

Original Research Article

QT prolongation associated with azithromycin/hydroxychloroquine combination in treatment of COVID-19: a single centre study

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ABSTRACT

Background: The long QT syndrome is characterized by prolongation of QT interval, which may lead to life-threatening cardiac arrhythmias. Objectives were to assess prevalence, quantity and severity of QTc prolongation with combined drugs (azithromycin and hydroxychloroquine) in adults COVID-19 patients treated on these agents at KFSHRC. And to characterize cardiac complications of QTc prolongation with combined drugs.

Methods: A retrospective cohort study at KFSH&RC, in Riyadh, Saudi Arabia. Baseline and daily ECG was done until completion of duration as per KFSH&RC guidelines for management of Covid-19, QTc prolongation >500 or increase of at least 60 ms compared with the pre-drug baseline value, or presence of cardiac conductive complications (torsades de pointes). The QTc prolongation was defined as >470 for male and >480 for female as per American Heart Association. A risk score that has been validated by Tisdale et al, for prediction of QT prolongation drug-related in admitted patients in cardiac care unit. The study duration was specified as one month after study approval by Research Ethics committee.

Results: A total of 74 patients were included in the study. The patients were distributed according to their risk score for prediction of QT prolongation as the following: low (67/74), medium (6/74), high (1/74). Two patients with medium risk were started on both azithromycin and hydroxychloroquine. one of them his baseline QT was 490, Azithromycin was stopped as QT reached 502. The second patient has QT baseline 471, after starting treatment; QT range was 472-475, hydroxychloroquine was stopped on day 4. None of them had torsades de pointes. Only one patient with low risk, no baseline QT was recorded, but QT was 499 on day three, so hydroxychloroquine was stopped. Repeated ECG showed: QT decreased to 478, no torsades de pointes.

Conclusions: In this single centered-retrospective cohort, we noticed that a small percentage of patients developed QT prolongation with the use of this combination. With the increasing the risk of developing QT prolongation the number of the patient who developed the condition increased. We used Tisdale score which is a scoring system Identifying hospitalized patients at risk for QT interval prolongation could lead to interventions to reduce the risk of torsades de pointes validated in May 2013.5 None of our population developed significant cardiac complications of QTc prolongation with combined drugs.

Keywords: COVID-19, QTc prolongation, Torsade

INTRODUCTION

Since World Health Organisation announced Coronavirus disease 2019 (COVID-19) as pandemic, a lot of studies are still trying to understand the virus and possible options for its treatment. One small study at time of preparing this project has mentioned that hydroxychloroquine alone or in combination with azithromycin reduced viral load in nasopharyngeal swabs.¹ Both of azithromycin and hydroxychloroquine have adverse effects and as well-known that QTc prolongation is one of them.^{2,3} The long QT syndrome is a syndrome that is characterized by impaired myocardial repolarization, in which the QT interval is prolonged on the electrocardiogram (ECG). This syndrome is associated with an increased risk of polymorphic ventricular tachycardia, a characteristic life-threatening cardiac arrhythmia also known as torsades de pointes. The primary symptoms in patients with LQTS include palpitations, syncope, seizures, and sudden cardiac death.⁴

Objectives

Objectives were 1) assess prevalence, quantity and severity of QTc prolongation with combined drugs (azithromycin and hydroxychloroquine) in adults COVID-19 patients treated on these agents at KFSHRC 2) characterize cardiac complications of QTc prolongation with combined drugs.

METHODS

Retrospective study to be carried in King Faisal Specialist Hospital and Research centre in Riyadh, Saudi Arabia. Baseline and daily ECG to be done until completion of duration as per KFSH&RC guidelines for management of COVID-19, QTc prolongation>500 or increase of at least 60 ms compared with the pre-drug baseline value, or presence of cardiac conducive complications (torsades de pointes). The QTc prolongation was defined as >470 for male and >480 for female as per American Heart Association. A risk score that has been validated by Tisdale et al., for prediction of QT prolongation drug-related in admitted patients in cardiac care unit (Table 1). Total number of patients were 74.

A Tisdale score of ≤6 predicts low risk, 7-10 medium risk, and ≥11 high risk of drug-associated QT prolongation.

Study conducted from September 2020 to November 2020.

Ethical considerations

This study is a retrospective review of charts, ECGs and lab results that does not involve collection of any tissue or specimens from the participants. Data will be obtained from hospital databases without patient identifiers. Therefore, consents will not be needed as the study does not involve any interaction with the patients.

Confidentiality will be maintained, and data will be accessible only to the study team.

Table 1: Risk score for drug-associated QTc Prolongation.⁵

Risk factors	Points
Age ≥68 y	1
Female sex	1
Loop diuretic	1
Serum potassium ≤3.5 mEq/L	2
Admission QTc ≥450 ms	2
Acute myocardial infarction	2
≥2 QTc-prolonging drugs	3
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3
Maximum risk score	21

RESULTS

A total of 74 patients were included in the study.

Table 2: Distributions of the patient according to gender.

Gender	Number	Percentage
Female	35	47
Male	39	53

Table 3: Distribution of the patients according to their risk score for prediction of QT prolongation.

Risk	Number	Percentage
Low	67	90
Medium	6	8.1
High	1	1.3

Table 4: Number of the patients according to the events with QT prolongation.

Risk	Number	Percentage	Torsades de pointes
Low	1	1.4% (of total low risk)	None
Medium	2	33% (of total medium risk)	None
High	0	0% (of total high risk)	None
Total	3	4%	None

A 35 were female gender and 39 were male gender. All the patients were of adults with age ≥18 years. The patients were distributed according to their risk score for prediction of QT prolongation as the following: low (67/74), medium (6/74), high (1/74). Two patients with medium risk were started on both azithromycin and hydroxychloroquine. one of them his baseline QT was 490, Azithromycin was

stopped as QT reached 502. The second patient has QT baseline 471, after starting treatment; QT range was 472-475, hydroxychloroquine was stopped on day 4. None of them has torsades de pointes. Only one patient with low risk, no baseline QT was recorded, but QT was 499 on day three, so hydroxychloroquine was stopped. Repeated ECG showed: QT decreased to 478, no torsades de pointes.

DISCUSSION

In the review of the previous evidence, we found that only a small study shows that hydroxychloroquine alone or in combination with azithromycin reduced viral load in nasopharyngeal swabs.¹ In this single centered-retrospective cohort, we noticed that a small percentage of patients developed QT prolongation with the use of this combination. With the increasing the risk of developing QT prolongation the number of the patient who developed the condition increased. We used Tisdale score which is a scoring system Identifying hospitalized patients at risk for QT interval prolongation could lead to interventions to reduce the risk of torsades de pointes validated in May 2013.⁵ None of our population developed significant cardiac complications of QTc prolongation with combined drugs. Our study had some limitations including the small sample size with no control group. In addition to that ECG was not done on daily basis on all patients, documentation was not enough about some patients, and Potassium and Magnesium were not done after starting medications. Further studies are needed to identify the impact of this these drugs and their safety profile on QT interval.

CONCLUSION

In this single centered-retrospective cohort, we noticed that a small percentage of patients developed QT prolongation with the use of this combination. With the increasing the risk of developing QT prolongation the number of the patient who developed the condition increased. We used Tisdale score which is a scoring

system Identifying hospitalized patients at risk for QT interval prolongation could lead to interventions to reduce the risk of torsades de pointes validated in May 2013. None of our population developed significant cardiac complications of QTc prolongation with combined drugs.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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