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QT interval measurement with portable device during COVID-19 outbreak



Nerea Torres González ^{a,1,*}, Luis Álvarez Acosta ^{b,1}, Diego Valdivia Miranda ^{b,1}, Alejandro Iriarte Plasencia ^{a,1}, Virginia Barreto Cáceres ^{a,1}, Marx Rivera Zambrano ^{a,1}, Julio Salvador Hernández Afonso ^{b,c,1}

^a Department of Cardiology, Hospital Universitario Nuestra Señora de Candelaria (HUNSC), Santa Cruz de Tenerife, Spain

^b Division of Arrhythmia and Electrophysiology, Department of Cardiology, Hospital Universitario Nuestra Señora de Candelaria (HUNSC), Santa Cruz de Tenerife, Spain

^c Head of Cardiology Department, Hospital Universitario Nuestra Señora de Candelaria (HUNSC), Santa Cruz de Tenerife, Spain

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ABSTRACT

Coronavirus Disease 2019 continues to spread and to date, no definitive treatment is available. Overcrowded and under-resourced healthcare centres have had to design different strategies to treat these patients, what includes the control of the electrocardiogram (ECG), as some drugs that have been used to treat this disease may prolong the QT interval as a side effect. During the COVID-19 outbreak, we designed a protocol for monitoring the QT interval using a portable device with Bluetooth connectivity. After a validation study with 50 patients, we found a very good correlation between the QT interval measured both with this device and with the conventional body surface ECG. In this article, we provide a brief overview of the protocol and then analyse the QT changes observed in a group of patients during their hospitalization and treatment for SARS-CoV-2 infection. 81 patients with confirmed SARS-CoV-2 infection were enrolled in the protocol (age 63.4 SD 17.2 years; 70.3% men), while being treated with lopinavir/ritonavir, azithromycin and hydroxychloroquine, both individually or combined. Ten patients developed long drug-related QT interval, and the QT prolongation was statically significant for all treatment schemes. All patients with drug induced QT prolongation corrected the QT interval following the indications of the protocol, and no patients died of arrhythmic causes after its implementation. In our experience, a protocol for the electrocardiographic monitoring of these patients minimizes the risk of iatrogenic QT interval prolongation and consequently reduces sudden death events, and for that purpose, portable devices like the one used in this protocol may constitute a useful tool to minimize the contact with such patients.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has so far infected more than 21 million people. Authorities have reported more than 770,000 deaths worldwide, although the actual death toll is most likely much higher. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has made evident that we are more interconnected than what we believed and has made us remember our vulnerability to the microbial world. A disease, especially an infectious one, is not only a local problem but also a global issue, both in spreading and in searching for solutions. In order to find

effective treatments and ultimately, an effective vaccine, the whole scientific community is responsible for analysing and sharing data. As we have faced a new disease, the therapeutic options have been limited and even controversial. During the first months of the pandemic it was suggested that some immunomodulators, such as hydroxychloroquine or azithromycin, could help inhibit the replication of the virus [1,2], but further studies have found that these drugs have not only questionable clinical benefits in post-exposure prophylaxis and in improving clinical outcomes and survival [3,4] but also non-negligible side effects, such as the prolongation of the QT interval, that can lead to fatal arrhythmias (TdP) [5]. This undesired and harmful side effect can be further accentuated by some concomitant treatments with possible, conditional or known risk for prolonging the QT interval (e.g., used for symptomatic relief of digestive disorders also frequent in these patients, such as diarrhoea, nausea or vomiting; hypnotic treatments for acute confusional state; or added antibiotics for treating bacterial lung

* Corresponding author at: Ctra. Gral. del Rosario, 145, 38010 Santa Cruz de Tenerife, Canary Islands, Spain.

E-mail address: nereatorres@gmail.com (N.T. González).

