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Comparison of QTc Interval Before and After Hydroxychloroquine Therapy in Covid-19 Patients at Kendari City Hospital

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ABSTRACT

Background: *Corona Virus Disease 19 (COVID-19) is caused by SARS-COV 2 which is of global public health concern. Hydroxychloroquine is a drug that is thought to be useful in treating COVID-19, but the mechanism of action of this drug is to block potassium channels and potentially extend the QTc interval. The purpose of this study was to determine the difference in QTc intervals before and after hydroxychloroquine therapy in COVID-19 patients at Kendari City Hospital.* ***Methods:****. This research is an observational analytic study, with a cross-sectional design, which was conducted at the Regional General Hospital of Kendari City. The number of samples in this study were 106 patients. Qtc interval values before and after hydroxychloroquine therapy were collected using medical record data according to the inclusion criteria. Data was processed using paired t test analysis.* ***Results****: Bivariate analysis showed that there was a difference in the average Qtc interval before and after hydroxychloroquine therapy (409.02 vs 426.10, p<0.05).* ***Conclusion:****. There are differences in QTc intervals before and after hydroxychloroquine therapy in COVID-19 patients at Kendari City Hospital*
Keywords*: covid-19; hydroxychloroquine; QTc interval*

INTRODUCTION

On December 31, 2019, the World Health Organization China Country Office reported a case of pneumonia of unknown etiology in Wuhan City, Hubei Province, China. On January 7, 2020, the source was identified as a betacorona virus similar to Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV). It has since been named SARS-CoV-2 and has caused the emergence of the 2019 coronavirus disease, which is referred to as COVID-19 (WHO, 2020).

On March 12, 2020, WHO declared COVID-19 as a pandemic. Based on the report on 05 October 2020, more than 2 million new cases of COVID-19 in the last 3 weeks with a total number of cases reaching 34.8 million cases and 1 million new deaths were reported to WHO (WHO, 2020). Indonesia reported its first case on 2 March 2020

In Southeast Sulawesi until October 6th 2020 there were 3,161 positive confirmation cases and 63 patients who died. In Kendari City, until October 6 2020, there were 1,570 positive cases and 26 patients who died (Dinkes Provinsi Sultra, 2020).

Until now, there is no drug that is truly effective in treating COVID-19. Various studies are continuing to be carried out to find the right formula to treat Covid-19. Hydroxychloroquine is considered capable of overcoming COVID-19, this drug has been observed to inhibit the entry of SARS-CoV-2 which is mediated by the ACE2 receptor through several mechanisms such as increasing intravesicular PH, inhibiting lysosomal activity, affecting antigen processing. In addition, hydroxychloroquine also has anti-inflammatory and immunomodulatory properties in inhibiting reactions caused by cytokines during COVID-19 infection. (Kapoor et al., 2020).

Administration of hydroxychloroquine in vitro prior to SARS-CoV-2 infection in Vero cells caused damage to terminal glycosylation Angiotensin-Converting Enzyme 2 (ACE2) which resulted in reduced bonds between ACE2 and the spike protein of SARS-CoV-2 and inhibited the initiation of SARS-CoV-2 infection 2 (Nugrahaningsih et al., 2020).

In general, hydroxychloroquine is relatively safe to use. However, these drugs block potassium channels and potentially prolong the QTc interval. Prolonging the QTc interval increases the risk of drug-induced torsades de pointes (DI-TdP) or drug-induced sudden cardiac death (DI-SCD) (PERKI, 2020).

According to research conducted by Mercuro et al in 2020, as many as 19% of Covid-19 patients who received hydroxychloroquine therapy experienced an extension of the QTc interval by 500 milliseconds or more (Mercuro et al., 2020).

Kendari City Hospital is a COVID-19 referral hospital based on the Governor's Decree (SK). Research on the differences in QTc intervals before and after hydroxychloroquine therapy in COVID-19 patients has never been carried out, especially in the Kendari City area.

METHODS

This study is an observational analytical study with a cross sectional approach, conducted to determine differences in QTc intervals before and after hydroxychloroquine therapy in COVID-19 patients at the Kendari City Hospital which was carried out in December 2020. The population in this study were all patients who were confirmed to have COVID-19 at In April-September 2020, 392 patients were treated at the Kendari City Hospital. A total of 106 patients who met the inclusion criteria were included in this study, while 286 patients were excluded due to incomplete medical record data. QTc Interval Change is the difference in QTc interval values before and after the 5th day of hydroxychloroquine therapy, taken from the patient's medical record.

To determine the difference in QTc interval values before and after hydroxychloroquine therapy, a paired t test was performed. This research has also received ethical clearance from the Ethical Commission for Health Research, Faculty of Medicine, Halu Oleo University.

