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Safety monitoring of chloroquine and hydroxychloroquine in COVID-19 patients in Indonesia on QT prolongation: hospital based monitoring study

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ABSTRACT

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are the challenging drugs used for COVID-19. Several studies show its beneficial, however, both medications can prolong the QTc interval and increase the risk of patients for torsades de pointes and death. The Tisdale score is identified to have successfully predicted the at-risk population of side effects of these drugs. This study aim to evaluate the QT prolongation caused by the administration of chloroquine and hydroxychloroquine in COVID-19 patients and the association with the treatment outcomes based on their Tisdale score. We conducted an observational study on 213 hospitalized patients with confirmed or suspect COVID-19 in 6 referral hospitals in Indonesia. All baseline demographic such as age and gender, RT-PCR test result, severity of disease, history of cardiovascular disease (myocardial infarction, heart failure, hypertension), serum kalium level at baseline, and the use of medication associated with risk QTc interval prolongation were collected. The Tisdale risk score was used for predicting high-risk patients for QT corrected (QTc) interval prolongation. Out of 213 patients who were treated with CQ/HCQ, there were 60 (28.2%) patients had QTc interval prolongation, included 43 patients (20.2%) who had normal QTc interval at baseline and at the end of treatment had prolong interval; or 17 patients (8.0%) who had QTc interval more than 470 msec at baseline and QTc interval prolongation was worsen at the end of treatment. Several factors, including age more than 50 years, COVID-19 confirm PCR, and had comorbidity heart failure, were statistically significant associated with QTc interval prolongation. The high-risk score of Tisdale score have increased risk significantly on QTc interval prolongation (RR: 2.15, 95%CI 1.07-4.32) and associated with risk of death (RR: 3.50, 95%CI 1.34-9.13) compared to low-risk score. Our findings showed that the treatment of CQ/HCQ in COVID-19 patients is associated with QTc prolongation. The Tisdale score can be used as a valuable tool to predict the COVID-19 patients' outcome after treatment of these QTc-prolonging drugs.

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ABSTRAK

Klorokuin dan Hidroksiklorokuin merupakan obat-obatan yang digunakan untuk COVID-19 pada awal pandemi. Beberapa penelitian observasional menunjukkan manfaatnya, namun, kedua obat ini dapat memperpanjang interval QTc dan meningkatkan risiko pasien untuk terjadinya torsades de pointes dan kematian. Skor Tisdale sering digunakan memprediksi populasi berisiko efek samping dari obat-obatan yang dapat memperpanjang interval QTc. Penelitian ini bertujuan untuk mengevaluasi perpanjangan interval QTc yang disebabkan oleh pemberian klorokuin dan hidroksiklorokuin pada pasien COVID-19 dan hubungan antara skor Tisdale terhadap hasil pengobatan. Studi ini adalah penelitian observasional pada 213 pasien yang dirawat di rumah sakit dengan COVID-19, baik yang dicurigai maupun yang terkonfirmasi, di 6 rumah sakit rujukan COVID-19 di Indonesia. Semua data demografi dasar seperti usia dan jenis kelamin, hasil tes RT-PCR, tingkat keparahan penyakit, riwayat penyakit kardiovaskular (infark miokard, gagal jantung, hipertensi), kadar kalium serum pada awal, dan penggunaan obat yang dikaitkan dengan risiko perpanjangan interval QTc dikumpulkan. Skor Tisdale digunakan untuk memprediksi risiko pasien terhadap perpanjangan interval QTc. Dari 213 pasien yang mendapatkan klorokuin atau hidroksiklorokuin, terdapat 60 (28,2%) pasien yang mengalami perpanjangan interval QTc, termasuk 43 pasien (20,2%) yang memiliki interval QTc normal pada awal dan akhir pengobatan memiliki interval yang lebih panjang; atau 17 pasien (8,0%) yang memiliki interval QTc lebih dari 470 msec pada awal dan perpanjangan interval QTc memburuk di akhir pengobatan. Beberapa faktor, termasuk usia lebih dari 50 tahun, konfirmasi PCR COVID-19, dan memiliki komorbiditas gagal jantung, secara statistik signifikan berhubungan dengan perpanjangan interval QTc. Skor Tisdale yang tinggi memiliki risiko untuk terjadinya perpanjangan interval QTc (RR: 2,15, 95%CI 1,07-4,32) dan berhubungan dengan risiko kematian (RR: 3,50, 95%CI 1,34-9,13) dibandingkan dengan skor Tisdale yang rendah. Penelitian ini menunjukkam bahwa pengobatan klorokuin dan hidroksiklorokuin pada pasien COVID-19 berhubungan dengan perpanjangan interval QTc. Skor Tisdale dapat digunakan sebagai alat untuk memprediksi hasil pasien COVID-19 setelah pengobatan obat-obatan ini yang memperpanjang QTc.

