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Mini Review

QTc Surveillance in COVID- 19 Era: Why and How?

Sachin Sondhi[1]*, Davinder Pal Singh[2], Kunal Mahajan[3] and Ayushi Mehta[4]

[1]*Consultant Cardiologist, Ace Heart and Vascular Institute, Mohali, India*

[2]*Cardiologist Specialist, NMC DIP, Dubai*

[3]*Assistant Professor, Department of Cardiology, Indira Gandhi Government Medical College, Shimla, India*

[4]*Senior Resident Department of Anaesthesia, PGIMER Chandigarh, India*

***Corresponding Author:** Sachin Sondhi, Consultant Cardiologist, Ace Heart and Vascular Institute, Mohali, India.

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Abstract

The safe and efficacious therapy against SARS-CoV-2 is still lacking. Because of antiviral and anti-inflammatory properties, the hydroxychloroquine and or azithromycin are used against Covid-19 pneumonia. However, these drugs carry a risk of QTc interval prolongation and would lead to drug-induced torsades de-pointes (TdP). Therefore, QTc surveillance is required before and during therapy with these agents..

Keywords: *Hydroxychloroquine Arrhythmia Risk; QTc Prolongation; Coronavirus; COVID-19.*

Introduction

COVID 19 (Coronavirus disease 2019) was declared as a pandemic disease by world health organization on Mar 11, 2020. It has already shattered the economies and health care infrastructure globally. No drug has yet shown promising results against this virus; however, there is an off-label use of hydroxychloroquine (HCQ), azithromycin, and or lopinavir/ritonavir based on *in vitro* and small observational studies [1,2]. These drugs possess the unwanted potential of QTc prolongation, which is further enhanced by underlying critical illness and other concomitant QTc prolonging drugs used in intensive care settings [3]. Therefore, the decision to use HCQ for Covid-19 should take into account the occasional possibility of the development of torsades de pointes (TdP) and drug-induced sudden cardiac death (SCD). This short review article provides health care professionals with information about the surveillance of QTc interval and safe usage of concomitant drugs.

Mechanism of action of chloroquine/hydroxychloroquine

Chloroquine and its analog hydroxychloroquine are in use for nearly 80 years as prophylactic pharmacotherapies for malaria. HCQ also possesses immunomodulatory activity and is used as a disease-modifying agent in rheumatoid arthritis. At intracellular levels, it causes an increase in endosomal pH, as a result of which there is, inhibition of serine proteases and downregulation of inflammatory signaling pathways and therefore prevents cytokine storm [4,5]. Besides, HCQ prevents glycosylation of angiotensin-converting enzyme 2 (ACE-2) and halts the entry of SARS-CoV-2 into the cell [6].

QTC prolongation potential of hydroxychloroquine

There is a structural resemblance of HCQ with Quinidine, which is a class 1a antiarrhythmic agent. It blocks outward potassium channels of the cardiac action potential leading to prolongation of QTc interval. This risk further enhances by other drugs used against SARS-CoV-2 like azithromycin and lopinavir/ritonavir [7,8]. The electrolyte disturbances in critically ill patients and the presence of underlying cardiac illness further enhances the risk of QTc prolongation and may lead to the development of torsades de pointes (TdP) and sudden cardiac death (Table 1). The Qtc prolongation of more than 500msec or more than 60msec from baseline was seen in 8 - 33% of COVID 19 patients, whereas VT was documented only in 1 - 2.7% of patients (Table 2).

Modifiable Risk Factors	Non-Modifiable risk factors

• Hypocalcemia (calcium < 4.65 mg/dL)
• Hypokalemia (potassium < 3.4 mmol/L)
• Hypomagnesemia (magnesium < 1.7 mg/dL)
• QTc prolonging drugs
  • Antibiotics (Macrolides, Fluoroquinolones, Azole antifungals, Trimethoprim).
  • Antihistaminics (Terfenadine, astemizole).
  • Antipsychotics (Haloperidol, droperidol, thioridazine).
  • Antiemetics (Ondansetron, metoclopramide).
  • Antiarrhythmics (Class 1a: Quinidine, procainamide, disopyramide. Class 3: Amiodarone, Sotalol, Ibutelide, Doefoetelide).
	• Elderly (age > 65 years).
	• Female sex.
	• Structural heart disease.
	• Left ventricular dysfunction (LVEF <40%).
	• Acute coronary syndrome.
	• Personal or family history of QT-interval prolongation or sudden unexplained death in the absence of a clinical or genetic diagnosis
	• Anorexia Nervosa or starvation.
	• Hypothermia.

