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The effects of combined hydroxychloroquine and azithromycin therapy on QRS wave in COVID-19 patients

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Ethics Committee Approval
The study was approved by the ethical committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (No: 2020-06/681).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Hydroxychloroquine and azithromycin are frequently used for the treatment of coronavirus disease 2019 (COVID-19). The use of these medications increases the risk of adverse cardiovascular events. The aim of our study was to investigate the effects of these drugs on the arrhythmogenic electrocardiographic (ECG) markers, QRS duration, and QRS dispersion, and also to evaluate gender differences with respect to these effects.

Methods: Between March and June 2020, 107 (54 males, 53 females) patients admitted to our hospital's isolation ward with COVID-19 diagnosis with no history, risk factors, or clinical findings of cardiovascular diseases were included in this prospective cohort study. All participants had a mild illness, and none of them required intensive care unit admission. ECGs of the patients were recorded before starting treatment with combined hydroxychloroquine and azithromycin, and a second ECG was recorded on the next morning following the last dose of the treatment. All ECGs were evaluated by two blinded cardiologists in terms of QRS duration and dispersion.

Results: Among study participants, QRS duration was significantly prolonged after treatment with hydroxychloroquine and azithromycin (81.14 (9.11) versus 85.5 (10.48) ms [$P < 0.01$]), and the same pattern was observed with QRS dispersion (36.67 (9.54) versus 40.18 (9.35) ms [$P < 0.01$]). When gender differences were evaluated, male patients also showed significant changes in both QRS duration (82.65 (8.04) versus 87.31 (10.7) ms [$P < 0.01$]), and dispersion (36.93 (8.61) versus 41.31 (9.63) ms [$P < 0.01$]), while in females the difference was statistically insignificant for both QRS duration (79.06 (10.18) versus 82.8 (9.79) ms [$P = 0.056$]), and dispersion (36.31 (10.83) versus 38.62 (8.86) ms [$P = 0.23$]).

Conclusions: The combined use of hydroxychloroquine and azithromycin led to an increase in both QRS duration and dispersion in all patients. These changes were more significant in males than in female patients. No clinical effects of these ECG changes were observed in the short-term, and further studies are needed to investigate the possible clinical implications of these drugs during longer follow-up periods.

Keywords: Hydroxychloroquine, Azithromycin, COVID-19, QRS wave, Arrhythmia

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Introduction

In late 2019 a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus disease 2019 (COVID-19) appeared in Wuhan China [1], and on March 11, 2020, the World Health Organization (WHO) declared that this virus had reached pandemic status [2]. In the absence of vaccines or curative medical treatment, COVID-19 exerted an unprecedented global impact on public health and health care delivery. In March 2020, a study claimed that the antiviral effects of hydroxychloroquine combined with azithromycin were found to be efficient against SARS-CoV-2 virus, and thus these drugs became part of the COVID-19 treatment protocols in many medical centers worldwide [3]. Because of the worldwide emergence and rapid spread of COVID-19 the use of these drugs has also increased. The increasing use of these drugs has raised concerns about their safety and the serious cardiovascular side effects associated with their use [4].

The antimalarial drug, hydroxychloroquine, and commonly used macrolide antibiotic, azithromycin, affect ventricular repolarization through alterations in myocardial ionic channels [5]. The earliest implications of these effects involve QT interval prolongation as seen on a surface electrocardiogram (ECG), which may lead to serious ventricular arrhythmias, such as torsade de pointes [6, 7]. Another fact is that hydroxychloroquine is metabolized by cytochrome P450 enzymes and combining it with azithromycin, which inhibits this enzyme, has led to an increase in concerns about the safety of this combination [8, 9].

Another ECG parameter that correlates with the occurrence of ventricular arrhythmias due to disturbances in ventricular repolarization is the QRS duration and its dispersion [10]. QRS dispersion is a novel ECG parameter and is measured as the difference between the maximal and minimal QRS duration using a standard 12-lead ECG. Studies have shown that increased QRS dispersion is associated with adverse cardiovascular events and mortality even in healthy asymptomatic individuals [11].

The effects of combined use of hydroxychloroquine and azithromycin therapy on QT interval were studied earlier [12], but the effects of this therapy on QRS duration and dispersion have not yet been investigated. The aim of our study was to investigate the effects of hydroxychloroquine and azithromycin combination therapy on changes in QRS duration and dispersion values before and after the treatment in patients diagnosed with COVID-19 who had no known history of cardiovascular diseases. Gender differences with respect to the effects of these drugs on QRS duration and dispersion were also investigated.

