Investigation of the Severity of Increased QT Interval Incidence in Young Patients with COVID-19

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ABSTRACT

Introduction: ECG abnormality is a major problem in COVID-19 patients, especially in theelderly, which can result in fatal dysrhythmias. In this article, QT interval prolongation was investigated in admitted Covid-19 patients of 20-50 years of age without any history of cardiac problems.

Methods: This study is a descriptive and analytical study. All consenting patients admitted to the hospital for Covid-19 infectionaged 20-50 years old entered the study.Patients wit hunderlying heart and kidney disease, history of taking any medication or cardiac dysrhythmias were excluded. An electrocardiogram was performed on admission and the third day of hospitalization.

Results: Theaverage length of hospital stay was 7.9 ± 3.68 days, and all patients had QT interval prolongation after 3 days, but no cardiac dysrhythmia occurred. Therewas no statistically significant increase in QTc interval for each drug usedalone, but the use of various drugs that affect the electrical conduction of theheart and also the presence of underlying inflammation, especially in patient'sheart cells can be the underlying cause of QTc interval prolongation. Many Covid-19 patients have QT interval prolongation. It can be due the infectionitself, the drugs used for treatment or viral myocarditis. The results of thepresent study showed that taking drugs such as kaletra even for 3 days cansignificantly increase the QTc interval in patients, so care should be taken inthe use of these drugs to avoid iatrogenic cardiac disease in patients, althoughin most cases the increase was mild and didn't cause mortality in patients.

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INTRODUCTION

In December 2019, there were reports of Pneumonia of unknown etiology which did not respond to common treatments in Wuhan, China. It was caused by a new genetically mutated virus from the coronavirus family called severe acute respiratory syndrome coronavirus 2 (SARS-COV0-2). It was called COVID-19 and, subsequently, the virus spread internationally.[1] The 2019 Corona virus pandemic is an unprecedented global public health challenge. So far, there is no known drug for the prevention and definitive treatment of this disease; yet, from the beginning of the epidemy, some drugs such as Hydroxychloroquine, Chloroquine, Azithromycin, Lupinavir and Ritonavir (kaletra) were used to reduce clinical signs and symptoms and viral load. Later, drugs such as ReciGen® (interferon beta-1a) and also Remdesivir (a newly known antiviral drug) were used. Administration of Hydroxychloroquine, Chloroquine and Azithromycin can increase the QT Interval and cause torsades de pointes and even sudden death.[2] Moreover, there have been reports of heart disease including myocarditis and dysrhythmia in patients with COVID-19.[3] In addition to the effect of drugs, patients with COVID-19 are at high risk for increased QTc interval due to severe inflammation, electrolyte imbalances, and also hypoxia. For instance, studies have revealed that although the appropriate dose of hydroxychloroquine is prescribed based on increased QTc interval, there is still some degree of QTc interval prolongation in patients with COVID-19.[2, 4]

Covid infection has numerous effects in cardiac and vascular system, such as arterial and venous thrombosis, hypotension and cardiogenic shock, myocardial infarction…. Moreover, it is reported that in the course of the COVID-19 pandemic, significant decline in rates of admissions in hospital for myocardial infarction (ST–segment elevation infarction) and other acute coronary syndromes and also a concerning increase in out-of-hospital cardiac arrests has been reported.[4] Unfortunately this may be a worldwide experience, leads to more cardiac death, and similar studies reported that from multiple countries around the world.[5] These data suggest that during COVID-19 pandemic, health care be witness in fewer complain of acute coronary syndromes in emergency departments and more out-of-hospital

cardiac events. On the other hand, disappointment to search for appropriate emergency cardiac care leads to increased number of cardiac arrests and deaths, more than the expected average during this period of time, with worse consequences among those who ultimately do seek care. Admission rates for MI may be goes back to baseline, recent information suggested that[6] but results will improve only if patients search for hospital systems and care promptly are not overwhelmed by COVID-19 surges.