INTRODUCTION

COVID-19 is an infectious disease caused by a new type of virus from the Coronavirus family, namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which attacks the respiratory system, for which limited drug was approved for definitive treatment of COVID-19.[1] To date, COVID-19 has afflicted as many as 758 million people and caused more than 6.5 million deaths globally.[2] On March 1, 2020, Indonesia reported the first cases of COVID-19, and the number of cases has steadily increased since then.

During the COVID-19 pandemic, the drugs used were based on empirical experience from previous generations of coronavirus treatments, such as Avian Flu, Swine Flu, SARS, MERS, and Ebola, and used drugs that are still in clinical trials around the world.[3] Considering that there are no drugs that have been approved as anti-COVID19 drugs, several drug regulatory authorities have implemented an approval for the use of drugs in emergency conditions (Emergency Use Authorization). Due to the limited data on the efficacy and safety of drugs given by the EUA, the requirements in the approval are the need to evaluate the drug's effectiveness in real world setting and safety monitoring with active pharmacovigilance. National Agency of Drug and Food Control (NADFC/Badan POM) in Indonesia has issued an emergency use approval (EUA) for several drugs for COVID-19, namely chloroquine/hydroxychloroquine (CQ/HCQ), favipiravir, remdesivir etc. The antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ), among others, have re-emerged as promising drugs to treat patients with COVID-19 disease.[4,5] Chloroquine and Hydroxychloroquine(CQ/HCQ) have known anti-inflammatory effects

including suppressing tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6) which mediate inflammatory complications of several viral diseases.[6] However, CQ/HCQ have a risk of side effects on the heart such as QTc interval prolongation.[7] In the fact sheet of the drug as information for health workers that is included in the approval of the regulatory authority, it has been stated the drug should be used of caution in patients with heart disease, QTc prolongation, history of ventricular arrhythmias, bradycardia, potassium-magnesium imbalances that have not been corrected, and the use of other risk drugs associated with prolongation of the QTc interval, such as azithromycin and some antibacterial drugs. An electrocardiogram or ECG baseline should be monitored before starting the therapy to assess the risk for prolongation of the QTc interval, and ECG monitoring should be continued during the drug administration. Several methods have been developed to monitor and assess the patient's eligibility to receive CQ/HCQ treatment for safe use. One of the methods developed by James E. Tisdale, namely Tisdale Risk Score for QT Prolongation.[8] This method can be used in hospitals in Indonesia, and it could reduce the risk of serious adverse drug reaction such as heart disease caused using CQ or HCQ.

Based on the conditions described above and in accordance with active pharmacovigilance monitoring is necessary for drugs that are approved for emergency use; therefore, this study was carried out at several COVID-19 referral hospitals in Indonesia to evaluate of the safety of the use of CQ/HCQ on QTc interval prolongation, and to assess if the Tisdale score associated with the QTc interval prolongation.

