Journal of
Antibiotics and Antimicrobial Agents

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Research Article Open Access

Hydroxychloroquine Vs Placebo for Treatment in Hospitalized Patients with COVID-19: A Randomized Controlled Double-Blind Trial in a Single Center in Brazil

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Received Date: January 10, 2024 **Accepted Date:** February 10, 2024 **Published Date:** February 13, 2024

Citation: Natalia Reis Fraga (2024) Hydroxychloroquine Vs Placebo for Treatment in Hospitalized Patients with COVID-19: A Randomized Controlled Double-Blind Trial in a Single Center in Brazil. J Antibiot Antimicrob Agents 1: 1-9.

Abstract

Background: Coronavirus disease 2019 (COVID-19) emerged in December 2019 and rapidly spread wide world causing a severe acute respiratory syndrome (SARS) that requires hospitalization. Given the urgent need for therapies for COVID-19 we aimed to evaluate the efficacy and safety of hydroxychloroquine (HCQ) associated with azithromycin in hospitalized patients diagnosed with COVID-19 compared with placebo.

Methods: We performed a prospective, randomized, controlled, double-blind placebo study that included all patients who required hospitalization, without the need for intensive care support, with confirmed diagnosis of COVID-19 and evaluated the need for mechanical ventilation, mortality and clinical and laboratory adverse events during hospitalization.

Results: We allocated 33 patients in HCQ arm and 30 patients in placebo arm. 61.9% (39/63) were male with a mean age of 59 years. 74.6% (47/63) had comorbidities and the mean time between the onset of symptoms and hospitalization was 8.4 days. Baseline characteristics of patients randomized to both groups are not statistically different. Also, the outcomes the need for mechanical ventilation (24,4% x 20%; p=0,68) and mortality (12,1% x 6,6%; p=0,46) had no statistically significant difference in both groups, respectively.

Conclusion: In this blinded, placebo-controlled randomized clinical trial conducted at one Brazilian's hospital, treatment with hydroxychloroquine did not improve or worsen clinical outcomes for adults hospitalized for respiratory illness from COVID-19. These findings strongly do not recommend the use of hydroxychloroquine for treatment of COVID-19.

Keywords: Hydroxychloroquine; Treatment; Hospitalization; COVID-19; Mortality

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Introduction

Coronavirus disease 2019 (COVID-19) emerged in late December 2019 in Wuhan, China, and in March 2020 the World Health Organization (WHO) declared COVID-19 a pandemic [1,2]. Most of COVID-19 patients present with the mild form of the disease, but a minority may develop a severe acute respiratory syndrome (SARS) requiring hospitalization [3] .

Given the urgent need for therapies for COVID-19, several previously existing drugs have shown promise based on in vitro results [4].

Hydroxychloroquine (an analogue of chloroquine) is approved by the Food and Drug Administration (FDA) in the United States as an antiparasitic agent for malaria and immunomodulatory for rheumatologic diseases [5-7]. In vitro, it has been shown to have an anti-SARS-CoV2 activity generating substantial interest as a potential treatment for COVID-19 due to its wide availability, antiviral activity, immunomodulatory and safety profile established for other indications [8,9].

Despite its unclear benefits, chloroquine and hydroxychloroquine were recommended in international and national treatment guidelines only in the context of clinical trials in hospitalized patients (4,10). Therefore, several studies have been conducted in an attempt to evaluate the efficacy of hydroxychloroquine for the prevention or treatment of COVID-19 [11].

Different studies conducted in different countries have tried to demonstrate the benefit of hydroxychloroquine in different settings also including different outcomes and doses. There are randomized controlled studies in inpatients and outpatients, evaluating the need for hospitalization, mechanical ventilation, mortality and adverse events [12-14].

The Coalition COVID-19 Brazil study evaluated 667 hospitalized patients and found no benefit of chloroquine when compared to standard therapy. However, this study was an open-label study compared with standard therapy and not with placebo [15]. There are no Brazilian studies evaluating the efficacy of chloroquine in hospitalized patients compared to placebo.

Our study aimed to evaluate the efficacy and safety of hydroxychloroquine associated with azithromycin in hospitalized patients diagnosed with COVID-19 compared with placebo.

