



The Use of Tisdale Risk Score during Hydroxychloroquine/Chloroquine Treatments on COVID-19 Patients

Anggoro Budi Hartopo^{1,3*}, Ika Trisnawati², Eko Budiono², Brilliant Winona Jhundy¹, Vita Yanti Anggraeni³

¹Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada– Dr. Sardjito Hospital, Yogyakarta, Indonesia

²Division of Pulmonology, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital, Yogyakarta, Indonesia.

³Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia.

ARTICLE INFO

*Corresponding author

Email:

a_bhartopo@ugm.ac.id

Address:

Jalan Farmako Sekip Utara, Yogyakarta 55281
Indonesia

Keywords:

COVID-19; hydroxylchloroquine; risk
assessment

Manuscript submitted: January 15, 2021

Revised and accepted: February 13, 2021

ABSTRACT

Background: The SARS-CoV-2 infection or COVID-19 disease caused significant morbidity and mortality. Early reports showed clinical improvement with hydroxychloroquine (HCQ) and chloroquine (CQ). However, due to the concern of QTc interval prolongation, the strict electrocardiogram monitoring was needed. The use of risk stratification score may help the decision of this monitoring.

Aims: The study purpose is to describe the use of Tisdale risk score in patients with COVID-19 who received HCQ/CQ treatment.

Methods: This was a prospective observational study. Subjects were patients with the diagnosis of high-probability-COVID-19 and confirmed-COVID-19 receiving HCQ/CQ as one of the treatments. The demographic, medical history and laboratory data were recorded. The Tisdale score was calculated based on baseline parameters and the risk categories were divided into three categories: low risk (score <7), moderate risk (score 7-10) and high risk (score ≥11). The HCQ/CQ daily dose, cumulative dose, time of administration, and duration were recorded.

Result: Forty-five subjects were analysed. Most subjects were males (66.7%) at mean age 50.9 years. Most subjects were hospitalized due to severe illness (44.4%). Medical comorbidity was mostly hypertension (31.1%). Most subjects had HCQ treatment (95.6%). Electrocardiogram showed mostly sinus rhythm (97.8%). Mean QTc interval based Bazett formula was 413.1 ms. Tisdale risk categories were low risk (57.8%), moderate risk (31.1%) and high risk (11.1%). Tisdale high risk had significantly lower cumulative dose of HCQ/CQ and shorter duration of HCQ/CQ treatment as compared to Tisdale moderate and low risks counterparts. The premature HCQ/CQ stop occurred in 1 subject (6.7%) with Tisdale moderate risk and 1 subject (6.7%) with Tisdale high risk.

Conclusion: The Tisdale risk score stratification was easily implemented in hospital as a tool to guide in treatment decision and monitoring while dealing with drugs potentially cause QTc prolongation, such as HCQ/CQ, in COVID-19 patients.

INTISARI

Latar Belakang: Infeksi SARS-CoV-2 atau penyakit COVID-19 menyebabkan angka kesakitan dan kematian yang bermakna. Laporan awal menunjukkan perbaikan klinis dengan terapi hidrosiklorokuin (HCQ) dan klorokuin (CQ). Namun, karena permasalahan pemanjangan interval QTc, maka pengawasan

ketat dengan elektrokardiogram diperlukan. Penggunaan skor stratifikasi risiko dapat membantu keputusan tentang pengawasan ini.

Tujuan: Tujuan penelitian adalah untuk mendeskripsikan penggunaan skor risiko Tisdale pada pasien COVID-19 yang mendapatkan terapi HCQ/CQ.

Metode: Penelitian ini merupakan penelitian observasional prospektif. Subjek adalah pasien dengan diagnosis high-probability-COVID-19 dan confirmed-COVID-19 yang mendapatkan HCQ/CQ sebagai salah satu pengobatan. Data demografi, riwayat penyakit dan laboratorium dikumpulkan. Skor Tisdale dihitung berdasarkan parameter dasar dan kategori risiko dibagi berdasarkan tiga kategori: risiko rendah (skor <7), risiko sedang (skor 7-10) dan risiko tinggi (skor ≥ 11). Dosis harian HCQ/CQ, dosis kumulatif, waktu pemberian dan durasi dicatat dan dikumpulkan.

Hasil: Empat puluh lima subjek dianalisis, sebagian besar laki-laki (66.7%) dengan rerata usia 50,9 tahun. Sebagian besar subjek masuk dalam sakit berat (44.4%). Komorbid utama adalah hipertensi (31.1%). Sebagian besar mendapatkan terapi HCQ (95.6%). Elektrokardiogram menunjukkan irama sinus (97.8%). Rerata interval QTc berdasarkan formula Bazett adalah 413.1 millidetik. Kategori risiko Tisdale adalah risiko rendah (57.8%), risiko sedang (31.1%) dan risiko tinggi (11.1%). Tisdale risiko tinggi mempunyai dosis kumulatif dan durasi HCQ/CQ yang lebih rendah dibandingkan Tisdale risiko rendah dan sedang. Penghentian HCQ/HQ lebih awal pada 1 subject (6.7%) Tisdale risiko rendah dan 1 subject (6.7%) Tisdale risiko tinggi.