Materials and methods

Study populations

In this prospective cohort study, 107 patients (54 males, 53 females) with a positive COVID-19 polymerase chain reaction (PCR) test fulfilled the inclusion criteria and were evaluated between March 18 and June 8, 2020. Patients included those with new onset mild symptoms who were admitted to the isolation ward following the Ministry of Health's guidelines. Patients with normal arterial oxygen saturation (SpO2) and computed tomography (CT) showed no or very limited pneumonic infiltration.

All patients were admitted to the isolation ward once they had a positive polymerase chain reaction (PCR) test. They were treated for five days with combination therapy consisting of hydroxychloroquine (2 x 400 loading and 2 x 200 maintenance doses) and azithromycin (Day 1: 500 mg and other days 1 x. 250 mg). No antiviral agent or any other treatment was used to treat these patients. All participants were asymptomatic and had a negative PCR test before discharge, and no patients needed transfers to more specialized wards or intensive care units. The mean hospital stay duration was 8.3 (1.15) days. ECGs of the patients were recorded on the first day before starting the treatment and on the morning following the last dose of therapy.

Exclusion criteria

Patients under the age of 18 and over the age of 65 with a systemic disease, such as hypertension and diabetes mellitus, history of any cardiovascular diseases, the presence of electrolyte disturbance in the routine biochemical tests, impaired liver and/or renal function tests, the presence of anemia or polycythemia, and hypothyroidism or hyperthyroidism were excluded. Patients with clinical findings that indicated the presence of cardiovascular diseases or have abnormalities on the baseline ECG were also excluded. To avoid selection bias, participant eligibility was evaluated separately by two blinded cardiologists, and a patient was excluded after the reports of both investigators matched.

Electrocardiogram

The 12-lead ECG recordings were obtained while the patient was in the supine position. ECG length was 10 s; therefore, depending on heart rate, 4–6 beats per lead were used. ECG parameters were manually measured using a magnifying Glass (TorQ 150 mm Digital Caliper LCD) and a digital ruler accuracy of 0.01 mm by two blinded cardiologists. The measure of agreement was done using Cohen's kappa method, and the result was found to be within acceptable levels (Cohen's K = 0.17).

QRS duration (expressed in ms) was calculated by measuring the distance from the initiation of the Q or R wave until the end of the R or S wave. QRS dispersion was defined as the difference between the maximal and minimal QRS duration. ECG recordings were obtained at a speed of 25 mm/s, amplitude of 10 mm/mV. Values in mm with the digital caliper, which was 1/100 mm in precision, were calculated as ms multiplied by 40.

Statistical analysis

The sample size analysis was done with a confidence interval of 95% and type 1 error of 0.05. Statistical power analysis showed a G*power of 0.8937. Continuous variables were examined by Shapiro–Wilk test to check for normality of distribution. Continuous variables are presented as a mean (standard deviation). Categorical data are presented as percentages or frequencies. Student t- and Mann–Whitney U tests were used to compare parametric and non-parametric continuous variables, respectively. Categorical variables were compared using a chi-squared (v2) test. Pearson's correlation test was used to determine the correlation between the variables. A two-tailed *P*-value of < 0.05 was considered statistically

significant. All data were analyzed using SPSS (IBM, Chicago, IL, USA) version 23.0.

Ethics

All procedures, including the informed consent process, were conducted in accordance with the ethical standards of the National Health and Medical Research Council of Turkey and the Helsinki Declaration. The patients were informed about the study, and they were included after their informed voluntary consent forms were obtained. The study was approved by the ethical committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (No: 2020-06/681).

Results

Between March 18 and June 8, 2020, 183 patients with a positive COVID-19 PCR test were evaluated, among which 107 patients (54 males, 53 females) fulfilled the inclusion criteria and were analyzed in the study (Figure 1). No significant differences between participants of different genders in terms of sociodemographic and baseline clinical characteristics (Table 1) were noted. Before starting treatment with hydroxychloroquine and azithromycin, a baseline ECG was obtained, and another ECG was obtained on the next morning after the last treatment dose. To avoid any interpretation or confirmation bias, ECG evaluations were done by two blinded cardiologists, and a measure of agreement was done using the Cohen's kappa method. This value was found to be within acceptable levels (Cohen's K = 0.17).