Methods

Study design

This is a prospective, randomized, controlled, double-blind placebo study to evaluate the efficacy and safety of hydroxychloroquine (HCQ) associated with azithromycin in hospitalized patients diagnosed with COVID-19. The study was carried out at the Hospital do Servidor Público Estadual de São Paulo (HSPE), a public, tertiary and teaching hospital, aimed at the care of public employees in the State of São Paulo, with 753 beds, of which 40 beds were adult intensive care units (ICU). Due to COVID-19 pandemic the hospital increased its capacity of ICU beds for 76. The study was conducted from April 2020 to August 2020.

Inclusion criteria

The study included all patients who required hospitalization, without the need for intensive care support, with confirmed diagnosis of COVID-19. The inclusion criteria were age 18 years or older and presence of at least one respiratory symptom in the last 14 days (cough, runny nose, sore throat) and anosmia, loss of taste or presence of axillar temperature greater than 37.8ºC or need for supplemental oxygen therapy based on oxygen saturation in ambient air ≤ 94% and/or respiratory rate > 24 breaths per minute or significant pulmonary involvement (tomographic aspect compatible with pulmonary involvement equal to or greater than 50%).

All patients included had COVID-19 diagnosis confirmed by RT-PCR performed at central laboratory of São Paulo state.

Exclusion criteria

The exclusion criteria were patients under the age of 18 years; pregnant women; patients with previous QT interval prolongation (corrected QT interval greater than 500 ms); previous history of heart failure and/or acute myocardial infarction; concomitant use of drugs that increase the QT interval; patients with retinopathy of any etiology; patients with severe acute respiratory distress syndrome who required orotracheal intubation on admission and those that did not consent to the participation of the study. All patients signed an informed consent form before randomization and the study was approved by the hospital's ethics committee under number 3.977.054.

Randomization

All investigators were blind to medication and only the pharmacist was not blind and responsible for randomization. Randomization was performed by the BioEstat 5.0 system and assigned a letter to the patient (letter A were cases of the hydroxychloroquine arm and letter B were cases of the placebo arm).

Patients were randomly randomized in a ratio of 1:1 to the hydroxychloroquine 400 mg VO group of 12/12 hours on the first day, followed by 400 mg VO 1x/day for 4 days or placebo at the same dosage. Placebo tablets were identical to hydroxychloroquine tablets.

Patients in both arms received ceftriaxone 1 g 12/12 hours IV plus azithromycin 500 mg orally once daily for 5 days. Heparin or corticosteroid treatment was prescribed according to standard hospital protocol, if necessary.

Follow-up

Randomized patients were followed up throughout the hospitalization period and followed by the investigators in pre-established visits: on admission, third and fifth day after randomization. Serial electrocardiograms were performed on admission and on the third and fifth day to evaluate QT interval prolongation and collection of laboratory tests and chest tomography were performed when requested by the assistant team.

At admission, epidemiological data, clinical evaluation, laboratory tests were collected for identify severity and prognosis assessment. Specific tests for COVID-19 (RT-PCR) were collected and computed tomography of the chest was also performed.

In the daily visits, we also collected data about adverse events and laboratory tests were collected according to medical decision during hospitalization.

Outcomes

The outcomes evaluated were the need for mechanical ventilation during hospitalization; mortality and clinical and laboratory adverse events during hospitalization.

Statistical analysis

All information regarding patients were collected in a standard clinical form and saved in a database using the Excel 5.0 program.

Data analysis was performed using relative frequency. The inferential analysis of qualitative variables was based on the determination of association using Pearson's Chi-square test (X2) or Fisher's exact test (TEF). The anova method of one factor was used to analyze the differences between the means of the quantitative variables.

The potential factors related to primary outcomes were compared by univariate analysis and all factors identified by this analysis as significant were submitted to multivariate analysis by multiple logistic regression model.

The independent variables were expressed using risk ratio ("odds ratios" - OR) and their respective confidence intervals (CI) of 95% were estimated. All probabilities of significance were considered as significant if $p< 0.05$. Statistical analysis was performed using the EPI-INFO program version 6.0.

Results

Patient's characteristics

During the study period, 1529 patients were attended at the hospital and had a confirmed diagnosis of COVID-19. Of these 583 (38.1%) required hospitalization being 156 (26.7%) in an intensive care unit. Although 427 patients could be eligible for the study, we found that the most common reason for patients not to be enrolled was the patient or legally authorized representative declining participation. The flowchart of randomization of patients is described in Figure 1.