Kesimpulan: Stratifikasi skor risiko Tisdale secara mudah dapat diterapkan di rumah sakit sebagai sarana untuk membimbing keputusan terapi dan pengawasan saat menggunakan obat-obatan yang berpotensi menyebabkan pemanjangan QTc, seperti HCQ/CQ, pada pasien COVID-19.

Introduction

The SARS-CoV-2 infection or COVID-19 disease had become a pandemic worldwide, including in Indonesia.¹ This disease has caused significant morbidity and mortality throughout the world.¹ Since the beginning of pandemic, Indonesia had increased numbers of patients without any known effective treatment.²

Some early reports showed clinical improvement and faster coronavirus clearance with hydroxychloroquine (HCQ) and chloroquine (CQ).^{3,4,5} Although the evidence came from non-randomized studies with small subjects, W.H.O and Indonesian COVID-19 national protocols adopted CQ and HCQ as treatment modalities for COVID-19.^{6,7} Despite its long experience with HCQ/CQ as treatment for malaria, the warning of potential risk due to fatal arrhythmia limited its use and required strict electrocardiogram monitoring.⁷

In the national protocol released in April 2020, a daily electrocardiogram monitoring in all patients receiving HCQ/CQ was mandatory to detect the potential fatal arrhythmia, namely QTc interval >500 ms (narrow QRS), QTc interval ≥ 550 ms (wide QRS), QTc lengthening >60 ms and the presence of ventricular ectopy.⁷ However this approach was impractical, due to the restriction of hospital staff contacts with patients. The Tisdale risk score was proposed to be used as risk prediction score of drug-associated QTc prolongation, which could assist the selection and monitoring of patients.^{8,9} Therefore, not all

patients needed strict electrocardiogram evaluation after selected by Tisdale risk score.

The studies aimed to describe the use of Tisdale risk score in risk stratification in patients with COVID-19 who received HCQ/CQ treatment and to assess its relation with HCQ/CQ cumulative dose and duration.

Methods

We conducted a prospective observational study at Dr. Sardjito Hospital, Yogyakarta, Indonesia from March 2020 until August 2020. Subjects were patients with the diagnosis of high-probability-COVID-19 (SARS CoV2 PCR-negative result) and confirmed-COVID-19 (SARS CoV2 PCR-positive result) receiving HCQ/CQ as one of the treatments. The use of HCQ/CQ was based on the clinical decision by attending physician according to hospital clinical practice guideline at the time of this study. The inclusion criteria were: patients' age ≥ 18 years old, patients with diagnosis of high-probability COVID-19 or confirmed-COVID-19, patients who received HCQ/CQ treatment, patients who hospitalized in hospital wards or ICU, and patients who agreed to participate in this study. The exclusion criteria were: the incomplete electrocardiogram recording and pregnant patients. The study protocol was approved by Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia.

The demographic, medical history and laboratory data were recorded from medical record into an electronic case

report form during admission. The Tisdale score was calculated based on baseline parameters and the risk categories were divided into three categories: low risk (score <7), moderate risk (score 7-10) and high risk (score ≥11).⁹ The disease severity was determined based on the national protocol classification and adopted by Dr. Sardjito Hospital clinical practice.⁷ The HCQ/CQ daily dose, cumulative dose, time of administration, and duration were in discretion of attending physicians. Twelve-lead electrocardiogram was obtained at baseline before HCQ/CQ using standardized electrocardiograph machines, with standard 12-lead resting electrocardiogram, paper speed of 25 mm/s, the amplitude of 10 mm/V, and a sampling rate of 250 Hz. The measurement of QT interval was performed by two cardiologists independently and manually by standard calipers aided by computer. The QTc interval was calculated by the Bazett's formula.

For statistics analysis, continuous data were reported as mean±standard deviation (mean±SD) and categorical data were reported as count and percentage (n (%)). The descriptive analysis was performed to report the characteristics of subjects. No hypothesis was generated and tested in this study.

Result

Forty-five subjects were eligible in this study. Table 1 showed the characteristics of 45 subjects in this study. Most subjects were males (66.7%) at mean age 50.9 years. The confirmed -COVID-19 was 51.1%. Most subjects were hospitalized due to severe illness (44.4%). Medical comorbidities were mostly hypertension (31.1%), diabetes mellitus (24.4%) and chronic kidney disease (11.1%). Mean bodymass index was 25.2, and obesity (bodymass index > 25) was 46.2%. Most subjects had HCQ treatment (95.6%).