It seems that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enter through the upper respiratory tract, and then bind to the angiotensin-converting enzyme 2 (ACE2) receptor, which is plentiful in the endothelium of veins and arteries along with the respiratory tract epithelium. This may clarify why hypertension and other cardiovascular conditions associated with adverse results in covid patients.[7] Other factors such as systemic inflammation, or hypoxia may lead to bad outcome in these patients, in addition to ACE2 receptor effects. On the other hand, covid in some patients rather than their severity of infection, influences on myocardium. A recent study which checked biomarker and cardiac magnetic resonance (CMR) imaging among 100 patients after recovery from confirmed COVID-19 infection, revealed that left ventricular volume was greater and ejection fraction was lower than that of a control group, this is despite that 67% of patients did not need hospitalization during their acute phase of disease. Moreover, 78%of patients had elevated T1 and T2 signals in CMR report and myocardial hyperenhancement abnormality in myocardial tissue, which was steady with myocardial edema and inflammation, 3 of them had evidence of active lymphocytic infiltration in myocardial biopsy. Elevated levels of high-sensitivity troponin T was seen in 71 patients.[8]

So according many reports, myocardial inflammation due to covid infection should be one of the most important differential diagnosis in these patients with cardiac problems (9, 10). In a study, 7.2% of patients with COVID-19 had cardiac dysrhythmia, most of whom were admitted to the intensive care unit. Common dysrhythmia include atrial fibrillation, atrial flutter, and ventricular tachycardia.[11] In van den Broek and colleagues' study, reported that A-fib were seen in 11% of population first ECG, this patients received antiviral remedies before[12] also, Saleh et al demonstrated 8.5% of patients developing atrial fibrillation after receiving treatment.[13] In a study by Deng et al, that was retrospective cohort in Wuhan, China researchers evaluated 112 patients with severe COVID-19 infection, which they were suspicious for possible myocardial injury, they recognized 12.5% of patients as suspected myocarditis based on American Heart Association's criteria. Abnormal ECG (i.e., ST-T changes) was detected in 22 cases of these patients, and two of them were possible myocarditis. Based on ECG and echocardiography results, the writers concluded that the myocardial injury is probably due to the systemic effects of disease more than the COVID-19 virus itself.[14]

Also, a case report in Italy studied myocarditis in the setting of COVID-19. This patient, according to Lake Louise's criteria had acute myocarditis. On his/her ECG, changes concluded diffuse ST elevations which was minimal, and were more significant in lateral leads and inferior leads, also had T inversion in aVR and V1 and synchronized ST depression (15). In a study, Myocardial infarction (MI) was detected in 44% Covid patients, they claim that 50% of all patients experienced angiography, whereas 56% of them had a myocardial injury but non- coronary, and six of them, presented signs of coronary obstruction. 72% of them were died, which 9 of them due to non-coronary myocardial damage, and 4 of them due to MI.[16] Various studies, reported different patterns of ST-T changes, but most of ECG findings, reported that these findings may be not related to medications, and might also be result of the potential injuries because of virus, but the evidence is still under disagreement. These forms might show the way of cardiac involvement and improve physicians in the management of ECG changes of COVID-19 patients. So, it is important to take strict attention to the variety of ECG findings in this patient. However, more studies needed to find other specific confounders, such as cardiac comorbidities.[9],[15]

These findings show different type of covid effect on the patient's heart. The question to be answered in the present study is whether the use of these drugs in young patients without risk factors for heart disease, will worsen the heart condition and increase the risk of dysrhythmia following an increase in QTc interval or not.

METHODOLOGY

The current study is a descriptive-analytical study approved by the Shahid Sadughi University of Medical Sciences Medical Ethics Committee with the moral code: IR.SSU.MEDICINE. REC.1400.003. Study was done in march 2019. All patients aged 20 to 50 years with covid-19 infection admitted to infectious disease ward or Emergency Room (ER) holding unit of Shahid Sadughi hospital, Yazd, Iran entered the study. The diagnosis of covid- 19 infection was based on clinical signs and symptoms, history of COVID-19 disease in the patient, his/her family or close contacts, CT scan findings, positive PCR for SARS-COV2 and the presence of lymphopenia. The diagnosis of COVID-19 was made by an emergency medicine physician and/or an infectious disease specialist. The researcher attended the patients' bedside on the admission day and the third day of hospitalization. After obtaining their consent, she took an ECG from the patients. The patients were treated by a specialist without the intervention of the researcher. Exclusion criteria were as follows: the presence of underlying heart and kidney disease, history of taking any medication, history of cardiac dysrhythmias, a negative PCR test, and non-consenting patients. Then both ECGs of the patients were examined and the amount of QTc Interval in lead V2 was calculated according to formula $QTC = \frac{duration}{\sqrt{RR\,\mathrm{int}\,erval}}$. Besides, the following information was extracted from patient's chats: patient's blood oxygen saturation at the time of admission, the serum level of electrolytes, the type of medication used, and the patient's demographic information. Eventually, the data were imported into the SPSS version21 and analyzed using multivariance, ANNOVA and student T-test.