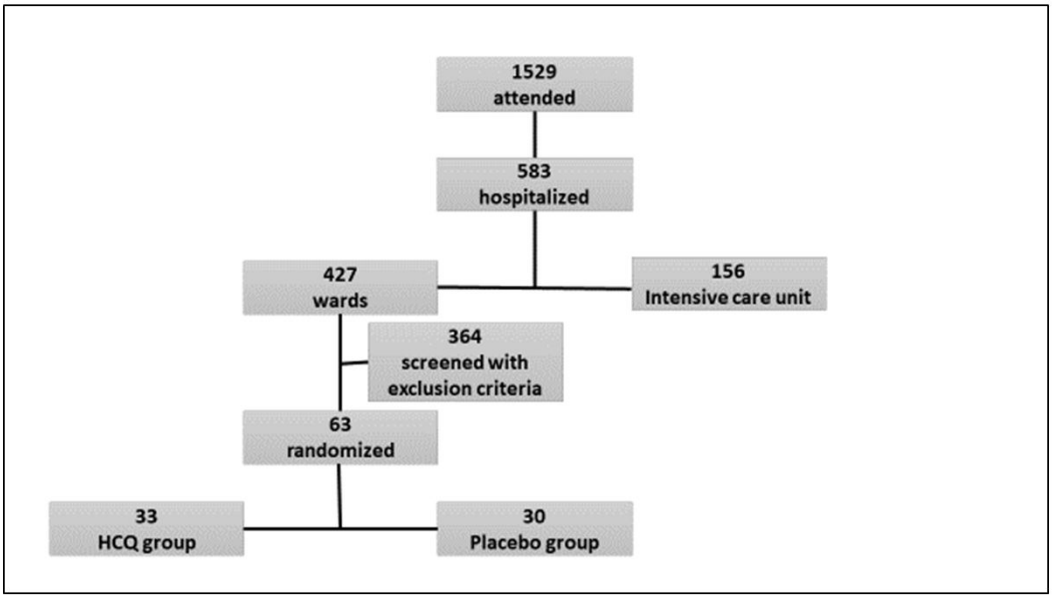

Figure 1: Flowchart of randomization of 1.529 patients attended at HSPE

61.9% (39/63) were male with a mean age of 59 years (±12 years). 74.6% (47/63) had comorbidities and the mean time between the onset of symptoms and hospitalization was 8.4 days (±4,6 days).

Baseline characteristics of patients randomized to the hydroxychloroquine group and placebo group are presented in Table 1

Table 1: Baseline characteristics of the patients by group

Baseline characteristics	**HCQ Group** **N=33** **N(%)**	**Placebo Group** **N=30** **N(%)**	***p***
Sex male	19 (57,5)	20 (66,6)	0,46
Age (mean; years)	60	59	0,85
Comorbidities	23 (69,6)	24 (80)	0,35
Diabetes mellitus	11 (33,3)	13 (43,3)	0,41
Systemic Arterial Hypertension	14 (42,4)	16 (53,3)	0,39
COPD/Asthma	5 (15,1)	2 (6,6)	0,20
Obesity (body mass index > 30)	6 (18,1)	11 (36,6)	0,10
Inclusion criteria			
Symptoms	33 (100)	30 (100)	
O2 supplementation	31 (93,9)	28 (93,3)	0,12
Infiltrates on chest CT > 50%	15 (45,4)	12 (40)	0,66
Symptoms of acute respiratory infection			
Axillary temperature (mean, IQR, º C)	36,5 (35,5-39,1)	36,7 (35,9-38,6)	0,40
Oxygen saturation (mean, IQR, %)	91 (77-99)	92 (84-98)	0,12
Respiratory frequency (mean, IQR, bpm)	21,6 (16-32)	21 (16-28)	0,87

