group 2: hydroxychloroquine+oseltamivir+levofloxacin.
ECG - electrocardiography; IQR - interquartile range; QTc - corrected QT interval; QTD - QTc dispersion; SD - standard deviation; Tp-e - T wave peak-to-end interval

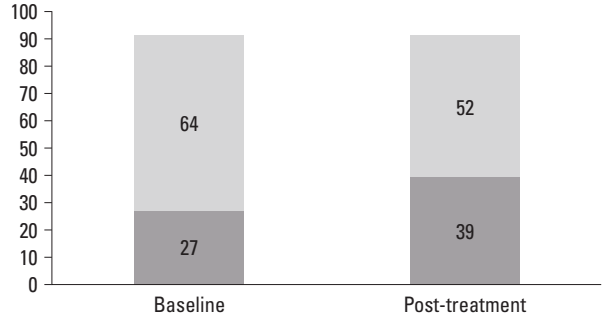

Figure 1. Baseline and post-treatment normal and prolonged QTc proportions

azithromycin (p>0.05), but the P wave duration was significantly prolonged in patients treated with levofloxacin (p=0.007). When P wave dispersion was estimated, no statistically significant differences were observed after either treatment (p=0.535 vs. p=0.055).

Figure 1 shows the presence of long QTc at baseline and after treatment. Although the QTc duration was prolonged before the treatment in 27 patients, this number increased to 39 patients after treatment (p=0.017). The baseline QTc duration was >500 ms in four patients, and this number increased to eight patients on the fifth day of treatment. Patients whose baseline QTc was >500 ms were closely followed, and a decrease in dose and electrolyte replacement were performed in one patient during the follow-up period. None of the patients experienced any overt ventricular arrhythmia.

Discussion

This study demonstrated important findings regarding ECG changes in COVID-19 patients. First, there was a significant number of patients with prolonged QTc duration at admission, and the incidence of prolonged QTc significantly increased following treatment in the study population. Second, COVID-19 treatment with triple combination therapy composed of hydroxychloroquine+oseltamivir+either azithromycin or levofloxacin significantly increased the durations of the P wave and QRS complex, PR segment, QTc and Tp-e lengths; in contrast, the QTD significantly decreased with treatment. Third, increases in QTc, QRS duration, Tp-e, and PR interval were observed in patients who were treated with either azithromycin or levofloxacin. Also of note, although the QTc increased significantly in both groups, the delta QTc change was significantly greater in the levofloxacin group than in the azithromycin group.

Although there is not any evidence-based recommendation, many potential QT prolonging agents are being used for COVID-19 treatment in current practice. So, a risk assessment for QT prolongation and TdP needs to be performed before the initiation of therapy; guidance documents about minimizing the risk of ventricular arrhythmias during the COVID-19 era have been published by cardiology societies (10, 11). We know that patients with inherited or acquired long QT syndrome are at an increased risk of TdP. Our findings pointed out that there were a significant number of COVID-19 patients who had an increased QTc duration at the start of treatment. Nearly 30% of our patients had QT prolongation at admission, and 4.3% of them had a QT duration >500 ms. The scientific reports about treatment associated with QT prolongation in COVİD-19 patients are increasing, but to our knowledge no study has mentioned the rate of baseline QT prolongation. But if we look at the details of the studies, we can find clues that the patients had long QT at admission. Van den Broek et al. (12) reported baseline QTc values of 432 (360–505) ms. This demonstrates that there were patients with long QT in their population. The reason why these patients have QT prolongation at admission is uncertain. Multiple medications, electrolyte disturbances, structural heart diseases, and bradyarrhythmias can cause acquired long QT (13). We excluded critically ill patients and patients with cardiac manifestations of COVID-19 from our study, and there were only three patients in our population who previously had used any medication that can cause QT prolongation. We could not find magnesium levels measured at admission for the vast majority of the patients and calcium levels in some patients. Although serum potassium levels were slightly lower in patients with long QT at admission, the difference was not statistically significant. Eventually, the QT prolongation measured at admission in COVID-19 patients and the potential underlying risk factors of this prolongation need to be investigated with further prospective studies.

Four agents administered in triple combinations were used to treat COVID-19 patients in our study population. We found that QTc values were significantly increased with treatment, and this finding is in agreement with prior studies (14, 15). Nevertheless, our study differs from previous studies which generally evaluated the QT prolongation in patients who received chloroquine/hydroxychloroquine alone or in combination with azithromycin. To the best of our knowledge, this study is the first to investigate QT prolongation in a population treated with triple combination therapy. Of the agents used in our study, hydroxychloroquine, oseltamivir (16) and azithromycin are known to be associated with QT prolongation and levofloxacin (17-19) is known to be relatively safe in terms of QT prolongation (1, 20). Before analyzing the results, we had expected to see a lower incidence of QTc prolongation in the levofloxacin group than in the azithromycin group, but our findings revealed the opposite result: that delta QTc was significantly higher in the levofloxacin group than in the azithromycin group. This seems to be strange at first glance, because levofloxacin is known to be relatively safe in terms of QT prolongation. But when we interpret this finding in view of a drug interaction, we can find a possible answer. Oseltamivir decreases the clearance of levofloxacin (21) and levofloxacin increases the QT prolonging effect of hydroxychloroquine (22). So, this finding gives us an important message that as a result of drug interactions even a safe agent like levofloxacin can cause unexpected QT prolongation when used concomitantly with a QT-prolonging agent.

Another important feature of our study was that we evaluated not only QTc changes but also P wave duration, PR duration, QRS duration, QTD, and Tp-e duration. We know that azithromycin, oseltamivir, and hydroxychloroquine have varying effects on Na, Ca, and K currents. These agents can affect different phases of the action potential, and previous studies demonstrated these effects (23-25). An interesting finding was the significant decrease of the QTD after treatment, especially in patients who were taking triple therapy with azithromycin. We could not find any specific study evaluating QTD changes with the particular agents used in our patients. Increased QTD has been associated with an increased risk of ventricular arrhythmias and adverse prognosis in a variety of cardiac and noncardiac conditions (26). Initially, we had expected to find an increase in QTD with treatment, but the results were again the opposite. This may translate into a partially decreased arrhythmia risk with treatment and might explain why no arrhythmia episodes were noted in our study. But this is only a hypothesis and before making such a judgement, further studies are required.

Study limitations

The study had certain limitations. First of all, our study was a single center, retrospective, and observational study. Second, we included only patients with mild-to-moderate COVID-19 symptoms; the results might be different in critically ill patients and patients with concurrent cardiac manifestations. Third, the sample size was relatively small and larger cohort studies are needed to confirm our conclusions. Finally, the retrospective nature of the study created some important defects such as the lack of informa-

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tion about measurements at admission of serum magnesium and calcium levels and echocardiographic parameters.

Conclusion

In conclusion, there were a great number of patients with baseline long QTc among patients with mild-to-moderate symptomatic COVID-19. Triple therapy with either hydroxychloroquine +oseltamivir+levofloxacin or hydroxychloroquine+oseltamivir+azithromycin increased the QTc, QRS duration, Tp-e, and PR interval. This information should be considered during the follow-up of COVID-19 patients.

Declaration of Helsinki: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest: None declared.

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