Hydroxychloroquine in COVID-19: The predictors of QT Prolongation

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Abstract

Background: We described the QTc interval prolongation and related adverse cardiac events during the administration of hydroxychloroquine (HCQ) and its combinations for treatment of COVID-19. Methods: The hospitalized patients who were infected with SARS-CoV-2 and received HCQ with initial and follow up ECGs from March 10th to May 30th were included. The critical QTc prolongation was accepted as QTc >500 ms if QRS<120ms and >550 ms if QRS >120 ms or [?]QTc levels >60 ms when compared with the initial ECG. Primary outcomes were critical QTc prolongation, ventricular tachyarrhythmia, and sudden cardiac arrest. Results: Out of 336 hospitalized patients with suspected or confirmed COVID-19, 297 received HCQ, and 94 met the inclusion criteria, and 66 cases were included in final analysis. The mean baseline QTc was 444.5 (sd= 39.5) ms. In total, 63% of the patients' QTc levels increased under HCQ treatment and critical QTc prolongation occurred in 8 cases (12%) all of whom were male. The male gender (p=0.033), DM (p=0.035) and oseltamivir use (p=0.047) were significantly associated with critical QTc prolongation. In multivariate analysis, DM (OR:5.8, %95 Cl:1.11-30.32, p:0.037), and concomitant use of oseltamivir (OR:5.3, %95 Cl:1,02-28, p:0.047) were found to be associated with critical QTc prolongation. Conclusion: Critical QTc prolongation was detected in 12% of the patients. The DM and concomitant oseltamivir use were associated with critical QTc prolongation. The use of concurrent drugs that have potential to enhance QTc interval should be kept in mind and special attention should be paid for ECG monitoring.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a recently emerged virus, which causes mild to severe pneumonia[1]. One of the most commonly used first-line treatment in COVID-19 disease is hydroxychloroquine (HCQ) with or without azithromycin (AZT)[2]. The HCQ may have a role between ACE-2 receptor and SARS-COV-2 attachment and may decrease pro-inflammatory response[3].

The HCQ is used for autoimmune disorders such as systemic lupus erythematosus and referred to be a safe and well-tolerated drug[4]. It is also known to reduce the cardiovascular risks in rheumatoid arthritis patients[5]. On the other hand, it inhibits the voltage-gated sodium and potassium channels and prolongs repolarization (QTc interval) of the cardiac cycle that might increase the risk of Torsade de Pointes (TdP) and sudden cardiac arrest[6-8]. Based on these cardiac events and insufficient evidence of efficacy, concerns and restrictions are increasing for its use in COVID-19 in all over the world. Serious adverse cardiac events related to HCQ use in treatment and prophylaxis were reported from recent studies[9, 10].

In this study, we aimed to describe the QTc prolongation and related cardiac events, associated with HCQ in patients with COVID-19.

Methods

Ethics

Institutional Review Board of Koc University approved the study with the reference number of 2020.145.IRB1.034

Patients and Study Design

In this retrospective study, we included the inpatients who were infected with SARS-CoV-2 and received HCQ from March 10^{th} to May 30^{th}, 2020 in our two affiliated hospitals.

The case definition of World Health Organization used for diagnosis of COVID-19 includes the probable and confirmed cases. The confirmation was defined as the positive viral result of COVID-19 infection, while the probable case was defined as inconclusive or a suspect case for testing for COVID-19[11]. We included defined and probable cases with COVID-19.

We analyzed COVID-19 patients who has initial and follow-up ECGs. We excluded the patients who have neither initial nor follow up ECG, or who were transferred from other centres while using HCQ. A hospital COVID-19 team including infectious disease\souts, internal medicine, chest medicine, intensive care unit physicians managed all the cases with regular meetings. The ECGs were examined by the cardiologists to assess QTc intervals. Biosafety monitoring document was used by hospital pharmacy department to follow up drug related adverse events.

The Electrocardiograms (ECG) and Monitoring

The ECGs on admission were evaluated among the patients who received HCQ. Lead II was utilized for the measurement of the QTc interval on ECG or on telemetry. The end of the T-wave was defined as the tangent drawn from the steepest last limb of the T-wave to its intersection with the baseline. Bazett's formula was used to calculate the corrected QT (QTc) interval. If the baseline QTc level is below 450 ms, ECG re-evaluated on the third to fifth day of HCQ treatment; if the QTc levels are between 450-499 ms ECG evaluated daily. Critical QTc prolongation was defined as prolongation of QTc or [?]QTc levels (>500 msn, >60 msn; respectively). If a baseline bundle branch block (QRS >120 ms) was present, critical prolongation of QTc interval was accepted as 550 ms[12].