Laboratory measurements			
Hemoglobin (mean, IQR, g/dL, normal range 12-17)	13.6 (10,1-19,3)	13.7 (9.4-16.9)	0,88
Leucocytes (mean, IQR, x10^3/μL, normal range 3.9-10.7)	7.144 (368-13.600)	6.669 (638-17.500)	0,55
Neutrophils (mean, IQR, x10^3/μL, normal range 1.8-8)	4.913 (46-11.433)	4.686 (81-15.000)	0,76
Lymphocytes (mean, IQR, x10^3/μL, normal range 1.2-6	1.206 (369-3.394)	1.156 (300-2.400)	0,76
Urea (mean, IQR, mg/dL, normal range 10-40)	37 (19-145)	46.1 (17-147)	0,20
Creatinine (mean, IQR, mg/dL, normal range 0.5-1.2)	1.1 (0.5-11.2)	1.5 (0.5-11.1)	0,39
AST (mean, IQR, U/L, normal range 6-30)	41 (12-124)	41 (13-98)	0,97
ALT (mean, IQR, U/L, normal range 7-40)	48 (9-174)	32 (5-91)	0,04
Reactive-C-protein (mean, IQR, mg/dL, normal < 0.5)	12.3 (1.6-34)	11.1 (1,2-40)	0,59
Ferritin (mean, IQR, ng/dL, normal range 4-300)	1.337 (156-9.697)	837 (102-3.449)	0,43
LDH (mean, IQR, U/L, normal range 240-480)	285 (44-505)	301 (142-611)	0,56
Dimer-D (mean, IQR, mcg/mL, normal range <0.5)	1.4 (0.3-9.6)	1.1 (0.19-5.4)	0,91
Troponin (mean, IQR, ng/mL, normal range 0-0.04)	0.003 (0.001-0.016)	0.01 (0.001-0.09)	0,03

COPD = chronic obstructive pulmonary disease; CT = computed tomography; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactic dehydrogenase; IQR = interquartile range; bpm = breath per minute

Signs of patient's severity randomized to the hydroxychloroquine group and placebo group on day 5 are presented in Table 2. The symptoms of acute respiratory infection when compared at baseline and at day 5 not show statistically significant difference (p=0,68).

Outcomes and adverse events of patients randomized to the hydroxychloroquine group and placebo group are presented in Table 3. Table 4 demonstrate the median of corrected QT interval in both groups.

Table 2: Signs of patient's severity on D5 of study

D5 characteristics	**HCQ Group N=33 N(%)**	**Placebo Group N=30 N(%)**	***p***
Symptoms of acute respiratory infection			
Axillary temperature (mean, IQR, º C)	36,5 (35,8-38)	36,6 (35,4-38,9)	0,78
Oxygen saturation (mean, IQR, %)	92,4 (82-98)	93 (79-97)	0,68
Respiratory frequency (mean, IQR, bpm)	18,9 (12-27)	20,8 (15-32)	0,12

bpm=breath per minute

Table 3: Comparison of outcomes and adverse events of patients randomized to the study

Outcome	HCQ Group N=33 N(%)	Placebo Group N=30 N(%)	*p*
Mechanical ventilation	8 (24,2)	6 (20)	0,68
Time to IOT (mean, days, IQR)	4 (1-7)	3 (1-8)	0,69
Death	4 (12,1)	2 (6,6)	0,46
Time to death (mean, days, IQR)	14.5 (6-21)	26 (7-45)	0,51
Adverse events			
Increase in hepatic transaminases	1 (3)	0 (0)	0,34
QTc interval prolongation	0 (0)	0 (0)	

Table 4: Corrected QT interval in both groups on D0, D3 and D5 of study

Corrected QT interval (mean, ms)	D0	D3	D5
HCQ (N=33)	396	406	402
Placebo (N=30)	382	386	398

ms= milliseconds

All patients in both groups received ceftriaxone plus azithromycin because these antimicrobials belonged to the standard prescription protocol for patients with COVID-19 at this time. Heparin was prescribed to 31 (93,9%) for HCQ group and to 25 (83,3%) for placebo group. Corticosteroids was prescribed to 22 (66,7%) for HCQ group and to 17 (56,6%) for placebo group. Heparin and corticosteroids were prescribed according to the needs and medical prescription, both without statistical significance (p= 0,62 and 0,41, respectively).

Two patients were excluded from the study; one patient in the hydroxychloroquine group due to increase in hepatic transaminases on D4 (ALT of 505 U/L) and one patient in the placebo group due to voluntary withdrawal.

Discussion

In this blinded, placebo-controlled randomized clinical trial conducted at our center, treatment with hydroxychloroquine did not improve or worsen clinical outcomes for adults with COVID-19.