Table 1: *The modifiable and non-modifiable risk factors associated with the development of QTc prolongation.*

Author	Type of Study	Number	Age (Mean)	Females	Drugs	Baseline Characteristics	Qtc > 500 ms and or Increase of ≥60ms	Documented Arrhythmia
Borboa., *et al*. [9]	RCT	N = 81	51	25%	High dose CQ (n = 41) – 600 mg BD for 10 days Low Dose CQ (n = 40) – 450 mg BD on day 1 then OD for 4 days	75% were men, Hypertension 46%, alcohol use disorder 27.5%, and diabetes 26%, Heart Disease 9%, Asthma 7%, CKD 7%	14% (19% in high dose group 11% in low dose group).	VT was seen in 2.7% (high dose group)
Bessiere., *et al*. [10]	Case Series	N = 48	68	32%	HCQ (200 mg, twice a day, for 10 days) with (n=18) or without (n=22) azithromycin (250 mg, daily, for 5 days)	68% were men. 75% on invasive ventilation & 63 % were on vasoactive drugs	33% in combination group. 5% in HCQS alone.	None
Chorin., *et al*. [11]	Cohort study	N=84	63	26%	HCQ (400 mg BD on day 1 followed by 200 mg BD for 4 days) with azithromycin (500 mg OD for 5 days)	CAD 11%, CKD 7%, DM 20%, COPD 8%, HF 2%, acute renal failure 6%	In 12%, QTc increased by ≥60 ms, and 11% developed QTc >500 ms	None

Mahevas., *et al*. [12]	Retrospective cohort study	N=84	57	22%	HCQ sulfate 600 mg/d; 20% also received azithromycin	COPD 6%, ADHF 1.2%, Cardiovascular disease 45.2%, IDDM 4.8%, CKD 5.0%, Immune suppression 9.5%	QTc increase ≥60 ms occurred in 8% and 1% Developed QTc ≥500 ms).	One patient had first degree heart block and one had LBBB
Molina., *et al*. [13]	Case series	N=11	59	36%	HCQ sulfate 600 mg/d for 10 days and azithromycin 500 mg day 1, then 250 mg/ d for 4 days	Obesity 18%, solid cancer 27%, hematologic cancer 18%, HIV 9%	9% (1/11) developed QTc ≥60ms, so stopped	None
Mercuro., *et al*. [14]	Cohort study	N=90	60	49%	HCQ (400 mg BD on day 1 followed by 200mg BD for 4 days), concomitant azithromycin was given in 59% patients	Hypertension 53%, Diabetes 29%, 51% had high >11 Tisdale score	HCQ Monotherapy, 19% had QTc >500ms and 8% had increase of ≥60ms Combination therapy, 23% had Qtc >500ms and 13% had increase of 60ms	1% (1/90) had TdP

Table 2: *Summary of Incidence of QTc Prolongation with Drugs Used Against COVID 19.*

Measurement and monitoring of QTC interval

Traditionally, QTc can be measured from lead II or V5 of the 12-lead electrocardiogram (ECG) and corrected for heart rate using the Bazett (Figure 1) or Fridericia formula [15]. However, in this Covid-19 Pandemic, daily ECG monitoring for a confirmed suspected case of Covid-19 poses an excessive risk to ECG technicians and overuse of personal protective equipment (PPE) kits. Hence, other methods of QTc measurements could be the following:

- Telemetry is an alternative option to ECG for QTc determination. Telemetry systems are equipped with real-time QTc detection as an option. In sick Covid-19 patients, this system prevents excessive infection exposure to the health care staff from an infected patient.

- Smartphone-enabled mobile ECG has become popular in detecting arrhythmias and has been approved by FDA for atrial fibrillation detection. The FDA approved mobile ECG device such "Alivecor" (Kardia Mobile-6L), has approved emergency clearance on March 2020 and can be used instead of ECG for QTc measurement and monitoring.

QTc values of healthy postpubertal males and females are 410ms and 420ms, respectively. On the contrary, a QTc value that exceeds the 99th percentile value for otherwise healthy individuals (i.e., 460 ms in both sexes before puberty, 470 ms in postpubertal males, and

480 ms in postpubertal females), without any other QTc-aggravating factors, may imply an individual at increased risk for torsades de pointes (TdP) [15].

