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EVALUATION OF QT/QTC INTERVAL PROLONGATION IN COVID-19 PATIENTS RECEIVED HYDROXYCHLOROQUINE (HCQ)

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ABSTRACT

BACKGROUND: COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused a pandemic that has raised serious public health concerns. Medical health practitioners are employing various treatment strategies that would have a potential to be effective in treating the COVID-19. Hydroxychloroquine (HCQ) has been revealed to have significant effect on the replication of SARS-CoV-2 virus in vitro. It has the antiviral characteristics in vitro that support the fact that this drug has efficacy in the treatment of COVID-19. Based on this hypothesis, it is appropriate to use this drug in clinical trials settings of preventing the COVID-19. **OBJECTIVE:** The main objective of this study was to investigate the degree of corrected QT (QTc) and QT/QTc ratio interval prolongation in patients with COVID-19 in association with their use of hydroxychloroquine (HCQ). **RESULTS:** In this Randomized controlled trial (RCT) study, we have found that the patients who received hydroxychloroquine (HCQ) for the treatment of COVID-19 were found to have no significant increase in final/last QT/QTc ratio (p=0.680) comparing to initial QT/QTc ratio. **CONCLUSION AND RELEVANCE:** In this study, patients who received HCQ for the treatment of COVID-19 were not found to be at high risk of QTc prolongation. Clinicians should carefully determine the risk and benefits of using HCQ with close monitoring of QTc changes.

Keywords: SARS-CoV-2; COVID-19; hydroxychloroquine, efficacy, adverse effects

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), also named COVID-19, has emerged and spread globally. It has raised great public health concern worldwide **[1].** Until May 13, 2020, it has infected 4170424 people with a mortality rate of 287399 (6.89%) **[2].** This virus belongs to the beta-coronavirus genus that also includes SARS-CoV (SARS) and Middle East respiratory syndrome CoV (MERS-CoV) features. The transmission mode of this virus is from animal to animal, animal to humans and subsequently humans to humans **[3].** Presently, there is no approved treatment for COVID-19 infection. Hydroxychlo- roquine (HCQ) and chloroquine have the same chemical basis. They also presents same cellular or molecular mechanisms of action **[4].** Current studies in the literature have projected the possible potential of these drugs as antiviral drugs to treat COVID-19 **[5].** An inhibitory effect of remdesivir (a new antiviral drug) and chloroquine (an old antimalarial drug) on the growth of SARS-CoV-2 in vitro study has been documented **[6].** Clinical trial conducted in COVID-19 Chinese patients, revealed that chloroquine had a very significant effect, both in terms of viral clearance and subsequently on clinical outcome, while comparing to their controls groups **[7].** It has been reported that Hydroxychloroquine (HCQ) therapy is significantly correlated with viral load reduction in patients of COVID-19 and its effect is reinforced by administration of azithromycin. So, HCQ, with or without azithromycin, has been studied as possible therapeutic agents for the patients of coronavirus disease 2019. Nevertheless, there is a very limited data on efficacy and associated adverse events associated with its usage in patients **[8].** Though, HCQ and azithromycin are generally well-tolerated medications administrated in clinics. They both can cause corrected QT (QTc) prolongation. Furthermore, observational evidences propose that COVID-19 itself disproportionately affects patients with underlying cardiac comorbidities and provokes myocardial injury **[9].** The current study aims to examine the degree of QT prolongation after administrating the drugs, hydroxychloroquine with azithromycin, in the treatment of COVID-19 infection in Bahria International Hospital, Lahore, Pakistan.

MATERIALS AND METHODS

Current study included twenty-six (n=26) COVID-19 positive subjects in this study after the approval from ethical committee of Bahria Town International Hospital, Lahore, Pakistan. Among these 26, 13 have been given hyroxychloroquinone

(HCQ) with azithromycin. Before including the patients, we thoroughly checked if the subjects were not suffering any G6PD deficiency, hepatic disease or porphyria. High dose of HCQ was given to the subjects. For 7 to 10 days the subjects received HCQ. At day one QT, QTc and QT/QTc intervals noted. Patients ECGs monitored very closely on day-by-day basis to avoid any abnormal prolongation of QT interval. After 7 to 10 days due do expected side effect of QT interval prolongation HCQ stopped and at the end of our study QT, QTc and QT/QTc intervals was again calculated to assess any abnormal findings. To analyze the data, statistical software SPSS (version 20.0) and The Mann-Whitney test was used to assess the continuous variables, with a *P* value of less than .05 to show the statistical significance.

RESULTS

Twenty-six (26) patients were diagnosed with COVID-19. The mean (SD) age was 50.54 (12.53) years. Among all these COVID-19 patients, 10 (43.5%) were males and 5 (38%) were females. 5% (38%) males were given the HCQ in comparison to 5 (50%). Likewise, 8 (61.5%) of females received HCQ in comparison to 5 (50%) of females. The most common comorbidities were hypertension 09 patients (69.23%) and diabetes mellitus 09 patients (69.23%) as shown in **Table 1**.

