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ORIGINAL ARTICLE

A Comparision of QT Interval Prolongation in Covid 19 Patients Treated with Hydroxycholoquin Alone and in Combination with Azithromycin

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ABSTRACT

Objective: The aim of this study is to compare the incidence of increase QT interval among COVID 19 patients treated with hydroxychloroquin alone and combination with azithromycin.

Study Design: Retrospective Cohort Study

Place and Duration: It is a multicenter study and conducted in cardiology departments of Farooq Hospital, Lahore, Govt Zakir Khan Shaheed Hospital Matta Swat and Category A Hospital, Batkhela Malakand for duration from March 2020 to February 2021.

Methods: Total 100 Covid-19 patients of both genders were enrolled in this study. Patients details demographics age, sex and body mass index were recorded after taking informed written consent. Patients were divided into two groups. Group I had 50 patients and received hydroxychloroquin and group II (50 patients) received hydroxychloroquin with azithromycin. Outcomes among both groups were assessed in terms of increase QT interval. Complete data was analyzed by SPSS 24.0 version.

Results: There were 32 (64%) males and 18 (36%) females in group I while in group II 30 (60%) males and 20 (40%) females. Mean age in group I was 57.65±9.87 years with mean BMI 28.18±4.23 kg/m^2 and in group II mean age was 61.09±6.26 years with mean BMI 29.18±6.53 kg/m^2. Hypertension was the most common co-morbidity found in 60%and 56% in group I and II followed by diabetes 26% and 28% among both groups. Prolong QTc was found among 10 (20%) cases in group I and in Group II 15 (30%) patients. Significantly QTc was increase in group II from 443.18±26.23 to 475.13±29.36 while in group I QTc increases from 442.37±33.25 to 468.09±26.37 ms. Among 15 cases in combination group 9 patients had change QTc of >500 milliseconds and 2 cases had QTc of > delta 60 ms while in monotherapy group 4 cases had change QTc of 500 milliseconds and 1 had > delta 60 milliseconds.

Conclusion: We concluded in this study that prolonged QTc and change of QTc was significantly higher in COVID 19 patients who received treatment with combination of hydroxychloroquin and azithromycin as compared to the patients who received hydroxychloroquin only.

Keywords: COVID 19, QTc interval, Hydroxychloroquin, Azithromycin

INTRODUCTION

Covid-19 spread rapidly from its origin in Wuhan, China to millions of people all over the world, causing a significant mortality rate, especially in patients with diabetes and congestive heart failure [1, 2]. When this pandemic was still in its infancy, there weren't enough clinical trials available, therefore guidelines suggested several therapies based on repurposing drugs, clinical trials and in vitro investigations, and on experiences from previous coronavirus outbreaks like SARS and MERS. Time and effort are needed to develop a definitive therapy or vaccination, however [3–6]. As well as Remdesivir and hydroxychloroquine, numerous other medications demonstrated antiviral activity in vitro. Hydroxychloroquine has been suggested to be more powerful than chloroquine by Yao and colleagues [7, 8]. Chloroquine and hydroxychloroquine were suggested as preventive drugs by Shah et al. [9]. Yet, clinical trials questioned the efficacy of hydroxychloroquine, and the National Institutes of Health (NIH) prohibited the use of hydroxychloroquine and chloroquine outside of clinical trials [10–12].

Treatments for the pandemic included hydroxychloroquine sulfate, which is used to treat malaria and autoimmune illnesses such as SLE and Rheumatoid arthritis. HCL inhibits virus fusion and entrance into cells, as well as acting as an antiviral agent in vitro [7,8]. Another cause is the immunomodulatory impact of hydroxychloroquine [13, 14]. This therapy, however, was met with some controversy.

When combined, hydroxychloroquine sulfate and macrolides, including azithromycin, impair the heart's normal electrophysiologic function. This can lead to QT prolongation, torsades de pointes and even death [15]. A risk evaluation is important due to the widespread and arbitrary usage of these medications. Patients with COVID-19 who were taking hydroxychloroquine with or without azithromycin were evaluated for QT prolongation risk and severity.