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superinfection). We acknowledge that electrocardiogram (ECG) monitoring during respiratory isolation in the midst of a pandemic in overcrowded hospitals along with the lack of health professionals and protective equipment is a big challenge. Professionals of all medical specialties have been forced to stop their usual medical assistance work and join ranks to face the COVID-19 crisis. In this context, from the Cardiology Service of our hospital, we designed a protocol for the electrocardiographic control of patients with COVID-19 treated with drugs with known risks for prolonging the QT interval through a small portable and wireless device. Other groups have shown the accuracy of some portable devices for the measurement of the QT interval [6], but it appears that different results are obtained by different devices [7]. Before the implementation of the protocol, we performed a small study as a validation process in which we compared the corrected QT interval (QTc) measured in the conventional surface ECG and the same in the one single lead registry of KardiaMobile®. We found a very good correlation between the two methods [8], which allowed us to choose this device to perform the monitoring. The objectives of this study are to provide a brief overview of the electrocardiographic monitoring protocol and to show the QT changes observed in a group of patients treated with different therapeutic schemes during their hospitalization for SARS-CoV-2 infection.

2. Material and methods

2.1. The device

We used the device KardiaMobile 6 L (AliveCor Inc., United States) for the monitoring of the patients. It is a small and portable device which uses Bluetooth technology to send the electrocardiographic registry to a smartphone or a tablet (for both Android and iOS platforms).

KardiaMobile 6 L can perform a 6-lead ECG, but we chose the 1-lead ECG option, because in this modality, the device does not need to make contact with one of the inferior limbs, so it can be done without the patient's cooperation, in elderly patients with impaired mobility or dementia. There is one simpler device available by the same company that allows only the 1-lead ECG option, but we discarded that alternative because it does not use a Bluetooth connection and a closer range is needed to obtain the signal.

KardiaMobile 6 L has several important features that make it better suited for this purpose. It is small, easy to clean and to disinfect. It does not require patient cooperation as it can be done simply placing the device over the chest, and it provides a quick remote digital ECG; the device records 30 s of electrocardiographic registry by default, but the process can be interrupted after a few seconds. All these features make medical and nursing work easier, since the "signal receiving smartphone" is located in the "clean area".

2.2. Diagnosis of COVID-19

All patients enrolled in the study were diagnosed according to a protocol designed by a multidisciplinary team at our hospital, which was based on interim guidance from the World Health Organization [9]. The diagnosis of SARS-CoV2 infection was confirmed as a positive result in reverse transcriptase polymerase chain reaction (RT-PCR) of a nasopharyngeal swab.

2.3. Correlation between the QTc interval measured with KardiaMobile® and surface ECG

Before the implementation of the protocol, we performed a small validation study in 50 patients, 33 of which were infected

by SARS-CoV-2, and 17 were admitted to Cardiology Service for non-infectious diseases. We compared the QTc interval measured in lead V5 of conventional body surface ECG and the registry of one single lead with KardiaMobile® and found very good agreement between the two methods [7] (intraclass correlation coefficient of 0.902 was obtained, 95% CI, 0.811–0.950). We chose the V5 of surface ECG for the comparison as it is one of the recommended leads for QT interval measurement, since the P-QRS-T vector axis is in the direction of this lead. As the ECG with KardiaMobile® can be done both using the fingertips or placing the device over the thorax, we compared the QT interval in both ways, and no differences were found.

2.4. QTc measurement, reference values and selection of drugs with risk of prolonging the QT interval

To perform the protocol, we chose the placement of the KardiaMobile® over the left side of the thorax, below the nipple in men and under the breast in women, close to the apex of the heart. The performance of the ECG in this position was easier for the nurses, and it does not require the patient's cooperation. Furthermore, in this placement, the ECG tracings were subjectively better quality, with a higher voltage and better demarcation of the T wave.

For a narrow QRS, the QT interval was measured from the onset of the first deflection of the QRS complex to the intersection of the terminal part of the T wave with the isoelectric line in the 1-lead option of the KardiaMobile®, then Bazett's correction was applied to obtain the corrected QT interval (QTc). For a wide QRS, the corrected JT interval was used, defined as the result of QTc – QRS duration. The reference values [10] are shown in Fig. 1.