METHODS

This study was an observational study using the secondary data taken from the medical records of COVID-19 patients who were hospitalized in 6 referral hospitals in Indonesia. Adult patients RT-PCR confirm or suspect COVID-19, who have been hospitalized with any severity, and treated using CQ/HCQ between period of July to November 2020 was consecutively included in the study. The patients were discharged or death within 24 hours of hospital admission were excluded.Data was collected among others are baseline demographic such as age and gender, RT-PCR test result, severity of disease, history of cardiovascular disease (myocardial infarction, heart failure, hypertension), serum kalium level at baseline, and the use of medication associated with risk QTc interval prolongation such as azithromycin, levofloxacin, and loop diuretic. The data on sepsis and discharge status of patients (death or not) were also collected.QTc interval from ECG (in msec) at baseline and at the subsequently after the treatment of CQ/HCQ was evaluated. The QTc interval was calculated using the Bazett formula. Patients was considered as prolong QTc if at baseline QTc interval was normal (<=470msec) and subsequent ECG after use CQ/HCQ showed interval >470 msec, or at baseline was prolong and subsequent showed more prolong, otherwise was considered as no QTc interval prolongation.

The Tisdale Score was calculated of each patient. The Tisdale score is a risk score using easily obtainable clinical variables to predict patients at highest risk for QTc interval prolongation and it is useful in guiding monitoring and treatment decisions.[8] The variables are included in this score are age ≥68 years old (score 1), Female sex (score 1), use of loop diuretic (score 1), level of serum Kalium≤3.5 mEq/L (score 2), admission QTC ≥450msec (score 2), history of acute myocardial infarction (score 2), ≥2 QTc-prolonging drugs (score 3), sepsis (score 3), Heart failure (score 3), and one QTc-prolonging drug (score 3). It is considered low risk if the total score is 6, medium risk with total score 7-10 or high risk when the score ≥11.

All information were recorded into the e-case report form and data was

analyzed using the SPSS. The minimum number of sample sizes was calculated using estimation a single proportion of the incidence of prolong QTc intervals in COVID-19 patients who use CQ/HCQ with or without macrolides is 15% Mercuro, *et al*.,[9] with 80% power and alpha = 0.05 with desire precision was 0.5, the minimum number of samples obtained was 200.

The baseline characteristics were presented with mean and standard deviation for continuous data, and frequency and proportion for categorical data. The number of patients experiencing a prolong QTc interval was calculated as the proportion. Relative Risk (RR) and 95% CI was calculated to estimate the risk factors for QTc interval prolongation in the administration of CQ/HCQ, as well as on evaluation of association between Tisdale score, QTc interval prolongation, and patient's outcome. Multivariate logistic regression analysis was used to adjust the relative risk for QTc interval prolongation for confounding factors.

RESULTS

Baseline characteristic and QTc interval prolongation

There were 213 patients who were treated with CQ/HCQ were included in this analysis. The patients were mostly male, with average of age was 52.3 years old (±15.0) with majority more than 50 years old, mostly had confirm COVID-19 using RT-PCR, half of patients had severe respiratory disease (mild, moderate and severe were 20 (9.3%), 88 (41.4%) and 105 (49.3%), respectively), and had abnormal serum potassium. Comorbidities were present in more than half of all participants, with the highest proportion of patients with hypertension (32.4%) and small proportion of patients had myocardial infarction, heart failure, and sepsis. The use of co-medication associated with QTc interval prolongation was mostly azithromycin and levofloxacin, and only small number use loop diuretics (TABLE 1).

From all patients who were treated with CQ/HCQ, there were 60 (28.2%) patients in this study had QTc interval prolongation, included 43 patients (20.2%) who had normal QTc interval at baseline and at the end of treatment had prolong interval; or 17 patients (8.0%) who had QTc interval more than 470 msec at baseline and QTc interval prolongation was worsen at the end of treatment. Nevertheless, two third of patients had either no QTc interval prolong at follow up when baseline is normal (115/213), or abnormal at baseline but normal at the follow-up (38/213).

