Original article

Hydroxychloroquine with azithromycin in patients hospitalized for mild and moderate COVID-19

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ARTICLE INFO

ABSTRACT

Objectives: To assess the efficacy of hydroxychloroquine in combination with azithromycin in terms of clinical and biochemical outcomes in adult patients with COVID-19 hospitalized for acute respiratory distress syndrome (ARDS), and to describe the occurrence of adverse events.

Method: Retrospective comparative study, based in a quaternary private hospital in Rio de Janeiro, Brazil, involving 193 adult patients hospitalized for mild and moderate COVID-19 related ARSD, analyzing treatment efficacy based on clinical and biochemical outcomes.

Results: The active group comprised 101 (52.3%) patients using hydroxychloroquine associated with azithromycin and the control group 92 (47.7%) patients who did not take these medications. Median age was 59 (47–70) in the active group and 65 (47–77) in the control group (p < 0.05). Patients in the control group had greater extent of pulmonary involvement on baseline chest CT scans (p < 0.05). All other baseline variables (BMI, comorbidities, previous use of medications and biochemical assessments) were similar between groups. In the medication group, 25% (25 out of 101) were admitted to the ICU, compared to 21% (19 out of 92) in the control group (p > 0.05). No difference in mortality, duration of non-invasive oxygen use or duration of hospitalization was seen between groups. The therapeutic regimen was well tolerated, with only eight (7.9%) patients presenting gastrointestinal symptoms and eight (7.9%) patients withdrawn treatment due to QTc prolongation.

Conclusions: Patients treated with hydroxychloroquine combined with azithromycin and the control group had similar clinical outcomes. This therapeutic regimen was considered

ineffective in hospitalized patients with mild to moderate COVID-19 related ARDS and was associated with few non-severe adverse events.

Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory illness with systemic manifestations caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is associated with considerable morbidity and mortality.[1,2] Main symptoms are fever, fatigue, dry cough, and myalgia, which can progress to dyspnea or, in more severe cases, acute respiratory distress syndrome (ARDS). While most adults with COVID-19 recover, a minority develop ARDS requiring hospitalization.[3,4] Approximately 80% of patients have mild illness, 15% have moderate to severe disease and 5% have critical illness.[3,5]

Hydroxychloroquine has generated interest and great debate as a potential treatment for COVID-19 due to widespread availability, low cost, antiviral and immunomodulatory activity, and established safety profile from historical use for other indications such as malaria and autoimmune diseases.[6,7] in vitro, hydroxychloroquine limits entry of SARS-CoV-2 into cells and late stage viral replication.[6–11] Furthermore, hydroxychloroquine reduces production of several pro-inflammatory cytokines potentially involved in the development of ARDS among infected patients.[12–14] Associated with azithromycin, hydroxychloroquine was suggested to decrease SARS-CoV-2 viral load in non-randomized studies.[11,15] Based on these mechanisms of action and clinical experience early in the pandemic, hydroxychloroquine was used as a treatment for COVID-19 in some settings and discussion regarding its efficacy is still in course.[16]

Treatment of COVID-19 with hydroxychloroquine has been recommended in many treatment guidelines, including in China, France, Italy, Netherlands, South Korea, United States and in Brazil, where national regulatory agencies have authorized the use of hydroxychloroquine in hospitalized patients.[17–19] Our primary aim was to assess the efficacy of hydroxychloroquine in combination with azithromycin in terms of clinical and biochemical outcomes in adult patients with COVID-19 hospitalized for mild to moderate ARDS. Secondary aim was to describe the occurrence of adverse effects potentially associated with the therapeutic regimen.

Material and methods

This was a retrospective study with analysis of electronic medical records of patients admitted for mild and moderate COVID-19 related ARDS in a single quaternary private hospital in Rio de Janeiro, Brazil, from March through June 2020. Consecutive patients aged 18 years and older with COVID-19 confirmed by a positive reverse transcription polymerase chain reaction (RT-PCR) testing (GeneXpert[R] Xpress – Cepheid, CA, USA) from nasopharyngeal sample were included. Patients who were initially admitted to the intensive care unit (ICU) or with no confirmation by RT-PCR for SARS-CoV-2 infection were excluded from this study.