The electrocardiogram showed mostly sinus rhythm (97.8%), with only 1 atrial fibrillation and 1 ventricular extrasystole. No significant arrhythmia found in electrocardiogram recording at baseline. The mean QTc interval based Bazett formula was 413.1 ms.

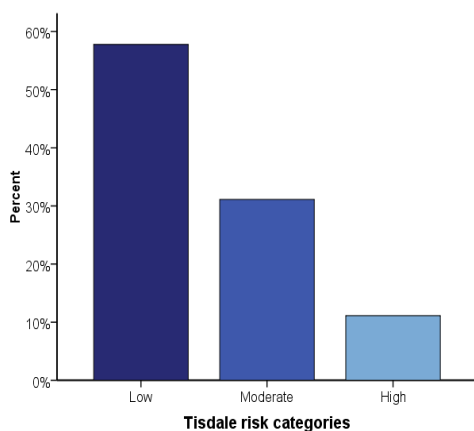


Figure 1. showed that most Tisdale risk category were low risk (57.8%), followed by moderate risk (31.1%) and high risk (11.1%).

Table 1.

The characteristics of subjects

Characteristics	Value
<i>Demography</i>	
Age, mean±SD	50.9±13.4
Sex, n (%)	
Male	30 (66.7)
Female	15 (33.3)
Bodyweight (n=39)	67.9±16.4
Bodymass index (n=39)	25.2±4.7
<i>Medical comorbidities and risk factors</i>	
Chronic heart failure, n (%)	3 (6.7)
Ischemic heart disease, n (%)	1 (2.2)
COPD, n (%)	1 (2.2)
Hypertension, n(%)	14 (31.1)
Diabetes mellitus, n(%)	11 (24.4)
Chronic kidney disease, n(%)	5 (11.1)
Obesity (n=39), n (%)	18 (46.2)
<i>Clinical presentation</i>	
Confirmed-COVID-19, n(%)	23 (51.1)
Disease severity category, n(%)	
Mild	9 (20.0)
Moderate	16 (35.6)
Severe	20 (44.4)
Systolic blood pressure, mean±SD	128.3±24.1
Diastolic blood pressure, mean±SD	76.8±13.7
Pulse rate, mean±SD	99.5±17.9
<i>Laboratory data</i>	
Haemoglobin, mean±SD	12.4±2.7
Leukocyte, mean±SD	10.0±5.4
Platelet, mean±SD	259.3±133.6
Creatinine, mean±SD	1.9±2.7
Glucose (n=39), mean±SD	146.9±63.4
Potassium level, mean±SD	4.0±0.7
<i>Electrocardiogram recording</i>	
Sinus rhythm, n (%)	44 (97.8)
Arrhythmia, n(%)	
Atrial fibrillation	1 (2.2)
Ventricular extrasystole	1 (2.2)
QT interval (Bazett formula), mean±SD	413.1±36.1
<i>Treatment</i>	
Type of HCQ/CQ	
HCQ, n (%)	43 (95.6)
CQ, n (%)	2 (4.4)

Table 2 showed that subjects with a Tisdale high risk had significantly lower cumulative dose of HCQ/CQ and shorter duration of HCQ/CQ treatment as compared to Tisdale moderate and low risks counterparts. The premature HCQ/CQ stop occurred in 1 subject (6.7%) with Tisdale moderate risk and 1 subject (6.7%) with Tisdale high risk. None of subjects with Tisdale low risk underwent premature HCQ/CQ stop.

Table 2.
The cumulative dose, duration and premature stop of HCQ/CQ based on Tisdale risk category

Tisdale risk category	Cumulative Dose (mg), mean±SD	Duration (days), mean±SD	Premature stop, n (%)
Low risk (n=26)	2738.5±1359.7	6.0±2.8	0
Moderate risk (n=14)	3342.9±1614.2	6.6±1.6	1 (6,7)
High risk (n=5)	1520.5±521.5	3.6±1.3	1 (6,7)
p value	0.050*	0.059*	0.742**

* ANOVA test

** Chi-squared test

Discussion

The result of our study indicated that among patients treated with HCQ/CQ due to COVID-19, the Tisdale risk category had been used as an easy and simple screening tool before prescribing HCQ/CQ. The most common subjects were those with Tisdale low risk category. Among Tisdale high risk subjects, who were only a minority, the HCQ/CQ cumulative dose and duration was significantly lower. One subject underwent premature HCQ/CQ stop in Tisdale high risk subjects, whereas none experienced premature HCQ/CQ stop in Tisdale low risk subjects. During this study, the daily electrocardiogram was not performed per-hospital clinical practice, due to pandemic restriction.