TABLE 1. Baseline characteristics and bivariate analysis of risk factors associated with QTc interval prolongation in patients treated with CQ/HCQ

Risk Factors	All patients (n=213)	Prolong QTc (n=60)	Not Prolong QTc (n=153)	RR (95% CI)
Gender				
Male	133 (62.4%)	40 (30.1%)	93 (69.9%)	1.20 (0.76-1.91)
Female	80 (37.6%)	20 (25.0%)	60 (75.0%)	Ref.
Age				
- >50 years	116 (54.5%)	40 (34.5%)	76 (65.5%)	1.67 (1.05-2.66)*
- ≤50 years	97 (45.5%)	20 (20.6%)	77 (79.4%)	Ref.
RT-PCR				
- positive	159 (74.6%)	51 (32.1%)	108 (67.9%)	1.93 (1.02-3.64)*
- negative	54 (25.4%)	9 (16.7%)	45 (83.3%)	Ref.
Severity				
- Severe	105 (49.3%)	34 (32.4%)	71 (67.6%)	1.35 (0.87-2.08)
- Mild to moderate	108 (50.7%)	26 (24.1%)	82 (75.9%)	Ref.
Laboratory Test				
Serum Kalium level				
- Abnormal	47 (24.7%)	12 (25.5%)	35 (74.5%)	0.91 (0.52-1.59)
- Normal	143 (75.3%)	40 (28.0%)	103 (72.0%)	Ref.
Comorbidities				
Co-morbidity				
- Yes	114 (53.5%)	37 (32.5%)	77 (67.5%)	1.40 (0.90-2.18)
- No	99 (46.5%)	23 (23.2%)	76 (76.8%)	Ref.
Type of comorbidity				
Heart Failure				
- Yes	17 (8.0%)	8 (47.1%)	9 (52.9%)	1.77 (1.02-3.09)*
- No	196 (92.0%)	52 (26.5%)	144 (73.5%)	Ref.
Myocardial infarction				
- Yes	12 (5.6%)	5 (41.7%)	7 (58.3%)	1.52 (0.75-3.09)
- No	201 (94.4%)	55 (27.4%)	146 (72.6%)	Ref.
Hypertension				
- Yes	69 (32.4%)	22 (31.9%)	47 (68.1%)	1.21 (0.78-1.88)
- No	144 (67.6%)	38 (26.4%)	106 (73.6%)	Ref.
Sepsis				
- Yes	14 (6.6%)	4 (28.6%)	10 (71.4%)	1.02 (0.43-2.39)
- No	199 (93.4%)	56 (28.1%)	143 (71.9%)	Ref.
Co-medications				
Use Qtc prolonging drugs				
- Yes	194 (91.1%)	56 (28.9%)	138 (71.1%)	1.37 (0.56-3.37)
- No	19 (8.9%)	4 (21.1%)	15 (78.9%)	Ref.
Type of Co-medications				
Use of azithromycin				
- Yes	155 (72.8%)	39 (25.2%)	116 (74.8%)	0.70 (0.45-1.08)
- No	58 (27.2%)	21 (36.2%)	37 (63.8%)	Ref.
Use of levofloxacin				
- Yes	76 (35.7%)	25 (32.9%)	51 (67.1%)	1.29 (0.84-1.98)
- No	137 (64.3%)	35 (25.5%)	102 (74.5%)	Ref.
Use of loop diuretics				
- Yes	25 (11.7%)	8 (32.0%)	17 (68.0%)	1.16 (0.63-2.14)
- No	188 (88.3%)	52 (27.7%)	136 (72.3%)	Ref.

The factors associated with QTc interval prolongation in patients treated with CQ/HCQ

The bivariate analysis of several factors (TABLE 1) showed that age more than 50 years, COVID-19 confirm PCR, and had comorbidity heart failure were statistically significant associated with QTc interval prolongation. Moreover, in multivariate analysis (TABLE 2) using logistic regression, these three variables were still statistically significant associated with QTc interval prolongation in patients using CQ/HCQ with RR adjusted (95%CI) was 2.10 (1.10-4.00), 3.19 (1.36-7.49) and 3.12 (1.04-9.41), respectively.