RESULTS

The present study was conducted on 51 patients with COVID-19 admitted to Shahid Sadoughi Hospital in Yazd. The patient's demographic information is as follows: 18 (35%) patients were female with mean age of 42.06±7.46 years and mean hospital

stay of 8.17 ± 3.5 days. 33 (65%) patients were male with mean age of 44.06 ± 7.0 years and mean hospital stay of 7.76 ± 3.82 days. The mean age of patients was 43.35 ± 7.16 years and the mean hospital stay time was 7.9 ± 3.68 days (Table 1).

Patients went under special treatment for their infection, they gave some drugs that affected QTc interval. ECG was done at the first day of interval and then, after three days, the second ECG was tacked. Mean QTc interval in both of ECGs were measured as you see them in Table 2.

The mean QTc interval on the admission day was 366.25±28.26 milliseconds. The mean QTc interval on the third day was 386.74±36.15 milliseconds. There was a statistically significant difference between QTc interval on the first and third day of hospitalization.

The mean QTc interval on the admission day for men was 363.45 milliseconds and for women was 371.39 milliseconds. The mean QTc interval on the third day for men was 386.73 milliseconds and for women was 386.78 milliseconds (Figure 1).

Almost all of patients received pantoprazole, Dexamethasone, Vit C And Acetaminophen as supportive treatment, but antiviral Drugs such as Remdesivir, Favipiravir, Hydroxy chloroquine (HCQ) and KaletraTM were prescribed according to patient severity of disease and physician`s guide, as well as Antibiotics. Other drugs such as salbutamol, promethazine and ondancetron were prescribed person to person (Figure 2).

Additional findings

In group which difference in QTc interval between the first and the third days was 20 to 40 milliseconds:

Favipiravir and interferon were used by about 6 patients in the group in which the difference in QTc interval was 20 to 40 milliseconds between the first and the third day while in only 4 of them, Remdesivir was used. Meropnem has been used in 6 of these patients due to pneumonia. Their serum calcium levels were in the normal range. Patients' blood oxygen saturation levels ranged from 77% to 94% upon admission. Two of the patients died, one on the 4th day and the other on the 11th day of hospitalization; yet, no dysrhythmia or cardiac complaints were reported about these patients before death. Then, the information obtained was analyzed by the ANOVA test and the following results were obtained (Table 3).

In group which difference in QTc interval between the first and the third days was 60 milliseconds or more:

The following were observed: Remdesivir and interferon were used jointly in all patients, together with one of the antiviral drugs Favipiravir or Kaletra (lopinavir/ritonavir), which has been used before. No cardiac events or torsades de pointes (TDP) have been reported in the patients. (Of course, these patients have not been under constant cardiac monitoring. In case of heart complaints such as palpitations, ECG was taken again, which did not happen in these patients).

From all of patient Blood calcium and magnesium was checked because of their weakness, or their underline disease such as diabetes or renal insufficiency, and level of them was in normal range in these patients. The initial blood oxygen saturation of these group patients was higher than 88% (Table 4).

The mean QTc interval in patients receiving interferon was 383 milliseconds on the first day and 396 milliseconds on the third day.

The mean QTc interval in patients receiving kaletra was 382 milliseconds on the first day and 393 milliseconds on the third day.

The mean QTc interval in patients receiving remdesivir was 379 milliseconds on the first day and 390 milliseconds on the third day.