Enthusiasm for hydroxychloroquine as a potential therapy for COVID-19 was sparked by in vitro studies that suggested it limited entry of SARS-CoV-2 into human cells by inhibiting glycosylation of cell receptors targeted by coronaviruses [16]. Additionally, hydroxychloroquine was investigated by reduce the production of several pro-inflammatory cytokines involved in the development of acute respiratory distress syndrome, a severe manifestation of COVID-19 [17]. These factors, combined with broad availability, oral administration and perceived safety based on historical use in the treatment of malaria and rheumatologic diseases led to an inadequate and widespread clinical use of hydroxychloroquine for COVID-19 [18].

In Brazil, since May 2020, the Ministry of Health released a protocol for the use of hydroxychloroquine. The drug was recommended for patients in the early stages of coronavirus infection and at lower dosages. The release of the substance has always been defended by President of the Republic of Brazil and the differences of understanding about its use were fundamental to the resignation of two Ministers of Health [19]. Despite the protocol, the Ministry admits in the document that there are no studies that prove the unequivocal benefit of this medication in the treatment of COVID-19. Also, it empowers the prescription to the doctor and requires a consent form by the patient [20].

In this context of doubt about the efficacy of hydroxychloroquine in the treatment of COVID-19 we decided to carry out a work with the best level of evidence in order to prove or not the benefit of this medication.

We started the study in April 2020 and during its course we had some difficulties in allocating patients because there were many questions and insecurity of patients to participate and also we had a boycott by hospital doctors in allowing their patients

to participate. So we decide to end the study even with a small number of participants.

The finding of this clinical trial demonstrate that hydroxychloroquine was not efficacious for the treatment of COVID-19 and it is consistent with results from recent studies that also demonstrated no clinical benefit [15,21,22].

These results provide one more strong evidence that hydroxychloroquine is not beneficial for COVID-19. Strengths of this trial included its blinded, placebo controlled design, high adherence to the study protocol, rigorous monitoring for safety events and adverse events and be performed in Brazil, one of the epicenters of the epidemic and where chloroquine is a cause of discord between the lay population, doctors and rulers.

However, this trial had some limitations. First, the trial only included hospitalized adults and findings may not be generalizable to other populations neither for prophylaxis. Nowadays, we already have evidence that hydroxychloroquine did not reduce the risk of acquiring SARS-CoV-2 infection. Pooled data from 12 studies, with 9917 participants showed that hydroxychloroquine should not be used neither in prophylaxis nor in treatment of patients with COVID-19 [23]. Second, the trial did not include collection of information on serum hydroxychloroquine concentrations, viral shedding or biomarkers of inflammation. Third, only one dosing regimen of hydroxychloroquine was studied in the trial. This regimen was selected based on in vitro studies of hydroxychloroquine, lung concentrations and doses commonly used for COVID-19. Other trials that evaluated higher doses of hydroxychloroquine also demonstrated no clinical benefit and had been associated with more severe toxicities [24].

Although our study found no benefit in the use of hydroxychloroquine for the outcomes of need for mechanical ventilation and mortality during hospitalization, we also did not find significant toxicity with use of the drug mainly in relation to cardiac arrhythmias and considering the concomitant use of azithromycin. In a systematic review and meta-analysis recently published, the hydroxychloroquine group has a significantly higher rate of any adverse event (RR 2.68; 95% CI 1.55-4.64), as compared to the control group [23]. So**,** we have to consider that the use of these drugs without scientific evidence can lead to serious adverse reactions [25,26].

Over this time, scientific knowledge and international experiences have shown that the proven measures to control the pandemic are non-pharmacological strategies, such as correct use of effective masks, hand hygiene, testing and screening capacity, distancing and social isolation always combined with wide vaccination coverage.

Conclusion

Among adults hospitalized with respiratory illness from COVID-19, treatment with hydroxychloroquine, compared with placebo, did not significantly improve need for mechanical ventilation neither mortality during hospitalization. These findings do not support the use of hydroxychloroquine for treatment of COVID-19 among hospitalized adults.

Acknowledgements

We thank all patients who agreed to participate in this study, even with all the politicization involving COVID-19 in Brazil. We also thank the families of all victims of this disease.

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