Figure 1: Flow chart showing the number of COVID-19 patients assessed for eligibility, the number of patients excluded and the final number of study participants

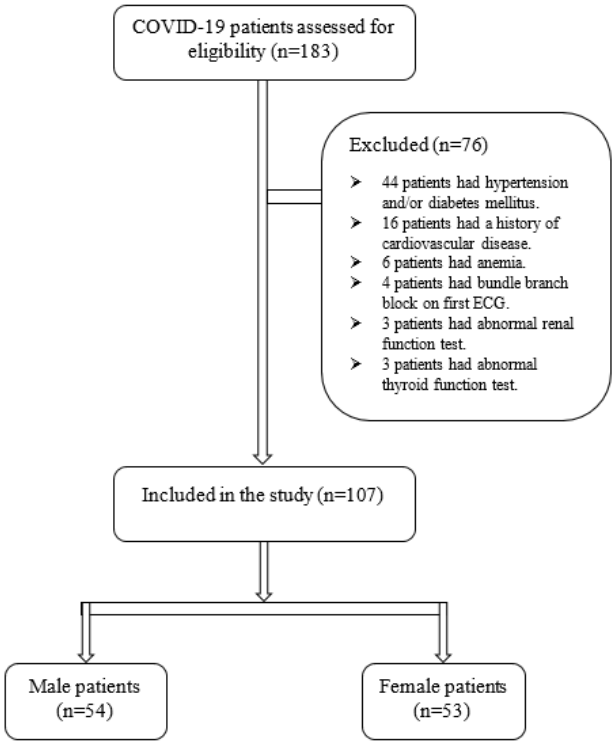


Table 1: The comparison of sociodemographic and baseline clinical characteristics of the study groups

Variables	Male group (n = 54)	Female group (n = 53)	T-value	*P*-value
Age, years	46.74 (12.52)	45.88 (13.61)	0.34	0.73
Basal HR, b/m	78.26 (13.51)	77.91 (12.45)	0.13	0.88
BMI, kg/m^2	26.81 (2.54)	26.37 (3.51)	0.74	0.45
Systolic BP, mmHg	122.84 (14.62)	121.53 (11.46)	0.51	0.60
Diastolic BP, mm Hg	74.88 (7.45)	72.56 (6.81)	1.68	0.09
Hemoglobin, gr/dL	14.2 (1.7)	14.3 (2.1)	0.27	0.78
TC. mg/dL	171.8 (27.4)	173.9 (31.7)	0.36	0.71
LDL, mg/dL	135.8 (22.6)	137.8 (31.9)	0.37	0.70
Triglyceride, mg/dL	137.8 (31.9)	139.5 (41.6)	0.23	0.81
HDL, mg/dL	31.7 (4.8)	31.9 (4.7)	0.21	0.82
Calcium, mg/dL	9.3 (0.8)	9.4 (0.6)	0.73	0.46
Sodium, mEq/L	140.5 (1.4)	140.7 (1.2)	0.79	0.42
Potassium, mEq/L	4.1 (0.7)	4.2 (0.5)	0.84	0.39
TSH, mIU/L	3.3 (1.3)	3.4 (0.8)	0.47	0.63

BMI; Body Mass Index, BP; Blood Pressure, TC; Total Cholesterol, LDL; Low-Density Lipoprotein, HDL; High-Density Lipoprotein, TSH; Thyroid Stimulating Hormone

The overall baseline heart rate was 78.26 (13.51) beats per minute (bpm), and the post-treatment heart rate was 77.91 (12.45) bpm (P = 0.84) as shown in Table 2. The mean QRS duration after treatment was significantly prolonged, with baseline QRS duration being 81.14 (9.11) ms and the post-treatment QRS duration being 85.5 (10.48) ms (P < 0.01) as shown in Table 2 and Figure 2. The mean QRS dispersion value also increased after treatment with a baseline QRS dispersion value of 36.67 (9.54) and a post-treatment QRS dispersion value of 40.18 (9.35) (P < 0.01) as shown in Table 2 and Figure 3. Significant prolongation of QT interval was also observed (Table 2).

Figure 2: Comparison of QRS durations for patients before and after the treatment with hydroxychloroquine and azithromycin.