MATERIAL AND METHODS

This multicenterrandomized controlled trial was conducted at cardiology departments of Farooq Hospital, Lahore, Govt Zakir Khan Shaheed Hospital Matta Swat and Category A Hospital, Batkhela Malakand for duration from March 2020 to February 2021. Total 100 confirmed patients of Covid-19 via Real-time PCR of both genders were enrolled in this study.Patient's detailed demographics age, sex, comorbidities and body mass index were recorded after taking informed written consent. Patients who were hospitalized, received HQ or HQ plus AZ treatment, had a baseline electrocardiogram (ECG), and had at least 1 ECG after treatment were included in the study. Patients with acute renal failure and those allergic to chloroquin were excluded.

Patients were divided into two groups. Group I had 50 patients and received hydroxychloroquin monotherapy and group II (50 patients) received hydroxychloroquin with azithromycin. Outcomes among both groups were assessed in terms of increase QT interval. To standardise QT length according to the heart rates of the patients, ECG records were examined by a cardiologist and Bazett formula (QTc = QT / √RR) was used for those with heart rate within the range of 60-100/min, and Framingham formula (QTc = QT + 0.154 (1- RR)) was used for those with heart rate outside the range of 60-100/min. Prolonged QTc was defined as an increase of more than 60 milliseconds (ΔQTc> 60 milliseconds) in QTc intervals compared to the beginning or a QTc of 500 milliseconds or above. Complete data was analyzed by SPSS 24.0 version. Chi square test was done to compare the QTc value among both groups. P-value <0.05 was taken as significant.

RESULTS

There were 32 (64%) males and 18 (36%) females in group I while in group II 30 (60%) males and 20 (40%) females. Mean age in group I was 57.65±9.87 years with mean BMI 28.18±4.23 kg/m^2 and in group II mean age was 61.09±6.26 years with mean BMI 29.18±6.53 kg/m^2. Hypertension was the most common co-morbidity found in 60%and 56% in group I and II followed by diabetes 26% and 28% among both groups. (Table 1)

Table No 1: Baseline details of all the included patients

Variables	**Group I**	**Group II**
Mean Age (Years)	57.65±9.87	61.09±6.26
Mean BMI (kg/m)	28.18±4.23	29.18±6.53
Gender		
Male	32 (64%)	30 (60%)
Female	18 (36%)	20 (40%)
Co-morbidities		
Hypertension	30 (60%)	28 (56%)
Ciabetes Mellitus	13 (26%)	14 (28%)
Cardiovascular Disease	5 (10%)	5 (10%)
CLD	2 (4%)	1 (2%)

Prolong QTc was found among 10 (20%) cases in group I and in Group II 15 (30%) patients. (Figure 1)

Significantly QTc was increase in group II from 443.18±26.23 to 475.13±29.36 while in group I QTc increases from 442.37±27.25 to 468.09±26.37 ms. Among 15 cases in group II 4 patients had change QTc of >500 milliseconds and 1 cases had QTc Delta >60 ms while in group I 2 cases had change QTc of 500 milliseconds and 1 had Delta QTc>60 milliseconds. (Table 2)

Figure No 1: Incidence of prolonged QTc among both groups

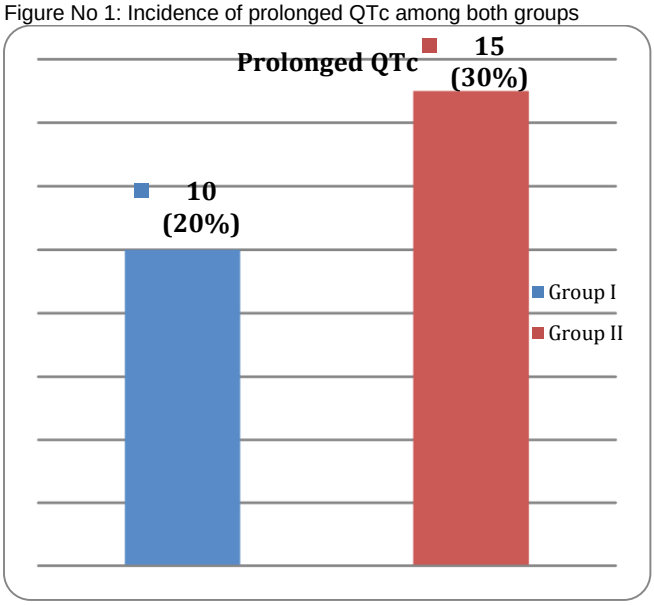

Table No 2: Changes in QTc among both groups

Measurement	Group I	Group II	P-value
Baseline QTc	443.18±26.23	442.37±27.25	
Post-treatment QTc	475.13±29.36	468.09±26.37	<0.05
Increased Prolongation			<0.05
>500ms	9 (18%)	4 (8%)	
>60 ms	2 (4%)	1 (2%)	

