The Effect of Chest Computed Tomography Findings on QT Interval in Patients with COVID 19 Using Drugs That May Prolong QT Interval

Abstract

Background

Some drugs used in the treatment of coronavirus disease 2019 (COVID-19) are likely to increase the risk of QT interval prolongation and related arrhythmias or death. Due to the low sensitivity of the reverse transcriptase-polymerase chain reaction (RT-PCR) test, chest computed tomography (CT) imaging is being used for COVID-19 diagnostic correlation and to evaluate whether there is pneumonic involvement in the lung.

Objective

In this study, we aimed to compare whether there was a difference in terms of QT interval prolongation and effect on heart rate in COVID-19 patients based on their chest CT findings and drug treatment regimes.

Methods

This was a single-center retrospective cohort study of non-intensive care unit (ICU) patients hospitalized . A total of 344 patients with a mean age of 46.34 ± 17.68 years were included in the study (56.1% men). Patients were divided into four groups according to their chest CT results as having typical, atypical, indeterminate, or no finding of pneumonic involvement. Mean QTc intervals and heart rates calculated from electrocardiograms at admission and after treatment were compared.

Results

There were no significant differences between groups with regards to age, gender, and body mass index (BMI). There were also no significant differences between the groups in terms of mean QTc interval values upon admission (p:0.127) or after treatment (p:0.205). Heart rate values were similar among the groups as well, with no significant differences in mean heart rate on admission (p:0.648) and post-treatment (p:0.229) ECGs.

Conclusion

This study has demonstrated finding of COVID-19 infection based on chest CT does not affect QT interval prolongation and bradycardia in non-ICU COVID-19 patients. There is a need for additional larger studies investigating the effect of chest CT findings on QT interval prolongation and bradycardia in COVID-19 patients.

What is already known about this topic?

-QTc interval prolongation can be observed more frequently in patients with critical disease or those being followed-up in the ICU, due to the higher number of risk factors (female gender, a history of acute myocardial infarction, presence of hypokalemia, presence of heart failure, use of two or more drugs to prolong QTc, presence of sepsis, advanced age (> 68), a QTc interval ≥ 450 ms on baseline ECG, and use of loop diuretics), and the increased pharmacodynamic and pharmacokinetic drug-drug interactions due to increased drug use.

- In COVID-19 patients, there is a significant relationship between pulmonary involvement scoring in chest CT and the need for intensive care, intubation and mortality.

- According to the RSNA classification, the type of lung involvement is not a mortality predictor.

What does this article add?

-Although qt interval prolongation is more common in patients with critical disease, it was observed in our study that the presence and type of lung involvement in COVID-19 patients who do not need intensive care has no effect on qt interval prolongation.

- Drugs that can prolong the qt interval given to COVID-19 patients who do not need intensive care are safe in terms of arrhythmic events and death.

Introduction

Several unidentified cases of viral pneumonia were reported in Wuhan City, Hubei Province, China, in December 2019 (1). An RNA virus from the coronavirus family was identified in samples taken from the respiratory tract of these patients. The International Virus Taxonomy Committee named this virus, which caused the pneumonia epidemic in China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) defined this disease as coronavirus disease 2019 (COVID-19) on February 11, 2020 (2) and declared a pandemic on March 11, 2020. Since that time, more than 100 million cases and over 2 million related deaths have been recorded.

Since emergence of the disease in China, reverse transcriptase-polymerase chain reaction (RT-PCR) has been used for diagnostic criteria based on WHO guidelines. According to published data on RT-PCR in the first stages of the epidemic, the sensitivity of the test was stated to be between 30% and 60% (3,4). The quality of the test kits and sampling were among the reasons for the low sensitivity reported. Chest computed tomography (CT) has been used with RT-PCR testing in many centers due to its high

sensitivity in detecting COVID-19 even without clinical signs of pneumonia in the early stages of the epidemic (4). Although, as of March 2020, the American College of Radiology suggests that chest CT should not be used as the first step for diagnosis of COVID-19 (5), since results can be obtained faster and the sensitivity of the RT-PCR test is low, chest CT is still used extensively in practice to provide earlier treatment and isolation in suspected COVID-19 cases.

