

# Electrocardiographic Safety of Daily Hydroxychloroquine 400 mg Plus Azithromycin 250 mg as an Ambulatory Treatment for COVID-19 Patients in Cameroon

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## Abstract

**Objective:** To determine the early electrocardiographic changes in a cohort of ambulatory cameroonian COVID-19 patients treated with hydroxychloroquine and Azithromycin. **Design:** Prospective study. **Setting:** Treatment centres of the city of Yaounde, Cameroon, from May 7<sup>th</sup> to 24<sup>th</sup> 2020. **Participants:** We enrolled 51 consecutive confirmed COVID-19 on RT-PCR who having mild forms of COVID-19 and treated by hydroxychloroquine 200 mg twice daily during seven #days plus Azithromycin 500 mg the first day and 250 mg the remaining 4 days as per national standard. **Main Outcomes**

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**Measures:** The primary end-point was the change in QTc interval between day 0 (D0), day 3 (D3) and day 7 (D7). Secondary endpoints were changes in all other cardiac electrical conductivity patterns and the occurrence of clinical arrhythmic events during the course of treatment. **Results:** The population (29 men and 22 women) was aged  $39 \pm 11$  years (range 17 to 61 years). Mean Tisdale score was  $3.35 \pm 0.48$ . No significant change from baseline (D0) of QTc was observed at D7 ( $429 \pm 27$  ms at D0 versus  $396 \pm 26$  ms at D7;  $p = 0.27$ ). A reduction of heart rate was observed between the D0 and D7 ( $75 \pm 13$  bpm versus  $70 \pm 13$  bpm,  $p = 0.02$ ) with increased QRS duration between D0 and D7 ( $95 \pm 10$  ms versus  $102 \pm 17$  ms,  $p = 0.004$ ). No symptomatic arrhythmic events occurred during the treatment course. **Conclusions:** No life-threatening modification of the QT interval was observed in non-severe COVID-19 patients treated ambulatory with hydroxychloroquine and azithromycin. Studies are needed in critical-ill and older patients.

## Keywords

Early Electrocardiographic Changes, COVID-19, Hydroxychloroquine, Azithromycin, Cameroon

## 1. Introduction

Coronavirus disease 19 (COVID-19) is a global public health emergency. Since March 2020, it is recognized as a pandemic [1]. By May 23, 2020, the total number of COVID-19 cases was 5,067,579 in the world with 332,711 global deaths [2]. The disease can range from mild to severe and critical forms. It has been reported that Severe Acute Respiratory Coronavirus 2 (SARS-CoV2), the viral pathogen of COVID-19 affects multiple organs and that one of the major causes of death attributable to COVID-19 was cardiovascular events [3] [4] [5]. The interaction between COVID-19 and the cardiovascular system has been attributed to both the direct effect of SARS-CoV2 in endocardial and myocardial cells through Angiotensin Converting Enzyme 2 (ACE2), but also via an indirect inflammatory mechanism with massive cytokine release. To date, there is no effective treatment for COVID-19. Treatment regimens such as the association of hydroxychloroquine and azithromycin are extensively used in Africa despite controversies on the efficacy and cardiovascular safety [6] [7]. In this preliminary report, we aimed to investigate short term electrocardiographic safety of the combination of 400 mg hydroxychloroquine and azithromycin among a population with high likelihood of previous exposure to chloroquine as part of malaria control efforts.

## 2. Methods

### *Study design, setting, study duration, population*

To inform decision about the discontinuation or not of the hydroxychloroquine and azithromycin based COVID-19 treatment protocol, we conducted a

prospective study in approved COVID-19 treatment centres in the city of Yaounde, Cameroon. From May 7<sup>th</sup> through 24<sup>th</sup> 2020, all consenting consecutive confirmed COVID-19 patients (by RT-PCR on nasopharyngeal swab) on ambulatory treatment due to the non-severe form of the disease were enrolled and follow-up for 7 days. The national standard for non-severe COVID-19 includes oral hydroxychloroquine 200 mg twice daily for seven days and Azithromycin 500 mg the first day and 250 mg from day 2 through 5.