QTc Measurement in difficult scenarios

- **In the presence of atrial fibrillation:** QT intervals that follow the shortest and longest R-R intervals and divide each by the square root of the R-R interval preceding it. The average of these intervals would then be used as the adjusted QT interval [16] (Figure 1).
- **In presence bundle branch block or paced rhythm:** Wide QRS adjusted QTc in msec = QTc – (QRS duration - 100 msec).
- **In the presence of U waves:** Erroneous Inclusion of U wave in QTc measurement will lead to overestimation of QTc interval. Besides, identification of the end of T wave is particularly tricky in the presence of U wave. The U wave is usually excluded from the measurement of QTc interval if it is distinct from T wave and or its height is less than half of T wave [17] (Figure 1).

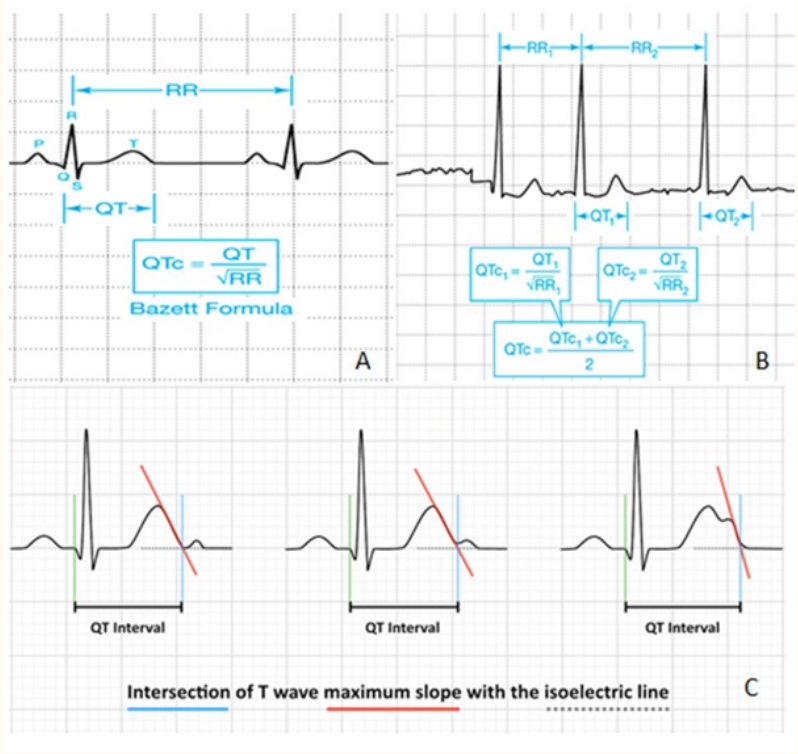

Figure 1: *The diagram demonstrates QTc measurement difficult scenario: (A) Measurement of corrected QTc by using bazzet formula. (B) Measurement of QTc in the presence of atrial fibrillation and average QTc of short and long cycles should be measured. (C) Measurement of QTc in the presence of U waves, U wave is usually excluded from measurement if its origin is distinct from T wave and or its height is less than half of T wave.*

Preinitiation and post initiation checklist after hydroxychloroquine

The risk of development of lethal arrhythmias will depend upon baseline QTc interval. The high risk or severely ill patients of Covid-19, in whom anti-COVID drugs are likely to be started, should undergo baseline QTc measurement. Similarly, it is mandatory to correct electrolyte disturbances: hypokalemia, hypocalcemia, and hypomagnesemia before initiation of HCQ (Figure 2). The patients are divided into the following three categories [15,18]:

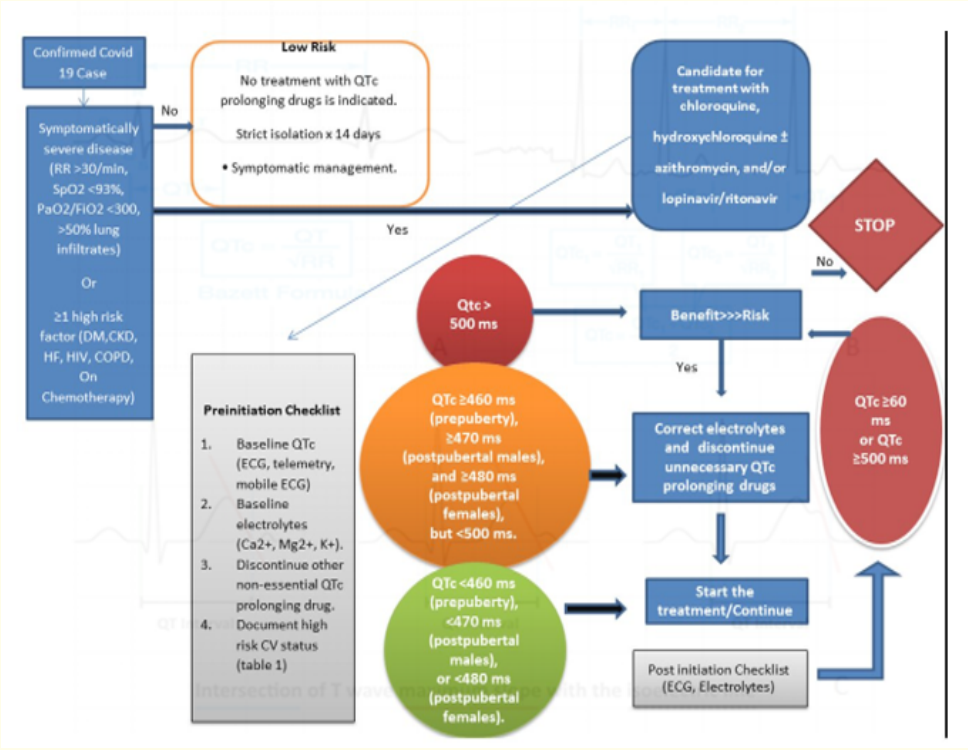

Figure 2: *Protocol for mitigating risk for the development of drug-induced torsades de pointes in Covid-19 patient based on the treatment algorithm advised by the scientific committee of the Indian Heart Rhythm Society [18]. The "red circle" has the highest risk for TdP, and treatment is given only if the benefit outweighs the risk. In "orange circle," treatment is started after the corrections of electrolyte along with other potential drugs causing QTc prolongation are discontinued. In "green circle" treatment can be started directly. Post initiation QTc surveillance is important and if excessive QTc prolongation is documented (the red circle on right side), reassess benefit versus risk of continuing HCQ therapy.*

- **Group 1:** Includes patients with normal baseline QTc interval [QTc < 460 ms (prepuberty), < 470 ms (postpubertal males), or < 480 ms (postpubertal females)]. HCQS can be started directly (Figure 1).
- **Group 2:** Includes patients with modest prolongation of QTc interval [QTc ≥ 460 ms (prepuberty), ≥ 470 ms (postpubertal males), and ≥ 480 ms (postpubertal females), but < 500 ms]. Further correction of electrolytes abnormalities and halting all other QTc prolonging drugs is required. In addition, azithromycin also needs discontinuation. HCQS can be started with QTc monitoring (Figure 2).

- **Group 3:** Includes highest risk patients [QTc > 500ms]. The decision to start HCQS is based on clinical judgment, and if the benefit is more than harm, then treatment with HCQS can be started under close surveillance after electrolyte correction. Azithromycin and other QTc prolonging medications should be discontinued (Figure 2).

The group 1 and group 2 require monitoring ECG to be done at 48 and 96 hours after initiation of HCQS, whereas group 1 requires ECG to be done at 4 hours, 48 hours and 96 hours. Excessive prolongation of QTc > 60 ms and or > 500 ms after initiation shifts patients in Group 1 and Group 2 to Group 3, in whom treatment decision is to be made on risk-benefit ratio. Tisdale has developed a scoring chart for predicting risk of drug induced Qtc prolongation (Table 3) [19].

Risk Factors	Points
Age ≥68 y	1
Female sex	1
Loop diuretic	1
Serum K+ ≤3.5 mEq/L	2
Admission QTc ≥450 ms	2
Acute MI	2
≥2 QTc-prolonging drugs	3
sepsis	3
Heart failure	3
One QTc-prolonging drug	3
Maximum Risk Score	21

Table 3: *Tisdale risk score for predicting risk of drug induced QTc prolongation. A Tisdale score of ≤ 6 predicts low risk, 7-10 medium risk, and ≥ 11 high risk of drug-associated QT prolongation.*

The knowledge gap exists between benefits and potential risks associated with HCQS therapy, which needs to be addressed on randomized trials. Two such trials are: Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease (ORCHID) trial [20] and the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial [21] will address safety and efficacy issues.

Conclusion

The social distancing, respiratory etiquettes, and washing hands are time tested preventive measures against COVID-19 infection. HCQS has been used against SARS CoV-2 based on *in vitro* studies, but no randomized control trial data is available. The uses of HCQS, along with other tested drugs against SARS CoV-2 possess the potential risk of developing drug-induced lethal arrhythmias in high risk patients. The determination of baseline QTc and its surveillance during treatment is necessary for the prevention of lethal arrhythmias and sudden cardiac death.

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