The website <https://www.crediblemeds.org/> was used to identify and stratify the drugs with risk of prolonging the QT interval.

2.5. ECG monitoring protocol

The protocol that we developed for monitoring the QT interval in those patients under treatment with drugs with a known risk for prolonging the QT interval, namely hydroxychloroquine, azithromycin and lopinavir/ritonavir, included the performance of an ECG every 24, 48 or 72 h depending on the characteristics of the patients and their arrhythmic risk level based on the QT interval length, periodic blood test for electrolyte control and different corrective actions depending on the situation. Given the situation we were in, we obviated other risk factors for QT prolongation in order to simplify the execution of the protocol. The follow-up period ended when drugs with a risk of prolonging the QT interval were discontinued and the QTc interval was normal. The algorithm is summarized in Fig. 1.

2.6. Study design and participant

The current study is a retrospective analysis of the patients who were included in the protocol of QTc monitoring in the Hospital Universitario Nuestra Señora de Candelaria in Santa Cruz de Tenerife, Canary Islands, Spain, from 26 March to 28 May 2020. The study included 81 patients during their treatment for COVID-19 with different therapeutic schemes, including drugs with a known risk of prolonging the QT interval.

2.7. Data collection

During the period that the patients were under the protocol, one ECG with KardiaMobile® was performed every 1, 2 or 3 days, depending on the arrhythmic risk. The QTc (or JTc) interval was measured in every ECG, developing an evolutive report of the mea-