After an interviewer-administered health status questionnaire and clinical examination, a trained nurse performed a 12-leads electrocardiography (ECG) prior to treatment (D0). We excluded all patients with a baseline QTc > 450 msec, a Tisdale score > 10, the use of concomitant drug that prolong the QTc interval or use of hydroxychloroquine or azithromycin within 10 days prior to inclusion. Subsequent ECG recording was performed on Day 3 and Day 7 after starting treatment with hydroxychloroquine and azithromycin. All the patients received FFP2 masks to come to their rendez vous and there was a patient flow ensuring safety. The analysis of ECG was done by three independent consultant cardiologists (LMK, WN, MNT), and findings communicated to participants. A treatment discontinuation was planned in case of prolongation of QTc interval > 500 ms or in case of major clinical arrhythmic events.

**Variables Assessed:** Study variables included sociodemographic (age and gender), clinical (blood pressure, heart rate and oxygen saturation) characteristics, and ECG findings such as the heart rhythm, heart rate, PR-interval, QRS duration and electric axis, QT-interval corrected by Bazett formula (QTc), [8] the ST-segment and the Tisdale arrhythmia risk score [9].

**Primary endpoint:** Change in QTc-interval from baseline (D0) at D3 and D7.

**Secondary endpoints:** Changes of all other electrical patterns of the ECG and the occurrence of clinical arrhythmic events during the treatment course.

**Statistical analysis:** Statistical analyzes were done using EPI Info version 7 Software. Categorical variables were expressed by frequency and percentage; quantitative variables were presented as mean with standard deviations. Mann-Whitney test was used to compare electrocardiographic change between D0-D3, D3-D7 and D0-D7 with p-value < 0.05 considered significant.

**Ethics:** Ethics approval was obtained on May 6<sup>th</sup> 2020 from the National Ethics Committee (N°2020/05/1505/L/CNERSH/SP) prior to inclusion of patients and all participants were adults who gave written informed consent before enrolment.

### 3. Results

#### *General characteristics*

A total of 51 participants were enrolled. The mean age of the participants was 39 ± 11 years (ranging from 17 to 61 years). The male gender was predominant (n = 29, 57%). Participants had few co-morbidities including hypertension in 5.9%. Fever and cough were the most frequently reported symptoms with 21.6% and 23.5% respectively (Table 1). Mean blood pressure was 130 ± 25 (systolic)/84 ± 19 (dia-

stolic) mmHg, and mean oxygen saturation level at enrolment  $98\% \pm 1\%$ . The risk of arrhythmia was low as evidenced by a mean Tisdale score of  $3.35 \pm 0.48$ . At baseline, electrocardiographic recordings presented few abnormalities with left ventricular hypertrophy in 9.8% and the depression of ST-segment in 2 patients.

### **Study endpoints**

**Table 2** shows the variations of ECG characteristics between D0, D3 and D7.

**Table 1.** General characteristics of the participants.

Variables	Frequency (N = 51)	Percentage (%)
<b>Level of Education</b>		
Primary	5	10
Secondary	12	24
University	33	66
<b>Past history</b>		
Alcohol consumption	2	3.9
Tobacco consumption	2	3.9
Hypertension	3	5.9
Diabetes	0	0
Dyslipidemia	0	0
<b>Symptoms</b>		
Asthenia	4	7.8
Fever	11	21.6
Anosmia	8	15.7
Agusia	6	11.8
Headache	5	9.8
Articular pain	4	7.8
Thoracic pain	2	3.9
Dyspnea	1	2
Cough	12	23.5
Rhinorhea	3	5.9

**Table 2.** Variations of electrocardiographic parameters at D0 - D3, D0 - D7, D3 - D7.

Variables	D0	D3	D7	p value		
				D0 → D3	D3 → D7	D0 → D7
Mean heart rate ± standard deviation (bpm)	75 ± 13	78.8 ± 14	70 ± 13	0.72	0.23	<b>0.02</b>
Mean PR interval ± standard deviation (msec)	170 ± 24	175 ± 30	183 ± 38	<b>0.002</b>	0.94	0.25
Mean QRS duration ± standard deviation (msec)	95 ± 10	93 ± 12	102 ± 17	0.1	0.73	<b>0.004</b>
Mean QTc duration ± standard deviation (msec)	429 ± 27	434 ± 29	396 ± 26	0.61	0.38	0.27

bpm: beats per minute; D: day; msec: millisecond.