Many medications have been used to treat COVID-19 since the outbreak started, but an effective treatment has not been found in almost two years. Hydroxychloroquine (HCQ), a drug used as an antimalarial and antirheumatic at the beginning of the epidemic, has been used in the treatment and prevention of COVID-19 (6). Azithromycin, which is an antibiotic from the macrolide group with immunomodulatory and anti-inflammatory effects, has also been used for treatment (7). For cases of atypical pneumonia that could not be distinguished and with the addition of secondary infection, moxifloxacin, an antibiotic from the fluoroquinolone group has also been included in the 'Republic of Turkey Ministry of Health (TR MoH) COVID-19 Treatment Guide'. Favipiravir, an RNA polymerase inhibitor shown to be effective in the treatment of other RNA viruses, especially influenza and Ebola, is also used for treatment. When these drugs are used, prolongation of the QT interval may cause cardiac side effects.

Arrhythmias and other cardiac complications may occur in patients with COVID-19. Drugs used in treatment such as HCQ, azithromycin, and moxifloxacin may also increase the risk of arrhythmia. In addition, cardiac arrhythmias are observed more frequently in patients with more severe COVID-19 disease (8).

In this study, we aimed to compare whether there was a difference in terms of QT interval prolongation and effect on heart rate in COVID-19 patients based on their chest CT findings and drug treatment regimes.

Materials and Methods

This study was a retrospective study of patients who were hospitalized and had started medical treatment based on a possible diagnosis of COVID-19 according to the TR MoH COVID-19 treatment algorithm (9). Patients over 18 years of age, with a positive airway RT-PCR test, chest CT imaging, Electrocardiography (ECG) before starting treatment and on the 5th day of treatment, and treated with only HCQ, HCQ/azithromycin, HCQ/moxifloxacin, or HCQ/favipiravir combinations were included in the study. According to the hospital protocol created under the guidance of TR MoH COVID-19 treatment recommendations and literature data, the patients were administered 5 days of treatment with a total dose of HCQ 400 mg orally twice a day as the loading dose on the first day and 200 mg twice a day on

following days. In patients with signs of pneumonia, azithromycin was administered 500 mg orally once a day or favipiravir 1600 mg orally twice a day on the first day as a loading dose, and then 600 mg orally twice a day on the following 4 days as a maintenance dose. Moxifloxacin was administered intravenously 500 mg once a day for 5 days to patients with suspected atypical pneumonia and/or findings of secondary infection. The daily blood calcium, magnesium, and potassium levels of the patients were measured, and electrolyte replacement was performed in patients with electrolyte imbalance.

Patients under 18 years of age, those with 500 ms QTc intervals and/or a heart rate below 50/min at baseline ECG, or without baseline and day 5 ECGs, using drugs to prolong QT concurrently with bundle branch block or QRS > 120 ms, with chronic renal failure (approximately glomerular filtration rate <60 ml/min according to the Cockcroft-Gault formula), and those with atrial fibrillation were not included in the study.

All patients included in the study had 12-channel ECGs recorded at a speed of 50 mm/sec. (Nihon Kohden ECG 1250, Tokyo, Japan). ECGs were taken before treatment and on the 5th day. Rhythm, heart rate, bundle branch block, QRS distance, QT interval, and QTc interval were recorded and calculated according to Bazett's formula ($QTc = QT \div \sqrt{RR}$). The Framingham method was also used in patients with heart rates above 100/min. ECG measurements of QT intervals and heart rate were performed by two cardiologists blind to the patient data.

In addition, patients' age, gender, body mass index (BMI), accompanying comorbid conditions, laboratory values of creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive peptide (CRP), angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker, antihypertensive use, and prognosis were recorded. Patients with missing data in their files were searched and their data were completed.

RT-PCR tests were conducted from nasopharyngeal and oropharyngeal swabs (SARS-CoV-2, qPCR Detection Kit by Bio-Speedy, Istanbul, Turkey). Imaging of all patients was performed in the supine position throughout the end of inspiration, based on conventional CT scans (Somatom go.Now; Siemens Healthineers). Because the study was retrospective, a standard CT protocol was not used. All CT images were 1.25 mm sections and multiplanar images were reformed. In the radiology clinic of our center, lung findings on chest CT images of COVID-19 patients were classified as typical, atypical, indeterminate, or negative according to the 'Expert Consensus Statement Classification of the Radiological Society of North America (RSNA). The reporting of COVID-19-related chest CT findings was

as follows: **Typical appearance** = peripheral, bilateral, ground-glass opacity (GGO) with or without consolidation or visible intralobular lines (crazy-paving), multifocal GGO of rounded morphology with or without consolidation, or visible intralobular lines (crazy-paving), reverse halo sign or other findings of organizing pneumonia (seen later in the disease); **Indeterminate appearance** = multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and nonrounded or nonperipheral, few very small GGO with a nonrounded and nonperipheral distribution; **Atypical appearance** = isolated lobar or segmental consolidation without GGO, discrete small nodules (centrilobular, tree-in-bud), lung cavitation, smooth interlobular septal thickening with pleural effusion; and **Negative for pneumonia** = no CT features to suggest pneumonia (10).