During early COVID-19 pandemic, the use of HCQ/CQ was one of the medications approved by WHO and also by Indonesian authority.⁷ Similar to what had occurred in other parts of the world, in Indonesia the use of HCQ/CQ for COVID-19 had been implemented in the national protocol since April 2020.⁷ The Indonesian COVID-19 national protocol gave the clear-cut requirement of daily electrocardiogram monitoring during HCQ/CQ treatment due to its potential impact on QTc prolongation and lethal arrhythmia.⁷ However, since the restriction of contact with patients and lack of dedicated electrocardiogram machine for pandemic, the protocol requirement could not be fulfilled. The ideal use of telemetry or portable device to detect electrocardiogram could not be provided by most hospitals. Therefore, the screening of fatal arrhythmia risk by Tisdale risk score was proposed and our study indicated it was easily implemented.⁸ The majority of our subjects did not undergo daily electrocardiogram, only those in ICU was daily monitored.

The HCQ and CQ are QTc-prolonging drugs which create a threat of fatal arrhythmia and cardiac arrest.^{10,11} About 13% COVID-19 patients had endure QTc prolongation due to the illness itself.¹² This also being aggravated by the use antivirals, antibiotics and other supportive drugs concomitantly or concurrently with HCQ/CQ. Tisdale et al. (2013) had identified several easily obtainable clinical parameters and developed a risk score using these parameters to predict patients at highest risk for QTc interval prolongation during hospitalization.⁹ This risk score was useful in treatment decision and monitoring guidance (strict or loose) decisions during COVID-19 pandemic in subjects taking HCQ/CQ. In our study, the

Tisdale score calculation and risk score stratification was feasible and can be implemented in clinical practice.

Our study had limitation that it did not assess the Tisdale risk score and risk stratification in subjects who did not receive HCQ/CQ treatment.

In conclusion, the Tisdale risk score stratification was easily implemented in our hospital as a tool to guide in treatment decision and monitoring while dealing with drugs potentially cause QTc prolongation, such as HCQ/CQ, in COVID-19 patients.

Acknowledgements

Authors were grateful to: (1) Medic and paramedic staffs at COVID-19 dedicated wards and ICU of Dr. Sardjito Hospital, Yogyakarta, Indonesia, (2) Internal Medicine Residents at COVID-19 dedicated wards and ICU of Dr. Sardjito Hospital, Yogyakarta, Indonesia, and (3) Mr. Untara Vivi Chahya who provided electronic case report form. This research received funding from RSUP Dr. Sardjito, Yogyakarta with contract number: HK.02.03/XI.2/37465/2020 to Anggoro Budi Hartopo as Principal Investigator.

References

- Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, et al. 2020. Current Status of epidemiology, diagnosis, therapeutics, and vaccines for novel Coronavirus Disease 2019 (COVID-19). *J Microbiol Biotechnol*, 30:313-324.
- Ariawan I, Jusril H. 2020. COVID-19 in Indonesia: where are we? *Acta Med Indones*, 52:193-195.
- Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. 2020. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*, 55:105932.
- Gao J, Tian Z, Yang X. 2020. Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*, 14:72-73.
- Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*, 56:105949.
- WHO. Antiviral Drugs that are Approved or Under Evaluation for the Treatment of COVID-19. vol. 19 47–88 <https://www.covid19treatmentguidelines.nih.gov/on> (2020).
- Burhan E, Susanto AD, Nasution SA, Ginanjar E, Pitoyo CW, Susilo A, et al. 2020. Protokol Tatalaksana COVID-19, edisi 1 April 2020. Perhimpunan Dokter Paru Indonesia (PDPI) Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI) Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia (PAPDI) Perhimpunan Dokter Anestesiologi dan Terapi

Intensif Indonesia (PERDATIN) Ikatan Dokter Anak Indonesia (IDAI). Jakarta: Indonesia.

8. Laksono S, Hermanto DY, Iqbal M. 2020. How to manage QT prolongation in COVID-19 patients. *Indonesian J Cardiol*, 41:108-111.
9. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. 2013. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual Outcomes*, 6:479-487.
10. Morissette P, Hreiche R, Turgeon J. 2005. Drug-induced long QT syndrome and torsade de pointes. *Can J Cardiol*, 21:857-864.
11. Agstam S, Yadav A, Kumar-M P, Gupta A. 2020. Hydroxychloroquine and QTc prolongation in patients with COVID-19: a systematic review and meta-analysis. *Indian Pacing Electrophysiol J*, S0972-6292(20)30116-9.
12. Wang Y, Wang Z, Tse G, Zhang L, Wan EY, Guo Y, et al. 2020. Cardiac arrhythmias in patients with COVID-19. *J Arrhythm*, 36:827-836.