Treatment algorithm and follow-up

All the suspicious/confirmed cases with COVID-19 older than 18 years received HCQ for at least five days. Loading dose of HCQ was 400 mg twice daily in the first day and 200 mg twice daily for the following days. Loading dose of azithromycin was 500 mg once daily and 250 mg once daily for the next four days. Primary outcomes were critical QTc prolongation, TdP, ventricular tachyarrhythmia and sudden cardiac arrest.

Data Collection

Demographics, comorbid diseases, sodium, potassium, calcium and magnesium, ICU admission, medications including major concomitant QTc prolonging agents (loop diuretics, SSRI antidepressants, proton pump inhibitors, macrolide antibiotics and Class I and III antiarrhythmic) were collected. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Statistical analysis

Categorical variables were compared by using Chi-square test. For the continuous variables, non-parametric Kruskal-Wallis test was used because of the low sample size. The STATA 16v was used for the statistical analysis, and the statistical significance was set as p-value <0.05.

Results

A total of 336 hospitalized patients with suspicious or confirmed COVID-19 were included in the study. Among them, HCQ was administered to 297 patients and 94 of them met the inclusion criteria. Twenty-eight cases were excluded because of concomitant drug use that might affect QTc and 66 cases were included in final analysis (Figure 1). The mean age of the study population was 57.3 (sd=21.7) years and 54.6% was older than 60 years old and 33% was female. Twenty patients (30.3%) had diabetes mellitus (DM) and 25 (37.9%) patients had hypertension (%37,9). In total, 67% of the cases were confirmed while 23% were probable. The HCQ and AZT combination treatment were given 38% of the study group. Twenty-four percent of the patients had ICU admission and 6.25% died. The ICU admission rate among patients who had HCQ mono-theraphy and HCQ plus AZT were similar (25.0% and 23.1%, respectively. p=0.86). The rate of mortality was also similar among mono and combined theraphy group (5.1% and 8.0%, respectively. p=0.64)

The mean baseline QTc was 444.5 (sd=39.5) ms and was similar in both males and females (442.7 and 448.1 respectively p=0.6). Forty-two percent of the cases had baseline QTc more than 450 ms. Among patients who has DM, the mean baseline QTc was 450.9 ms (sd=48.8) while it was 441.8 ms (sd=35) in non-diabetics (p=0.4). The mean interval of baseline QTc was 455.6 (sd=35.8) ms in hypertensive patients, and 437.8 (sd=40.5) ms in patients without hypertension (p=0.076)

In total, 63% of the patients' QTc levels increased under HCQ treatment and critical QTc prolongation occurred in 8 cases (12%) all of whom were male (Table 1). In the critical QTc prolongation group the mean level of baseline QTc was 457.4 (sd=55.4) ms, while it was 442.75 (sd=37.1) ms in cases without critical QTc prolongation (p=0.3). AZT was given to 25 patients (38%). The patients who had combination therapy with AZT had a mean baseline QTc level of 448.5 (sd=45.7) ms, while the group without AZT had a mean baseline interval of 442.1 (35.6) ms (p=0.53). The control QTc levels were 460.3 (sd=48.6) ms in AZT combination group and were 451.2 (sd=51.8) ms in patients without AZT (p=0.48). Twenty-one cases used oseltamivir in combination with HCQ (32%). Among these patients, the mean baseline QTc level was 439.7 (sd=35.2) ms while it was 446.8 (sd=41.5) ms in non-oseltamivir group (p=0.5). The mean control QTc levels were 465 (sd=52) ms and 449.8 (sd=49.5) ms in patients with and without oseltamivir treatment, respectively (p=0.26).

The comparison of critically QT prolonged patients with others is shown in Table 1. The mean age and frequency of hypertension were similar among each group while male gender and DM were significantly higher among patients with critical QTc prolongation. AZT use was higher in critical QTc prolongation group but it was not significant (p=0.126) while oseltamivir use was significantly higher in critical QTc prolongation group (p=0.047). In the multivariate analysis, DM was found to be higher among patient who had critical QTc prolongation (OR:5.8, %95 Cl:1.11-30.32, p:0.037). Concomitant use of oseltamivir was also higher in the same group (OR:5.3, %95 Cl:1,02-28, p:0.047. Table 2).

Although a significant proportion of critical QTc prolongation was detected in our study population, none of our patients suffered from cardiovascular end points.

Discussion

One of the most commonly used treatment is HCQ in COVID-19 patients in all over the world[2]. In this study, we evaluated the effect of HCQ on QTc prolongation in patients with COVID-19. Critical QTc prolongation was detected in 12% of the population which is similar with two recent studies[10, 13]. However, in another one, critical QTc prolongation was reported as 20%[14].