Approval of the TR MoH COVID-19 Research Assessment Commission and the Ethics Committee of Celal Bayar University (Istanbul, Turkey) was obtained for the study.

Statistical analysis was performed using the IBM SPSS Statistics 26 program, and figures were constructed using GraphPad Prism 8. Baseline demographic and clinical characteristics of all participants at the time of admission were presented as means (standard deviations) for continuous variables and as frequencies (percentages) for categorical variables. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test in cases where applicability conditions were not met. Continuous variables were compared using paired or unpaired Student's t-tests or non-parametric Wilcoxon rank-sum tests if the normal distribution of the variables could not be demonstrated. The Shapiro-Wilk test was used to check whether the continuous variables were distributed normally.

Results

A total of 344 eligible patients were included in this study. Clinical characteristics of the study population are presented in Table 1. Median follow-up for the cohort was 8 days (range 5-12). The study sample consisted of 56.1% males with an average age of 46.34 years. Mean BMI (calculated as weight in kilograms divided by height in meters squared) was 26.72 kg/m^2. The prevalence of medical comorbidities was substantial, as 11.3% of patients had a history of hypertension, 12.2% had a history of diabetes mellitus, 4.9% had a history of coronary heart disease, 0.8% had a history of heart failure, and 10.7% had a history of chronic obstructive pulmonary disease. In addition, 19.4% of patients were smokers. Laboratory test results are reported in Table 1. All patients received HCQ, 15 (4.4%) patients received HCQ plus azithromycin, 146 (42.4%) patients received HCQ plus moxifloxacin, and 17 (4.9%) patients received HCQ plus favipiravir.

Patients were divided into four groups according to their chest CT findings as negative, indeterminate, atypical, or typical. When we compared age, gender, and BMI, there were no significant differences between the groups. Although diabetes was observed at a lower level in patients with atypical chest CT findings compared to the other groups, there was no significant difference between the groups in terms of other comorbid conditions. Hemoglobin levels were slightly lower in patients with indeterminate chest CT findings, but no anemia requiring erythrocyte transfusion was observed in any group. Serum creatinine, potassium, AST, ALT, WBC, and CRP levels were also similar between groups. When we evaluated the groups in terms of treatment regimens, no statistically significant difference was observed. According to chest CT findings, 44% of the patients in the negative group, 54.5% in the indeterminate group, 46% in the atypical group, and 50% in the typical group received HCQ alone.

Electrocardiographic parameters of the study population according to chest CT findings at admission and after 5 days of treatment are shown in Table 2. There was no significant difference between the groups in terms of mean QTc interval values at the beginning of treatment (p:0.127) and after the treatment period (p:0.205). We also observed similar findings in heart rate changes, as no significant changes in mean heart rate were observed among the groups on admission (p:0.648) and post-treatment (p:0.229) ECGs. The mean change in QTc (Δ QTc – the difference between control and baseline QTc) for the negative group was 22.38 ± 17.46 ms, the indeterminate group was 17.12 ± 16.72 ms, the atypical group was 17.71 ± 18.45 ms, and the typical group was 21.21 ± 23.64 ms. There was no statistically significant difference between the groups in terms of Δ QTc (p:0.236) (Table 2, Figure 1).

Out of 344 patients with serial ECGs, QTc intervals ≥ 500 ms were observed in 6 (1.74%) after treatment. Chest CT findings of 4 of these patients were typical, 1 was atypical, and 1 was indeterminate. There were no instances of ventricular tachycardia, ventricular fibrillation, or significant conduction delay during follow-up.

Discussion

In this study we divided patients in to the four groups according to their chest CT findings as a typical, atypical, indeterminate or negative. We aimed to investigate whether QT interval prolongation and bradycardia develop in patients receiving medical treatment for COVID-19, which can prolong the QT interval and cause bradycardia (HCQ, azithromycin, moxifloxacin, favipiravir). There was no significant difference in the drugs used in all groups when separated according to their chest CT findings. There was significant QT interval prolongation after medical treatment in all groups, but no significant difference was found

between the groups in terms of QT interval prolongation and bradycardia after medical treatment.