The mean QTc interval in patients receiving interferon, remdesivir and kaletra together was 371 milliseconds on the first day and 403 milliseconds on the third day.
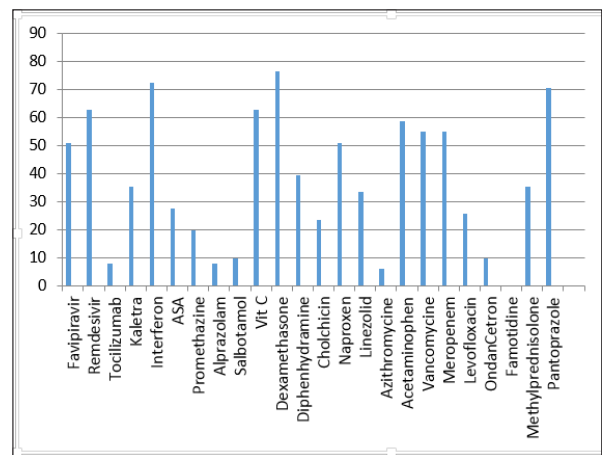

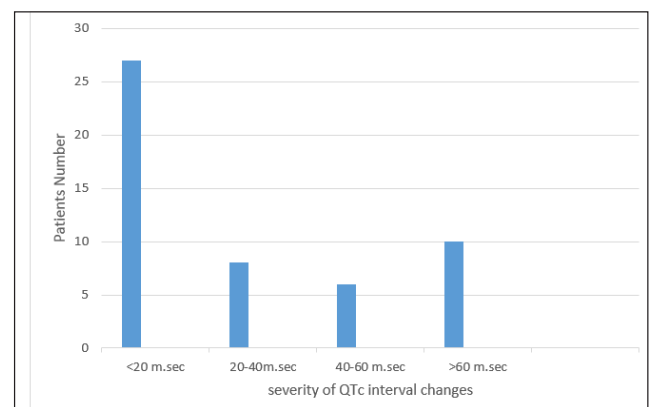**Figure 1:** Frequency of each drug taken by patients with COVID-19

Figure 2: Severity of QTc interval changes in patients with COVID-19 on the first and third days of hospitalization, and frequency of each group (m.sec: milliseconds)

Table 1: Patients' demographic information

	No. of patients	Age (year)	Hospital stay (day)
Female	18	42.06±7.46	8.17±3.5
Male	33	44.06±7.0	7.76±3.82
Total	51	43.35±7.16	7.9±3.68

Table 2: Mean QTc interval of patients at the time of admission and on the third day

	Mean QTc interval on admission	Mean QTc interval on the third day	P-value
Female	371.39	386.78	>0.05
Male	363.45	386.73	
Total	28.26±366.25	386.74±36.15	

Table 3: Characteristics of patients whose QTc 2 interval was higher than normal (QTc 2> 450)

Age (year)	Gender	QTc 1 interval	QTc 2 interval	Oxygen saturation	Hospital stay day)	Drugs used	Electrolyte imbalances
40	Female	420	464	%88	8	Kaletra/ Interferon/ Ondancetron/ Remdesivir /levofloxacin/meropnem	Ca: 7.5 P: 3.5
44	Femal e	420	461	%94	5	Kaletra Interferon/ Ondancetron/Remdesi vir/ linezolide	Ca: 8.5 P: 3.8

Table 4: The QTc interval of the intended drugs

Intended drug	QTc interval		P-value
	On admission	On the 3rd day after admission	
Interferon	383	396	0.20
lopinavir/ritonavir	382	393	0.30
Remdesivir	379	390	0.20
Simultaneous consumption of I+K+R	371	403	

I: interferon, K: kaletra (lopinavir/ritonavir), R: remdesivir

In order to decrease the effect of cofounding variables (the other drugs and serum electrolytes) multivariance analysis was performed. Interferon (p value: 0.2), kaletra (p value: 0.3) and remdesivir (p value: 0.2) didn't cause a statistically significant increase in QTc interval alone but a combination of these drugs caused a significant increase in the QTc interval. This shows synergetic effect of multiple drugs in increasing the QTc interval.

DISCUSSION

There are many evidences during covid pandemic showing that dysrhythmias are one of the main complications among infected patients, this may be because of infection or drug side effects [17]. Pallotto et al paper reported about transient bradycardia in patients with coronavirus-19 disease (COVID-19) receiving remdesivir, as we know, remdesivir is a novel and specific antiviral agent which was approved for the treatment of severe COVID-19 in addition to dexamethasone and heparin infusion. This drug has antiviral activity which is approved for Ebola infected patient's treatment too. In Covid-19 patients, remdesivir shows shortening of patient recovery time, but it cannot reduce the mortality rate. They suggested that this may be due to other factors, such as toxicity of the drug itself, increase in severity and progression of the disease in patients receiving remdesivir, adverse drug interaction between the used drugs. [18-20]