The HCQ treatment for autoimmune disorders is cited to be safe in*in vitro* and small non-randomized trials[4]. However, the populations of these studies do not represent the COVID-19 patients because of the differences in clinical aspects, dynamics and severity of the diseases[14]. Myocarditis, that has potential to enhance QTc interval, was reported in 4.8% of the cases in the course of COVID-19[15]

For understanding the adverse events of HCQ, there is not an established threshold for blood or plasma. During clinical practice, monitoring HCQ cardiotoxicity by QTc seems practical. As the nature of COVID-

19 disease, the concurrent treatments such as AZT, possible underlying cardiac disorders and electrolyte imbalances have potential to affect the QTc interval and related TdP and sudden cardiac arrest.

AZT has potential to prolong QTc and is an additional risk factor for ventricular arrhythmias[16]. The risk of QTc prolongation in patients who use HCQ and AZT combination was reported to be higher than HCQ mono-theraphy[14], however in some other studies there was no significant increased risk as we detected in our study (Table 1)[13, 17].

The patients with DM had significantly higher rates of critical QTc prolongation in univariate and multivariate analysis (OR:5.8, %95 Cl:1.11-30.32, p=0.037. Table 2) although the baseline QTc levels were similar (p=0.4). Even the pre-diabetic and newly diagnosed DM patients are under risk of cardiac autonomic neuropathy (CAN), the diabetic patients who has poorly controlled blood glucose levels and long-lasting disease time, are at higher risk[18, 19]. Likewise, tachycardia, orthostatic hypotension, reverse dipping, and impaired heart rate variability, QTc prolongation is also shown to be one of the non-invasive methods to display the existence of (CAN)[18-20]. Even if the baseline QTc levels are normal, medications may easily influence the QTc interval in patients with DM because of this underlying/hidden autonomic neuropathy. Further randomized and high-volumed studies are needed to solve this association.

Oseltamivir which is an antiviral against influenza virus was used in early dates of the pandemic because of the possibility of influenza co-infection. In our study, it was used in more than 30% of the patients (21 out of 66 patients) and in multivariate analysis, oseltamivir use was found to cause critical QTc prolongation more than 5 times. In a Cochrane systematic review, it was stated that oseltamivir may cause QTc prolongation[21]. In a two cases series, QTc prolongation was reported in patients who used oseltamivir in addition to sotalol which is both an anti-arrhythmic and pro-arrhythmic drug. However, there is no human study that demonstrates whether oseltamivir causes QTc prolongation and prospective well-designed studies are required. Female gender has been accepted as an underlying risk factor which result in repolarization reserve reduction[22, 23], but in our study the critical QTc prolongation occurred solely in men.

Limitations

The major limitation of our study is the lack of a control group who were not treated by HCQ. The subgroup analyses may have reached a significant number if the study population was further. We also don't know the exact number of cardiomyopathies related with COVID-19 among our patients because they did not have echocardiographic evaluation if not required.

Conclusion

HCQ use in COVID-19 may cause a significant proportion of critical QTc prolongation. In our study population, DM and concomitant oseltamivir use were found to raise the incidence of critical QTc prolongation but none of our patients suffered from TdP, ventricular arrhythmia and sudden cardiac arrest. Because of the nature of COVID-19, the use of concurrent drugs and the clinical situations that have potential to enhance QTc interval should be kept in mind while using HCQ and special attention should be paid for ECG monitoring.

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Transparency declarations

None to declare.

Competing interest

None

Figure legend:

Figure 1. Study population. HCQ: Hydroxychloroquine, ECG: Electro cardiogram

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Table 1. Critical QTc prolongation compared to other patients.

	Critical QTc prolongation n=8	Other than Critical QT prolongation n=58	p
Gender			0.033
Male	8 (100)	36 (62)	
Female	0 (0)	22 (38)	
Mean age (sd)	68 (sd=16)	56 (sd=22)	0.134
Hypertension	4 (50)	21 (36.2)	0.451
Diabetes Mellitus	5 (62.5)	15 (25.8)	0.035
Chronic obstructive pulmonary disease	1 (12.5)	1 (1.7)	0.096
Others	5 (62.5)	28 (48.2)	0.451
Being in intensive care unit	4 (50)	12 (20.6)	0.07
Concurrent Drugs for COVID-19			
Azithromycin	5 (62.5)	20 (34.4)	0.126
Oseltamivir	5 (62.5)	16 (27.5)	0.047

Table 2. Univariate and multivariate analyses for critical QTc prolongation (n=66), lroc=76%

	Univariate analysis	Univariate analysis	Univariate analysis	Multivariate analysis	Mult
	OR	CI	*p*	OR	CI
Age	1.03	0.98-1.07	0.145	-	-
Diabetes mellitus	4.7	1.01-22.45	0.048	5.8	1.11-
Being in intensive care unit	3.8	0.83-17.6	0.084	-	-
Concurrent Azithromycin	3.1	0.68-14.62	0.14	-	-
Concurrent Oseltamivir	4.3	0.93-20.46	0.061	5.3	1.02-

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`Figure 1.docx` available at https://authorea.com/users/339022/articles/469086-hydroxychloroquine-in-covid-19-the-predictors-of-qt-prolongation