DISCUSSION

In the absence of a standard treatment, COVID-19 patients' treatment poses a severe dilemma over the world. In terms of patient management, clinicians are concerned about hydroxychloroquine and azithromycin's extended QTc and Torsades de Pointes [16-17]. Aiming to investigate the incidence of QTc prolongation in covid-19 patients receiving hydroxychloroquin and azithromycin, we conducted this study. 100 patients were enrolled in this study. 62 percent of patients were male, and the average patient age was 59.5814.34 years old. Male patients accounted for a large proportion of those who tested positive for covid-19, and the average age of the patients was 55 years old [18-19].

Both the HQ and HA groups show a substantial difference between pre- and post-treatment QTc readings. This difference appears to be more pronounced in both groups following therapy. Compared to pre-treatment measurements, both the HA group and the HQ group's QTc values were prolonged post-treatment. Compared to baseline values, the QTc times of patients who took hydroxychloroquine (HQ) and hydroxychloroquine with azithromycin (HA) were prolonged, but there were no ventricular arrhythmias that could have led to the discontinuation of treatment.

Patients with chronic inflammatory diseases have found hydroxychloroquine to be safe and well tolerated, according to the U.S. Food and Drug Administration [20]. Kv11.1 (HERG) blockade and QT prolongation are known effects of this medication, which is one of the preferred COVID-19 treatments. 14 The most common causes of arrhythmic toxicity are prolonged usage, QT-prolonging drugs (such as azithromycin), metabolic abnormalities (such as hypokalemia), kidney failure or acute overdose [21].

HQ is administered for a relatively brief period of time during COVID-19 treatment, according to the American Heart Association's guidelines (5-10 days). The drug should be used with caution in patients with known congenital prolonged QT syndrome and those who are also taking QT-prolonging drugs. Patients with severe renal failure should have their dosage lowered, and patients with electrolyte imbalance should only take this drug after the electrolyte irregularity has been corrected [22].

Many research were conducted on the effects of HQ and HA therapies on QTc during the COVID-19 pandemic. Forty-five percent of the patients treated in the intensive care unit received hydroxychloroquine alone (400 mg/day for 10 days) or hydroxychloroquine plus azithromycin (250 mg/day for five days). The QTc at baseline was not extended in this population (median, 414 milliseconds). QTc was observed to be less than 500 milliseconds in just 5 percent of individuals who received hydroxychloroquine and 33 percent of patients who took both medicines [23].

90 COVID-19 individuals were studied by Mercuro and colleagues to determine the association between hydroxychloroquine and QT. Patients who got hydroxychloroquine were given azithromycin at the same time. QTc was measured before and after hydroxychloroquine treatment in 53 of 90 patients. The median QTc at baseline was longer than usual (only hydroxychloroquine group: 472 milliseconds; hydroxychloroquine plus azithromycin group: 442 milliseconds). The QTc was less than 500 milliseconds in seven patients who took hydroxychloroquine alone (19 percent), while it was less than 500 milliseconds in 21 patients who got combination therapy. a patient with various cardiac and respiratory problems was revealed to have torsades de pointes [24].

In our study we found that among 15 cases in combination group 9 patients had change QTc of >500 milliseconds and 2 cases had QTc Delta >60 ms while in monotherapy group 4 cases had change QTc of 500 milliseconds and 1 had >60 milliseconds. These results were similar to some previous studies [25-26].

CONCLUSION

We concluded in this study that prolonged QTc and change of QTc was significantly higher in COVID 19 patients who received treatment with combination of hydroxychloroquin and azithromycin as compared to the patients who received hydroxychloroquin only.

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