COVID-19 is a highly contagious infection; therefore, diagnostic methods should be fast and reliable. Early diagnosis and treatment reduce morbidity and mortality rates. Patients, especially those who are asymptomatic, can be isolated by early diagnosis and the transmission rate in the community can be reduced. Since the sensitivity of the RT-PCR test, which was used as a diagnostic method in the early stages of the epidemic, was around 60%, chest CT imaging has become an additional diagnostic method routinely used in many centers due to its sensitivity of over 90% and its rapid results (4). In addition, chest CT imaging greatly contributes to monitoring the progression of the disease and evaluating the effectiveness of treatment (5).

Although a long period has passed since the beginning of the epidemic and many treatment methods have been used, the desired level of success has not yet been achieved and current treatments have side effects. One of these side effects is QT interval prolongation, which forms the basis of our study. HCQ, which is used as an antirheumatic and antimalarial drug, has been used extensively in the early stages of the epidemic, but contradictory study results have been published. With the recommendation of the WHO, HCQ is no longer used in many countries, but it is still in the COVID-19 treatment guide in Turkey. Although it prolongs the QTc interval in patients when used for COVID-19, it has been shown to rarely cause arrhythmias (11). Azithromycin, a macrolide group antibiotic with known immunomodulatory and anti-inflammatory effects, has been shown to reduce viral load more when combined with HCQ for the treatment of COVID-19 (12). While it has been shown to significantly prolong the QTc interval, the incidence of associated malignant arrhythmia and arrhythmic death is quite low (13). For patients with clinical suspicion of COVID-19 and signs of atypical pneumonia on chest CT, in accordance with the TR MoH COVID-19 treatment guidelines, moxifloxacin, a broad-spectrum antibiotic in the fluoroquinolone group commonly used in atypical pneumonia cases, has also been used for treatment. Moxifloxacin causes QTc interval prolongation as do all fluoroquinolones (14). Favipiravir, an RNA polymerase enzyme inhibitor, was one of the first to be used in the treatment of COVID-19 from the antiviral drug group and is still an antiviral agent used extensively in Turkey. Although there are data showing that favipiravir, which is effective in the treatment of many RNA viruses, especially influenza and Ebola virus, has no effect on QT interval, there is also a case report stating that it can cause prolongation (15,16).

Independent risk factors for QTc prolongation are female gender, a history of acute myocardial infarction, presence of hypokalemia, presence of heart failure, use of two or more

drugs to prolong QTc, presence of sepsis, advanced age (> 68), a QTc interval ≥ 450 ms on baseline ECG, and use of loop diuretics (17). QTc interval prolongation can be observed more frequently in patients with critical disease or those being followed-up in the ICU, due to the higher number of risk factors mentioned above, and the increased pharmacodynamic and pharmacokinetic drug-drug interactions due to increased drug use (18).

In a study by Francone et al., the severity and prognosis of COVID-19 were compared with CT-based semi-quantitative pulmonary involvement scores. As a result of the study, a significant relationship was found between the severity of the disease and laboratory parameters such as CRP, D-dimer, and CT score. Also, a significant relationship between a high CT score and mortality were found to be predictive of increased mortality (19). Abbasi et al. similarly determined that a high chest CT score is an independent predictor of mortality. In addition, a significant correlation was found between chest CT score and the need for intensive care and intubation. However, when analyzed in terms of typical, atypical and indetermine involvement findings according to the RSNA classification, it was found that did not predict mortality, unlike the CT scoring (20). In a study by Barman et al., no significant relationship was found between the severity of disease and QTc interval prolongation in COVID-19 patients, but the number of patients with a QTc interval > 500 ms was found to be significantly higher in those with more severe disease (21).

Conclusions

A significant relationship has been found between the severity of pneumonic involvement in COVID-19 and the severity of the disease, intensive care need, intubation, and mortality. According to the RSNA classification, no data has shown a significant relationship between the presence of pneumonic involvement and typical, atypical, or indeterminate involvement findings, and the severity of disease and mortality. The patient groups in our study consisted of individuals whose disease was not severe and who did not require intensive care. Likewise, there were not many associated risk factors that would prolong the QT interval. As a result, we conclude that the absence or presence of typical, atypical, indeterminate pneumonic involvement according to the RSNA classification (regardless of the severity of the involvement) does not affect QT interval prolongation and bradycardia in non-ICU COVID-19 patients. Larger prospective studies are needed to evaluate the effects of treatments on QT interval and bradycardia using the scoring system that evaluates the severity of pneumonic involvement together with the RSNA classification in COVID-19 patients.

Limitations

Our target population was non-ICU patients and the severity of pneumonic involvement in ICU patients may be more severe, thus findings may differ from those of our patient groups. Also, not using a scoring system to calculate the severity of involvement in patients with pneumonic involvement is another limitation of the study.

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