RESULTS

The average age of the respondents was 38 years, most were 26-35 years old (40.6%), followed by 46-55 years old (18.9%), aged 36-45 years old (17.9%), aged 17-25 years old were 12 respondents (11.3%), and aged >55 years old were 12 respondents (11.3%) (table 1). A total of 54 respondents (50.9%) were male and 52 respondents (49.1%) were female (table 2). Table 3 shows the sample distribution based on the therapy used, namely 106 (100%) hydroxychloroquine, 106 (100%) azithromycin, 68 (64.2%) levofloxacin, 19 (17.92%) oseltamvir, and antioxidants were 106 (100%). Table 4 shows the average QTc interval before therapy of 409.02 and the average QTc interval after therapy of 426.10 with an average change of 17.07 and p=0.000. These results indicate that there are differences in the value of the QTc interval before and after hydroxychloroquine therapy in COVID-19 patients at the Kendari City Regional General Hospital.

DISCUSSIONS

A total of 106 respondents were analyzed to determine QTc interval values before and after hydroxychloroquine therapy. The data analysis showed that there was a significant difference in the value of the QTc interval before and after hydroxychloroquine therapy in COVID-19 patients at the Kendari City General

Hospital (409.02 ± 19.42 vs 426.10 ± 20.41), with a difference of 17.07 ± 11.11 and p = 0.000. This is in line with a study conducted by Chorin et al in 2020 which showed that hydroxychloroquine and azithromycin can extend the QTc interval in patients with COVID-19.

Another study conducted by Mercuro, et al, in 2020, found that 19% of COVID-19 patients who were given hydroxychloroquine therapy experienced an extended QTc interval to 500 milliseconds or more.

Hydroxychloroquine is known to cause prolongation of the QTc interval through blockade of the hERG potassium channel, which can increase life-threatening ventricular arrhythmias. Prolonged QTc was defined as an increase in the QTc interval of more than 60 ms (ΔQTc > 60 ms) compared to baseline or a QTc of 500 ms or more (Bessiere et al., 2020).

Drug-induced prolongation of the QTc interval is an important substrate for TdP, a potentially lethal polymorphic ventricular tachycardia. In a study conducted on 251 COVID-19 patients, a high incidence of QTc interval prolongation with at least one documented polymorphic VT (suspect TdP) was found at a rate of 0.4% (Chorin et al., 2020).

Another study conducted by Garcia et al, in 2020, showed that hydroxychloroquine therapy at a dose of 800 mg given for 10 days was associated with a rapid viral reduction rate of patients with detectable viral load (9%), but was predicted to result in a significant for QTc prolongation. Administration of hydroxychloroquine with a longer duration and at a higher dose resulted in a higher QTc prolongation. A patient with a baseline QTc value of 420 ms or less can receive a dose of 400 mg over 5 or 7 days with minimal risk (1.0% and 2.0%) of QTc prolongation.

According to a study conducted by Mahevas (2020), 8 respondents who received hydroxychloroquine 600 mg therapy (9.5%) experienced changes in the ECG picture that required discontinuation of hydroxychloroquine with a median of 4 days (3-9) after it was started, according to French national guidelines. Among them, 7 had a QTc interval prolongation of more than 60 ms (including 1 with a QTc > 500 ms).

In this study, changes in the QTc interval in patients receiving hydroxychloroquine therapy at the Kendari City General Hospital did not exceed 500 ms, so that it did not increase the risk of Torsades de Pointes or sudden cardiac death. This happened because the dose of hydroxychloroquine in COVID-19 patients who were treated at the Kendari City Hospital only received a therapeutic dose of 400 mg.

CONCLUSSION

Based on the research that has been done, it can be concluded that there are differences in the QTc interval before and after hydroxychloroquine therapy in COVID-19 patients at Kendari City Hospital. However, the prolongation of the QTc interval is still within normal values which does not increase the risk of lethal arrhythmias.

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Table 1. Distribution of Respondents by Age

Age (Years old)	(n)	%
17-25	12	11,3
26-35	43	40,6
36-45	19	17,9
46-55	20	18,9
>55	12	11,3

Table 2. Distribution of respondents by gender

Gender	n	%
Male	54	50,94
Female	52	49,60
Total	106	100

Table 3. Distribution of respondents based on the therapy

Therapy	n = 106	%
Hydroxychloroquine	106	100
Azitromisin	106	100
Levofloksasin	68	64,2
Oseltamivir	19	17,92
Antioksidan	106	100

Table 4. Differences in QTc intervals before and after Hydroxychloroquine therapy

	n	Mean ± SD	Mean Difference ± SD	*p*
QTc before therapy	106	409,02±19,42	17,07±11,11	0,000
QTc after therapy	106	426,10±20,41		