In the study conducted by O'Connell TF et al among 415 patients who received concomitant HCQ/AZM, the mean QTc increased was from 443 ± 25 milliseconds to a maximum of 473 ± 40 ms. 87 [21%] patients had a QTc ≥500 milliseconds. Factors associated with QTc prolongation ≥500 ms were age (p < 0.001), body mass index <30 kg/m2 (p = 0.005), heart failure (p < 0.001), elevated creatinine (p = 0.005), and peak troponin (p < 0.001). like our study no mortality occurred.[1] Many studies reported QTc prolongation following antiviral drugs consumption [21]. In Rav-Acha and et al study 7.2% of patients had cardiac dysrhythmia during hospitalization. There was a significant correlation between disease severity and arrhythmia prevalence.[2]

Diaz-Arocutipa and et al concluded that COVID-19 patients treated with hydroxychloroquine or chloroquine with or without azithromycin had a relatively high prevalence and risk of QTc prolongation. However, the prevalence of dysrhythmic events was very low.[3] Despit many reports about remdesivir cardio toxicity, Szendrey mentioned that QT prolongation may not be because of remdesivir consumption. And it is a significant result of HCQ[22, 23] and [24]. In a systematic review study, mentioned that QT prolongation during monotherapy occurs not as much of combination therapy, but it reported very rare dysrhythmia because of that.[25] COVID-19 infection can cause complications such as myocarditis which can cause changes in the electrocardiogram, including changes in the QTc interval.[26], [10] A retrospective study in Wuhan, China, showed that ST-T abnormalities (40%), dysrhythmias (38%), and then coronary vascular disease were the most common ECG changes in Covid-19 patients, at the beginning of admission. This finding shows extensive effect of Covid-19 virus on electrocardiography of patients but there was no report of QT prolongation at the first of hospital admission.[27]

On the other hand, it is reported in William Regan paper that chidren with multisystem inflammatory syndrome (in children) (MIS-C) due to covid 19 infection, had abnormality in their EKG findings too, these findings were: low amplitude ECGs, transient T-wave inversion particularly in the precordial leads. But the prevalence of ST-segment changes and tachydysrhythmias was rare among these patients. This finding emphasized on virus effects on cardiac electric and conduction system.[28]

Many studies have discussed the effect of various drugs on the QTc interval of patients, including Kaletra(lopinavir/ ritonavir), Interferon and Remdesivir. In the present study, all patients studied were under 50 years of age, had no prior known heart disease were not taking any medication other than COVID19 treatment. The results of the present study showed that taking the aforementioned drugs even for 3 days can significantly increase the QTc interval in patients, although in most cases the increase was mild and was not a cause of mortality in patients. The use of these drugs can quickly lead to an increase in the QTc interval in the ECG even in young people; hence, regardless of the age of patients, care should be taken in the use of these drugs to avoid iatrogenic heart disease in patients. The results of the multivariance analysis performed suggested that there was no statistically significant increase in QTc interval for each drug used alone, but the use of various drugs that affect the electrical conduction of the heart and also the presence of underlying inflammation, especially in patient's heart cells can be the underlying cause of QTc interval prolongation. Consequently, it is recommended that in future studies, researchers study the effect of COVID-19 infection alone on the electrical conductivity of the heart.

LIMITATIONS OF THE STUDY

The patients under study had all taken drugs for the treatment of Covid-19 before being hospitalized, which may have affected the patients' QTc interval, but were not included in this study. However, the initial QTc interval of all patients was checked and all were normal. The reason for using two types of antiviral drugs in these patients which have been prescribed by infectious disease or internal specialists was probably the critical condition of patients. This study was done during 2nd pick period of covid disease, and may be the treatments performed, was not in line with new protocols, because of our poor knowledge of covid disease and therapy at that time.

SUGGESTIONS

Most of QTc interval prolongation in our study was mild so if the patient has a sever prolongation of QTc interval other causes of QTc interval prolongation such as electrolyte disturbance or cardiac involvement with the virus should be considered. In order to quickly diagnosis and treat dangerous cases of QTc interval prolongation we suggest careful monitoring of QTc interval in all covid-19 patients receiving drugs such as remdesivir, kaletra, Hydroxychloroquine and Chloroquine.

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