Changes in QTc were not ( $429 \pm 27$  ms at D0 and  $396 \pm 26$  ms at D7,  $p = 0.27$ ). A reduction of heart rate was observed between the D0 and D7 ( $75 \pm 13$  bpm versus  $70 \pm 13$  bpm,  $p = 0.02$ ) with increased QRS duration between D0 and D7 ( $95 \pm 10$  ms versus  $102 \pm 17$  ms,  $p = 0.004$ ). No clinical arrhythmic events were observed during the treatment course. No death or sudden death was reported.

#### 4. Discussion

Management of COVID-19 patients is a major challenge worldwide as no effective specific treatment is standard. The reported risk of ventricular arrhythmia has raised additional concerns in the use of hydroxychloroquine and azithromycin based protocols [6] [7]. While such protocols are extensively used in Africa since COVID-19 outbreak, little is known about the cardiac safety in this relatively young population with high likelihood of previous exposure to chloroquine or its derivatives in the fight against endemic malaria.

QT interval prolongation exposing to Torsade de Pointes is a well-known side effect of hydroxychloroquine and azithromycin [6] [7] [10] [11] [12]. The main hypothesis for QT prolongation in patients administered chloroquine or hydroxychloroquine is inhibition of the rapidly activating component of delayed rectifier potassium current (iKr). The arrhythmogenic mechanism of azithromycin has been postulated in animal model by the potential to increase cardiac  $\text{Na}^+$  current to promote intracellular  $\text{Na}^+$  loading [13]. In the COVID-19 context, some other pathological conditions linked to QT prolongation are: myocardial injury, renal failure, hepatic failure and electrolyte imbalance such as hypokalemia or hypomagnesemia [6] [14].

Our findings in a young population with limited comorbidities and mild symptomatic COVID-19 do not support short term adverse effects on major ECG measurements, of hydroxychloroquine at 400 mg daily when used in combination with azithromycin. No clinically significant ECG changes nor arrhythmic events were observed during the treatment course. The fact that we did not find the significant modification of the QTc interval in the current study may be explained by the fact that all the patients had mild forms of COVID-19 and few co-morbid conditions. A risk score has been derived and validated by Tisdale *et al.*, for prediction of drug-associated QT prolongation among cardiac-care-unit-hospitalized patients. A score  $\geq 11$  is highly predictive of QT prolongation during treatment, hence, risk of severe cardiac arrhythmia. Our population had a mean Tisdale score of 3 that predicted a low risk of cardiac arrhythmia [9].

We found a significant reduction in heart rate and an increase of QRS duration. Heart rate reduction could be the reflection of inflammation control by the immunomodulatory effect of hydroxychloroquine [15]. Increase QRS duration even if it did not reach the set of definitions of QRS widening has also been reported in patients treated by hydroxychloroquine [16]. These changes were not clinically significant in our cohort and could predict the safety of both hydroxychloroquine and azithromycin in non-severe forms of COVID-19.

## 5. Study Limitations

These results should be interpreted taking into account the limited sample size, the young age of the population with very few co-morbidities and the short term exposition to hydroxychloroquine and azithromycin in the Cameroon national standard protocol to manage COVID-19 patients.

## 6. Conclusion

We did not observe a significant increase in QTc-interval. Only mild and not clinically significant electrocardiographic abnormalities were observed in non-severe COVID-19 patients with low risk of arrhythmia assessed using the Tisdale score, treated with hydroxychloroquine and azithromycin in Cameroon. These preliminary data should be validated by future large cohort study in our setting.

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## Contributions

The authors all contributed equally.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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