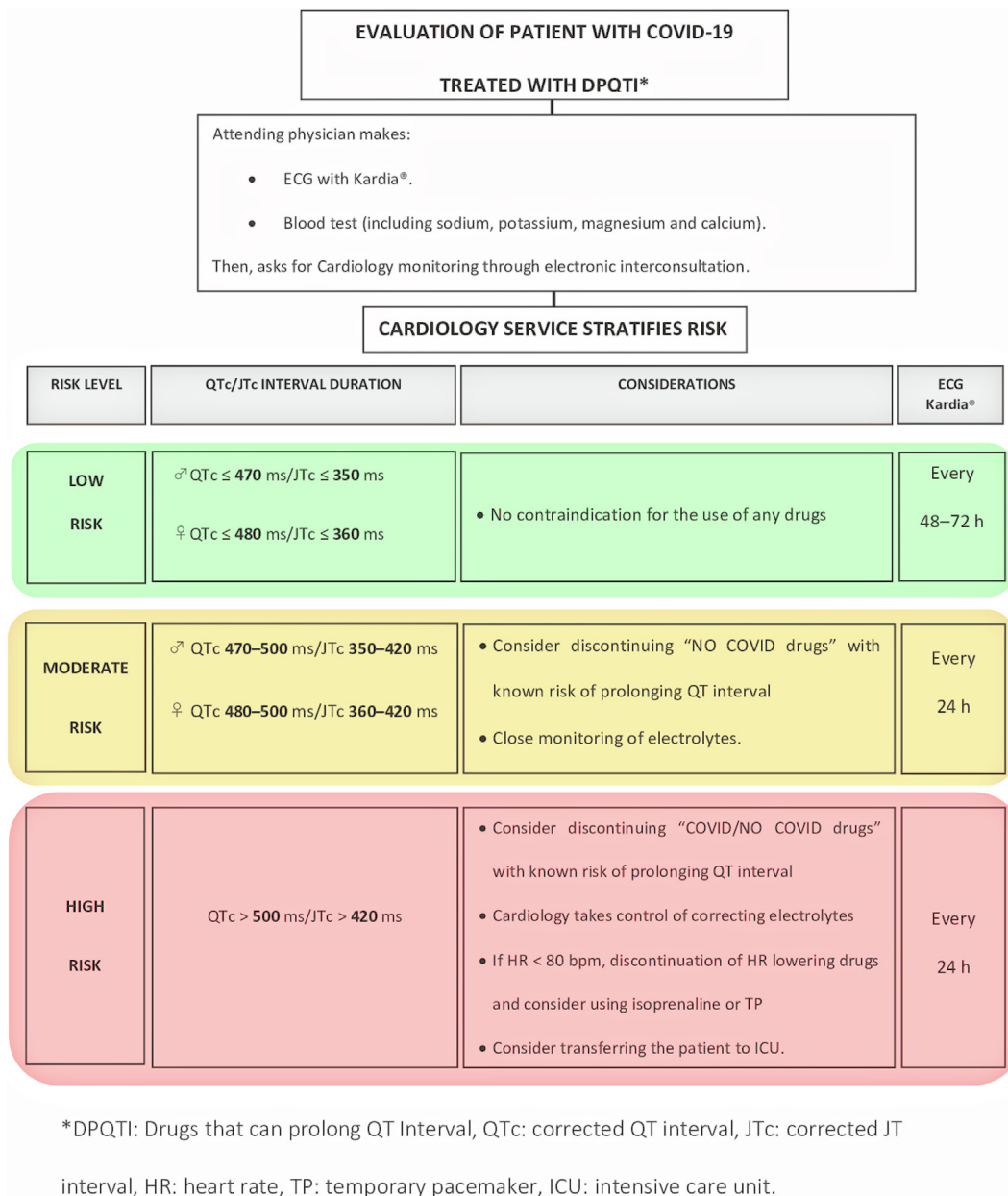


Fig. 1. Electrocardiographic monitoring protocol with KardiaMobile® in patients with COVID-19 treated with drugs with a known risk for prolonging the QTc interval.

measurements and the different drugs possibly involved in QT prolongation for each patient.

2.8. Statistical analysis

The statistical analysis was carried out using SPSS version 23 (IBM Corp., Armonk, NY, USA). Sample characteristics were summarized as numbers and percentages for qualitative variables and means ± standard deviations (SDs) for continuous variables. Student’s T-test was used for testing the association between the mean QT interval for each therapeutic scheme. A 5% level was chosen as a level of statistical significance.

3. Results

We monitored 81 patients (age 63.4 SD 17.2 years; 70.3% men) with confirmed SARS-CoV-2 infection during the months of April

and May 2020, while they were being treated with lopinavir/ritonavir, azithromycin and hydroxychloroquine, both individually or combined. One patient was treated with hydroxychloroquine, and three patients were treated with lopinavir/ritonavir. In 17 patients, a combination of hydroxychloroquine and lopinavir/ritonavir was used, and in 17 patients, the chosen therapeutic scheme included azithromycin + hydroxychloroquine; 43 patients were treated with the combination of azithromycin + hydroxychloroquine + lopinavir/ritonavir. Patients admitted to the intensive care unit (ICU) were excluded from monitoring. The comorbidities of the patients are listed in Table 1, with dyslipidaemia (65.4%), hypertension (60.5%) and obesity (defined as BMI > 30 kg/m²) (48.1%) being the most frequent conditions. Concerning acute phase reactants and other serum molecules, ultra-sensitive troponin I (hs-cTnI) was determined in 50 patients, and only nine of them had detectable hs-cTnI blood levels, with a mean serum level of 0.05 ± 0.15 ng/mL (below the reference 99th percentile provided

Table 1
Chronic diseases present in our cohort of patients.