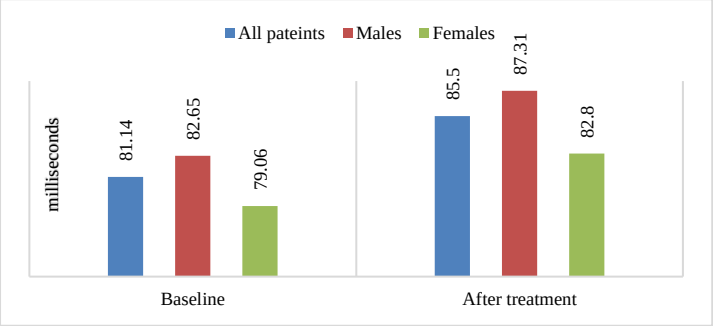
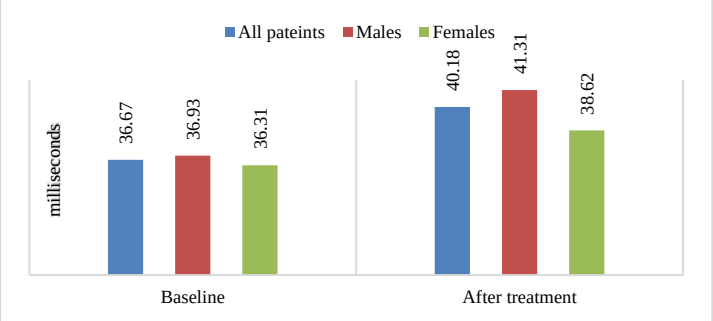


Figure 3: Comparison of QRS dispersions for patients before and after the treatment with hydroxychloroquine and azithromycin.



When comparison was made according to patients' genders, both gender groups showed prolongation of QRS duration and an increase in QRS dispersion values after combined treatment with hydroxychloroquine and azithromycin; however, males were significantly affected more by the treatment than females (Table 2). The mean baseline QRS duration of male patients before the treatment was 82.65 (8.04) ms, and after treatment it was 87.31 (10.7) ms (P < 0.01), while in female patients, the baseline QRS duration was 79.06 (10.18) ms, and after treatment, it was 82.8 (9.79) ms (P = 0.056) as shown in Table 2 and Figure 2. In terms of QRS dispersion, in

male patients, the baseline QRS dispersion was 36.93 (8.61), and after treatment, QRS dispersion was 41.31 (9.63) ($P < 0.01$), while in female patients, the baseline QRS dispersion was 36.31 (10.83), and after treatment, the QRS dispersion was 38.62 (8.86) ($P = 0.23$) as shown in Table 2 and Figure 3. No cases of treatment discontinuation because of serious ECG changes were noted, and none of the patients experienced a life-threatening malignant ventricular arrhythmia during hospitalization. No correlation was found between COVID-19-related signs and symptoms and changes in ECG parameters.

Table 2: The comparison of electrocardiogram (ECG) findings of all patients before and after treatment with combined hydroxychloroquine and azithromycin

Variables	Before Treatment (ms)	After treatment (ms)	T-value	*P*-value
Heart rate	78.26 (13.51)	77.91 (12.45)	0.19	0.84
QRS duration (ms)	81.14 (9.11)	85.5 (0.48)	3.24	< 0.01
- QRS duration Males (n = 54)	82.65 (8.04)	87.31 (10.7)	2.65	< 0.01
- QRS duration Females (n = 53)	79.06 (10.18)	82.8 (9.79)	1.92	0.056
QRS dispersion (ms)	36.67 (9.54)	40.18 (9.35)	2.72	< 0.01
- QRS dispersion Males (n = 54)	36.93 (8.61)	41.31 (9.63)	2.49	< 0.01
- QRS dispersion Females (n = 53)	36.31 (10.83)	38.62 (8.86)	1.21	0.23
QT duration (ms)	361.73 (27.08)	381.67 (32.85)	4.84	< 0.01
- QT duration Males (n = 54)	358.96 (28.62)	378.86 (34.91)	3.83	< 0.01
- QT duration Females (n = 53)	365.16 (24.96)	385.36 (29.94)	3.77	< 0.01
cQT duration (ms)	416.22 (36.74)	435.89 (31.61)	4.19	< 0.01
- cQT duration Males (n = 54)	407.04 (32.92)	422.35 (35.01)	2.34	0.021
- cQT duration Females (n = 53)	420.57 (34.13)	434.35 (36.62)	2.01	0.047

Discussion

The effects of combined hydroxychloroquine and azithromycin treatment on QRS duration and dispersion in COVID-19 patients who had no previous history or clinical findings of cardiovascular diseases were evaluated in this study. Two main findings are reported: (1) the use of hydroxychloroquine and azithromycin led to an increase in both QRS duration and dispersion in all patients and (2) the increases in QRS duration and dispersion were more significant in male than female patients.