Association of QTc interval prolongation and Patient's outcome

From 60 patients who had QTc interval prolongation, 12 patients were died, while 23 out of 153 patients who were not experienced QTc interval prolongation were died during hospitalization. The association of QTc prolongation in patients treated with CQ/HCQ with patient outcome (death) was not statistically significant (RR: 1.33, 95%CI 0.71-2.51).

TABLE 2. Multivariate analysis of risk factors associated with QTc interval prolongation in patients treated with CQ/HCQ

Risk Factors	RR (95%CI)
Age >50 years	2.10 (1.10-4.00)
COVID test positive	3.19 (1.36-7.49)
Heart Failure	3.12 (1.04-8.41)

Association of Tisdale Score with QTc interval prolongation and Patient's outcome

TABLE 3. Analysis of association between Tisdale score with QTc interval prolongation and Patient's outcome

Tisdale Score	Overall (N=191)	Prolong QTc (N=52)	No Prolong QTc (N=139)	RR (95% CI)
High risk score	7 (3.6%)	4 (57.1%)	3 (42.9%)	2.15 (1.07-4.32) *
Moderate risk score	37 (19.4%)	9 (24.3%)	28 (75.7%)	0.92 (0.49-1.72)
Low risk score	147 (77.0%)	39 (26.5%)	108 (73.5%)	ref
Tisdale Score	Overall (N=191)	Death (N=30)	No Death (N=161)	RR (95% CI)
High risk score	7 (3.6%)	3 (42.9%)	4 (57.1%)	3.50 (1.34-9.13) *
Moderate risk score	37 (19.4%)	9 (24.3%)	28 (75.7%)	1.99 (0.97-4.06)
Low risk score	147 (77.0%)	18 (12.2%)	129 (87.8%)	ref

Out of 191 patients who were assessed using Tisdale Score (TABLE 3), 147 (77%) patients had low-risk score and only 7 (3.6%) patients had high-risk score. However, QTc interval prolongation and death were found significant in patients with high-risk score compared to low-risk score, 57.1% and 42.9%, respectively. The high-risk score of Tisdale score have increased risk significantly on QTc interval prolongation (RR: 2.15, 95%CI 1.07-4.32) and associated with risk of death (RR: 3.50, 95%CI 1.34-9.13) compared to low-risk score.

DISCUSSION

The main findings of this study were the administration of chloroquine and hydroxychloroquine had a substantial impact on the lengthening of the corrected QT (QTc) interval in COVID-19 patients, in hospitalized COVID-19 patients and the use of Tisdale score as a reliable tool to identify COVID-19 patients who were treated with CQ/HCQ at highest risk for QTc interval prolongation and linked to the risk of patient's outcome. Coronavirus disease 19 (COVID-19), originated in Wuhan, China in early December 2019, has spread rapidly around the world and resulted millions of deaths. A coronavirus disease 19 known as COVID-19 that first appeared in Wuhan, China in early December 2019 has spread quickly over the world and caused millions of fatalities. Chloroquine and hydroxychloroquine (CQ/HCQ) have gained popularity as COVID-19 therapies since the FDA removed its authorization and emergency status. The potential effect of CQ or HCQ to reduce the expression of phosphatidylinositol binding clathrin assembly protein (PICALM) might be useful as a COVID-19 prophylactic option. The restriction of SARS-CoV-2 endocytosis into host cells is caused by the inhibition of PICALM expression, one of the three most abundant proteins in clathrin-coated pits.[10] However, the effectiveness of these drugs in treating SARS-CoV-2 virus-infected patients has received little meaningful clinical evidence, needs to be further investigated in large-scale research.