Comorbidities	No.	%
Type 1 diabetes	1	1,2
Type 2 diabetes	24	29,6
Hypertension	49	60,5
Dyslipidaemia	53	65,4
Current smoker	14	17,3
Former smoker	27	33,3
BMI > 30 kg/m ²	39	48,1
Asthma	17	21
COPD	13	16
Stroke	8	9,9
Ischaemic heart disease	13	16
Chronic kidney disease	19	23,5

BMI: body mass index, COPD: chronic obstructive pulmonary disease.

by the manufacturer, 0.056 ng/mL). D-dimer elevation (>500 ng/mL) was present in 71 patients (87.6%), with a mean value of 2612.4 ± 3348.3 ng/mL, and a significant increase in C-reactive protein (>0.5 mg/dL) was observed in 96,3% (78) of patients, with a mean of 12,1 ± 9,1 mg/dL. A total of 60 patients (74%) presented with ferritin levels above the laboratory reference range (30–400 ng/mL) with a mean of 1253 ± 1446.1ng/mL. We corrected electrolyte levels in risky patients as part of the protocol. Hypokalaemia was the most frequent electrolyte disturbance, presenting in 11 patients (13.5%), followed by hypocalcaemia in seven

patients, (8.6%), hyperkalaemia in four patients (4.9%) and hypomagnesaemia in three patients (3.7%).

The median length of hospital stay was 15 days. While they were under the protocol, nine patients needed to be admitted to the ICU, and six patients died due to respiratory complications; the mean QTc value in deceased patients was 468.5 DS 11.8 ms in 4 patients, and JTc 327.5 DS 17.7 ms in 2 patients. Five of the six patients had increasing levels of D-dimer before their death. During the period of surveillance, we analysed 240 ECGs performed with KardiaMobile®. Ten patients developed at least moderate risk for drug-induced QTc prolongation (defined as QTc > 470 ms or JTc > 350 ms for men and QTc > 480 ms or JTc > 360 ms for women). All of them corrected the QT prolongation after following the protocol steps. Of them, in two patients, all COVID-19 medications had to be discontinued. The mean QTc interval measurement at the beginning of the treatment was 402.5 DS 25.2 ms, and the mean longest QTc during the treatment was 445 DS 32.1 ms (p < 0.001). The mean basal and longest QTc intervals of the population are represented in Fig. 2. The prolongation of the QT interval was statistically significant in patients with combined therapy of hydroxychloroquine and azithromycin, hydroxychloroquine and lopinavir/ritonavir or the three drugs together (p < 0.001), and also in patients treated with lopinavir/ritonavir alone (p = 0.019). No patient died of arrhythmic causes during the monitoring protocol. Table 2 provides a summary of the data.

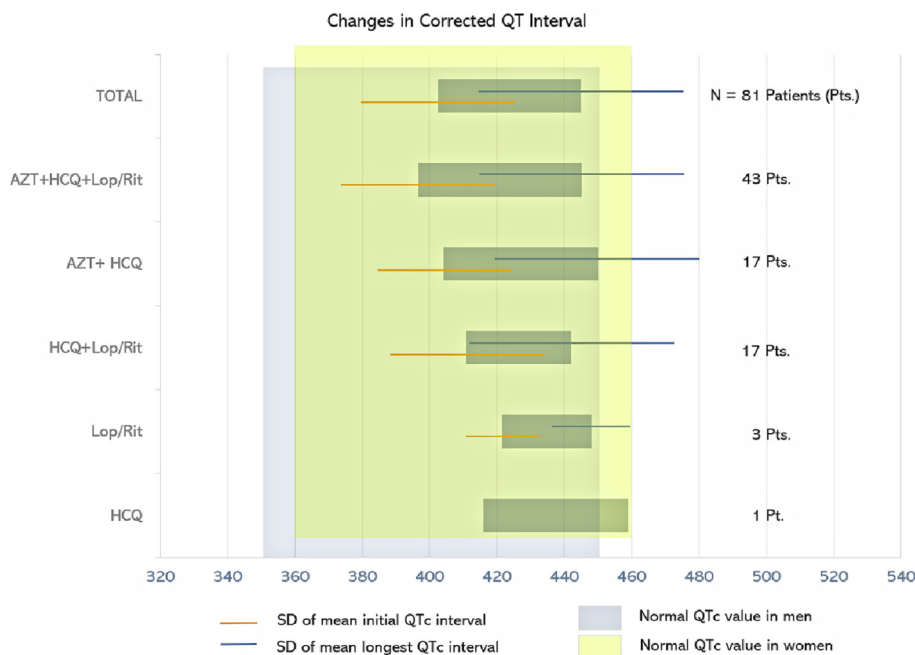


Fig. 2. Changes in QTc during the treatment with different drugs for COVID-19. AZT: azithromycin, HCQ: hydroxychloroquine, Lop/Rit: lopinavir and ritonavir.