The overall mean Mean±S.D baseline/initial QTc was 347±155.052 milliseconds, and initial ratio (QT/QTc) was 0.7414±0.3336. However, final QTc and last QT/QTc ratio was 378.23±118.58 and 0.8545±0.2618, respectively. Among the 13 patients receiving HCQ having initial median (min-max) QTc 0.741 (0.00-0.96) was compared with the last QTc Median 0.8545 (0.79-1.06). However, a slight change has been observed between the initial and last QT/QTc ratio (0.741 (0.00-0.96, *p*=1.000) or 0.8545 (0.79-1.06, *p*=0.680), respectively) as shown in **Table 2**. However, the percentage difference that was observed between QTc and QT/QTc ratio was 8.55% and 13.8%, respectively.

Table 1: Baseline Characteristics of 26 Patients Who Initiated Hydroxychloroquine for COVID-19

		HCQ		Total
		Not Treated Group (n=10)	Treatment Group (n=13)	
Gender	Male	5(50%)	5(38%)	10(43.5%)
	Female	5(50%)	8(61.5%)	5(38%)
Diabetic	Not	6(60%)	4(40%)	4((30.7%)
	Yes	4(40%)	9(69.2%)	9(69.23%)
Hypertensive	No	5(50%)	4(40%)	4((30.7%)
	Yes	5(50%)	9(69.2%)	9(69.23%)

Table 2: Individual Changes in Corrected QT (QTc) Interval

		Mean±S.D	Median (Min-Max)	Mann-Whitney Test
Initial QT	Patients	302±136.58	302(0.00-416)	0.100
	Control	386.4±49.12	380.0(312-477)	
Initial QTC	Patients	347±155.052	347(364-436)	0.140
	Control	426.3±31.90	435.5(364-456)	
Initial Ratio (QT/QTC)	Patients	0.7414±0.3336	0.741(0.00-0.96)	1.000
	Control	0.9046±0.073	.883(0.81-1.05)	
Last QT	Patients	351.69±112.54	351.69(283-430)	0.100
	Control	386±64.96	381(283-493)	
LAST QTC	Patients	378.23±118.58	378.23(0.00-468)	1.000
	Control	423.90±35.41	428(336-466)	
Ratio Last (QT/QTC)	Patients	0.8545±0.2618	0.8545(0.79-1.06)	0.680
	Control	0.9078±0.0926	.8900(0.79-1.06)	

Table 3: The percentage change in the Initial final QT, QTc and and QT/QTc ratio

	Initial	Final	% Difference
QT	302	351	15.00765697
QTC	347	378	8.551724138
Ratio QT/QTc	0.74	0.85	13.83647799

DISCUSSION

Hydroxychloroquine (HCQ) has been used to treat patients with COVID-19. HCQ with azithromycin both have been used for the treatment of COVID-19. Both drugs have been documented to associate with the increased risk of QTc prolongation, however, the correct incidence in COVID-19 is still not known. Literature in last few years has provided the evidences of QT prolongation in response to HCQ and azithromycin therapy **[10]**. A study by Mercuro and colleagues reported that on hospitalizing 90 COVID-19 patients in Boston corrected QT (QTc) was measured before and after HCQ administration (400 mg/day, dosage after day 1). 53 received concomitant Azithromycin. The baseline median QTc was clearly found higher than normal (HCQ-alone group, 472 milliseconds; HCQ+AZ group, 442 milliseconds). 19% of these patients who received HCQ alone got QTc ≥500 milliseconds, a generally agreed-upon measure to discontinue or stop QT-prolonging drugs. For patients on combination treatment, 21% had QTc ≥500 milliseconds. In their study, 01 patient with multiple cardiac and respiratory complications experienced torsades de pointes **[11]-**. However, in our study we have NOT found the baseline QTc was longer or higher (347±155.052, p= 0.140) comparing to final/last QTc (378.23±118.58, p= 1.000) and was found not significantly changed. While speaking about the change in the QT/QTc ratio, our initial QT/QTc's mean was 0.7414±0.3336, *p*-1.000) comparing to last 0.8545±0.2618, p=0.680). Another study

by Bessière and colleagues reported on the QTc changes in response to HCQ administration. There were 40 patients in their study who were admitted in ICU and were receiving administered HCQ (400 mg/day for 10 days) either alone or in combination of Azithromycin (250 mg/day for 5 days; 55%). Baseline QTc was not prolonged in their cohort (median, 414 milliseconds). QTc ≥500 milliseconds was observed in 5% of those receiving HCQ alone and 33% of those receiving both medications **[12].** This also contradicts our findings that we have not seen any significant change in our patients **[13-24]**.

CONCLUSION

This research has partially revealed the realization about the consequence about the HCQ drug risk factor of initial QTc interval ratio and last QTc interval ratio in Bahria International Hospital of Pakistan. It is clearly showed from the results that this drug is insignificant factor of QTc interval in Bahria hospital Lahore, Pakistan. There is a dire need for large-scale studies before initiating COVID-19 therapeutics, with careful consideration to interactions of medicines, cardiac manifestations, routine electrocardiograms (ECG) monitoring.

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CONFLICT OF INTEREST

Authors declare no conflict of interests.

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