The possibility of QT prolongation has been one of the main issues with the treatment of CQ/HCQ. Moreover, some studies reported the electrocardiography (ECG) of COVID-19 patients has revealed corrected QT (QTc) interval prolongation.[11-15] In this study, there were 60 (28.2%) patients who received CQ/HCQ and experienced QTc interval prolongation. Of these, 43 patients (20.2%) had normal QTc intervals at baseline but developed prolong intervals at the end of treatment, and 17 patients (8.0%) had QTc intervals longer than 470 msec at baseline but experienced worsening of their QTc interval prolongation at the end of the treatment. There are multiple mechanisms involving QTc prolongation by these medications used to treat COVID-19 patients. The main mechanism is through blocking the human ether-a-go-go-related gene's K+ channel in myocytes, which delays repolarization and lengthens the QT interval.[16-18] A serious consequence of QTc prolongation, Torsades de Points (TdP), can result in deadly ventricular arrhythmias like ventricular tachycardia/ fibrillation and sudden cardiac death.[19] In this study, 12 patients of 60 patients who had QTc interval prolongation were died. However, the association of QTc prolongation in patients treated with CQ/ HCQ with patient outcome (death) was not statistically significant.

According to another study, the QTc prolongation is greatly increased by age, a history of the cardiovascular disease, obesity, hypertension, diabetes, and hypokalemia with the ability to extend QTc.[10] In this study, we found that age more than 50 years, COVID-19 confirm PCR, and had comorbidity heart failure were statistically significant associated with QTc interval prolongation. Similar to previous study,[21,22] this result was consistent with some retrospective cohort studies that demonstrated that

older individuals with COVID-19 who were receiving hydroxychloroquine experienced QTc prolongation. The increase in QTc interval in the elderly may be due to physiological changes in the cardiovascular system and cardiac hypertrophy.[23] Furthermore, COVID-19 patients with pre-existing cardiovascular disease have a worse prognosis, indicating that COVID-19 potentially has pro-arrhythmic effects.[24]

The use other QTc prolonging medications is found as a factor that affect QTc prolongation. Cardiac potassium channel blockage is considered to be the primary cause of drug-induced QTc prolongation.[25] Azithromycin and levofloxacin were two QTc prolonging drugs used concurrently in this study, while only a small percentage of participants utilized loop diuretics. However, in this study, this co-medication associated with QTc prolongation was not statistically significant.

Since April 2020, Indonesia has adopted the national protocol for the use of CQ/HCQ for COVID-19.[26] The Tisdale risk score stratification was proposed in several referral hospitals in Indonesia as a tool to guide in treatment decision and monitoring while dealing with medications potentially cause QTc prolongation, such as CQ/HCQ, in COVID-19 patients due to the restriction of contact with patients and lack of dedicated electrocardiogram machine during pandemic.[27] In our study, out of 191 patients were assessed using Tisdale Score. Majority patients had low-risk score and only 7 (3.6%) patients had high-risk score.

Based on Tisdale risk score, QTc interval prolongation and death were found significant in patients with high-risk score compared to low-risk score, 57.1% and 42.9%, respectively. Similar to previous study, Those with medium to high Tisdale scores had significantly worse outcomes, including longer hospital stays, readmissions, intubations, admissions to intensive care units, and hospital death.[28] In our study, patients with high-risk Tisdale score were 2.15 times more likely to have QTc interval prolongation compared to patients with low-risk Tisdale score. Moreover, compared to individuals with low-risk scores, people with high-risk Tisdale scores had a 3.5 times higher mortality risk.

The limitation of study is the number of patients with underlying cardiac disease in this study is relatively small, potentially limiting generalizability to that population. The study is subject to the same limitations as other observational studies.

CONCLUSION

This retrospective study demonstrated that patients with high-risk Tisdale scores were considerably more likely to experience QTc prolongation and death than other COVID-19 patients. Patients with COVID-19 confirm PCR, comorbidity heart failure, and age greater than 50 were more likely to have QTc prolongation. Patients who used QTc prolonging medications (CQ/HCQ), especially those with risk factors, should be regularly monitored. In those patients, the Tisdale risk score can be a valuable tool in treatment decisions for QTc prolonging medications.

Ethical Committee: The study was held in compliance with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guideline and the Declaration of Helsinki). This study has been approved by Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada-Dr. Sardjito General Hospital, with reference no. KE/FK/0705/EC.

Data Availability Statement: The authors declare that the data supporting the findings of this study are available within the article.

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