Table 2
Mean basal and longest QTc for each therapeutic scheme used in our cohort of patients.

Therapeutic scheme	N	Mean basal QTc (ms)	Mean longest QTc (ms)	Mean of QTc prolongation (ms)	p-value
HCQ	1	416	459	43	-
Lop/Rit	3	421,6 DS 11,9	448 DS 14,2	26,3 DS 5,2	0,019
HCQ + Lop/Rit	17	410,9 DS 27,9	441,9 DS 33,7	31 DS 17,5	<0,001
AZT + HCQ	17	404,18 DS 19,8	449,9 DS 32,4	45,8 DS 19,4	<0,001
AZT + HCQ + Lop/Rit	43	396,6 DS 25,2	445,1 DS 32,3	48,4 DS 21,9	<0,001
TOTAL	81	402,5 DS 25,2	445 DS 32,1	43,25 DS 21,3	<0,001

HCQ: hydroxychloroquine, Lop/Rit: lopinavir/ritonavir, AZT: azithromycin.

3.1. Discussion

This study aimed to analyse the QT interval changes in a cohort of hospitalized patients treated with QT prolonging drugs in the context of COVID-19 infection and after the implementation of a monitoring protocol. We have observed that the prolongation of the QTc interval is statistically meaningful in this cohort of patients treated with lopinavir/ritonavir, azithromycin and hydroxychloroquine, both individually or combined. After close monitoring of the patients, we did not find any sudden deaths due to arrhythmic events.

With regard to the characteristics of patients, they were elderly patients, most of them with associated comorbidities. Dyslipidaemia, hypertension and obesity were the most prevalent chronic diseases among these patients. Myocardial injury was not a frequent finding in our study, as it has been described in other studies [11], while we have observed that the infection caused a significant elevation of circulating levels of acute phase reactants, such as ferritin, D-dimer and C-reactive protein.

No country was prepared for facing the sudden outbreak of the COVID-19 pandemic and overcrowded and under-resourced healthcare centres have had to adjust to new ways of working. Improvisation has been necessary to get round the lack of health personnel and individual protection equipment. In this regard, some devices as the one used in our protocol are accurate enough and have certain features that make them a cost-effective and efficient tool in this pandemic context, such as their quickness to obtain the ECG registry, simplicity of use and ease of cleaning, and their capability of digitally transferring the ECG recording to a "Covid-free zone", which allows to reduce the contact with patients placed in respiratory isolation. These advantages are applicable to other sanitary circumstances and infectious diseases that require contact precautions.

Our study has some limitations. First, although the data were collected prospectively, the analysis was retrospective in nature. Second, the sample was small (n = 81 patients), what may limit the generalization of the results. Although the measurement of the QT interval was made following the strict indications of our protocol, they were carried out by four different investigators. The proposed protocol has a limited applicability to all COVID patients due to the heterogeneity of this population group. In addition, the doses of employed drugs were different and the duration of the treatment varied during the pandemic, following the changing recommendations and evidence that scientific societies published.

4. Conclusions

Some drugs that have been used for COVID-19 treatment prolong the QT interval as a side effect. The implementation of a mon-

itoring protocol can identify susceptible patients to reduce the risk of sudden death. Portable wireless devices may represent a quick and useful alternative for QT interval monitoring, especially in the setting of respiratory isolation. In our centre, no patients died of arrhythmic causes during the implementation of the protocol.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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