Several authors have explained the physiopathology for ventricular repolarization and depolarization disorders that may lead to ventricular arrhythmias [13]. Some drugs can affect the duration of ventricular repolarization and depolarization via causing changes in the ion channels (especially the potassium channel) of the myocardium and disturbances of the ventricular action potential [14]. Many risk factors, including advanced age, history of heart disease, electrolyte imbalance, diuretic use, kidney and liver failure, can increase the risk of drug-related malignant arrhythmias [15].

During the COVID-19 pandemic, hydroxychloroquine and azithromycin were frequently used due to their anti-inflammatory and immunomodulatory effects [3]. A major concern with the use of these drugs is the risk of arrhythmias. Many studies have shown that the use of these drugs leads to disturbance in ventricular repolarization and as a result, these drugs can cause prolongation of the QT interval leading to serious arrhythmias, such as torsade de pointes and sudden cardiac death [6, 16].

On the other hand, both hydroxychloroquine and azithromycin were found to cause changes in ECG wave durations and alterations in the dispersions of these waves [17, 18]. ECG wave durations and dispersions are non-invasive cardiac markers that are useful for predicting the risk of arrhythmias and sudden cardiac death. The QRS wave represents the ventricular depolarization on the surface ECG, and its relationship with ventricular arrhythmias have been studied for many years. QRS prolongation has been found to be as a predictive parameter for ventricular arrhythmias and sudden cardiac death in many studies [19, 20]. Another more recent parameter used to predict ventricular arrhythmias and sudden cardiac death is the QRS dispersion, which has also shown to be associated with adverse cardiovascular events and cardiac death [21, 22].

QRS dispersion is measured as the difference between maximal and minimal QRS duration on the 12-lead ECG, and it occurs due to the heterogeneity and conduction delays through the ventricle [23]. Kountouris et al. [24] reported that QRS dispersion exhibits a stronger association with left ventricular systolic function than does QRS duration. Recently, an increased QRS dispersion was shown as a prognostic marker of adverse cardiovascular events and mortality among asymptomatic population with no history of cardiovascular diseases in the Multi-Ethnic Study of Atherosclerosis (MESA) study.

As shown in previous studies, increases in QRS duration and dispersion are associated with adverse cardiovascular events and mortality even in individuals with no symptoms or history of cardiac diseases; thus, it is an important non-invasive ECG marker in patients who are at potential risk of myocardial conduction defects because of use of hydroxychloroquine and azithromycin.

In our study, the relationship between the use of hydroxychloroquine and azithromycin in COVID-19 patients with no history or clinical findings of cardiovascular diseases with QRS duration and dispersion was evaluated. The results of our study show that both QRS duration and dispersion after treatment with hydroxychloroquine and azithromycin significantly increased when compared with baseline values. When the evaluation was done based on gender differences, the changes in QRS duration and dispersion were also statistically significant in male patients, while in female patients the difference was statistically insignificant. All study participants received the same doses of both drugs for five days, and the hospitalization periods were similar. No drug- or disease-related complications were observed, and none of the patients required intensive care unit admission.

The results of our study show that the use of combined hydroxychloroquine and azithromycin therapy for COVID-19 patients may affect the duration and dispersion of the QRS wave on the surface ECG, especially in male patients. These changes did not correlate with COVID-19 signs and symptoms.

Although patients experienced QRS prolongation and increases in QRS dispersion during the study period, no cases of treatment discontinuation because of serious ECG changes were reported, and none of the patients experienced a life-threatening malignant ventricular arrhythmia during hospitalization. On the other hand, in our study, the clinical effects of these changes in

short term were evaluated, and longer follow-up periods are needed to show whether these changes have negative clinical implications on longer follow-up periods or are merely benign and reversible conditions.

Limitations

This study is subject to the same limitations as other observational studies. The main limitation was the absence of a control group of patients with COVID-19 infections who were not treated with any of these medications. Another import limitation is the small number of patients included in the study because of the focus on choosing patients with no past medical histories. Further work is needed to confirm our findings in a larger group of patients and to investigate the clinical implications of these findings in the long-term.

Conclusions

Besides its known effects on QT duration, combined hydroxychloroquine and azithromycin therapy was found to cause significant prolongation of both QRS duration and dispersion in COVID-19 patients with no histories or clinical findings of cardiovascular diseases. These effects show gender differences as ECG changes were more significant in male versus female participants. No clinical effects of these ECG changes were observed in the short-term, but further studies are needed to investigate this combination's clinical implications over longer follow up periods.

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