The severity of patients was defined as mild to moderate if, at baseline, quick sequential organ failure assessment (qSOFA) score was 0 or 1, and as severe if patients required invasive ventilatory support in the first 24 h of hospital admission.

In our hospital, from March through May 2020, hydroxychloroquine was prescribed as initial therapy associated with azithromycin. Patients received a total dose of 2400 mg of oral hydroxychloroquine prescribed for five days (400 mg b.i.d. in the first day and 400 mg once a day thereafter), associated with azithromycin 500 mg a day by oral or venous route also for five days. Although this combination was prescribed according to our hospital's initial protocol, some patients refused to take hydroxychloroquine or had contraindication [arrythmia, corrected QT interval (QTc) >470 ms in men or 480 ms in women, renal or hepatic dysfunction] and they constituted the control group.

Data regarding age, sex, severity, body mass index (BMI), comorbidities, previous medication use, and patients' initial extent of pulmonary involvement on chest computed tomography (CT) scans were collected retrospectively. The following clinical outcomes were assessed: discharge, transfer to ICU for invasive oxygen use, death, duration of hospitalization, duration of non-invasive oxygen use, occurrence of gastrointestinal symptoms (nausea, vomiting, abdominal pain or diarrhea) and QTc abnormalities. The electrocardiogram (ECG) was recorded on a Pagewriter TC30 device (Koninklijke Philips N.V., Netherlands) in 12 leads, with manual, automatic and rhythm measurements, maximized by the Glasgow algorithm. Biochemical assessment included serum global leucometry count and lymphocyte count (Sysmex – XE/XN; Sysmex America Inc./USA), aspartate aminotransferase (AST), alanine aminotransferase (ALT) (Alinity – CI – series; Abbott Diagnostics/USA), troponin, D-dimer and fibrinogen (ACL TOP; Werfen/Spain), and C-reactive protein (CRP) levels (Immage 800 – Beckman Coulper Inc./USA), analyzed at baseline and during hospitalization.

In patients who were receiving hydroxychloroquine, QTc interval was analyzed daily. Hydroxycholoquine was withdrawn if QTc interval increased 60 ms from baseline or was superior to 470 ms in men or 480 ms in women, and an ECG was repeated to monitor cQT interval.

Chest CT scans were obtained in helical tomography with 64 channels (Brilliance 40, Philips, Medical Systems, OH, USA). In none of the tests performed, iodinated contrast medium was used. The extent of pulmonary involvement was defined as mild (when viral pneumonia affected less than 25% of the lungs), moderate (26%–50%) and severe (>50%). To make the assessment less subjective, a scoring scheme was used, with one point for each affected lung segment. The score varied from 0 to 40 and was graded as follows: from 1 to 10 points:

Table 1 – Baseline demographic and clinical characteristics of the participants.

Characteristic	Total (N = 193)	Active group (N = 101)	Control group (N = 92)	p-Value
Male sex – n.(%)	117 (61%)	59 (50.4%)	58 (49.6%)	>0.05
Age, median (IQR) – years	68 (47−72)	59 (47−60)	65 (47−77)	**<0.05**
BMI, median (IQR) – kg/m²	28.3 (32.4−25.9)	29 (26−33)	28 (25−31)	>0.05
Current smoker – n. (%)	12 (6%)	9 (9%)	3 (3%)	>0.05
Hypertension – n. (%)	100 (51.8%)	54 (54%)	46 (50%)	>0.05
Diabetes mellitus – n. (%)	57 (29.5%)	22 (21.8%)	35 (38.0%)	>0.05
Heart disease – n. (%)	30 (15.5%)	13 (12.9%)	17 (18.5%)	>0.05
Pulmonary disease – n. (%)	13 (6.7%)	6 (5.9%)	7 (7.6%)	>0.05
Oncologic disease – n. (%)	10 (5.2%)	5 (4.9%)	5 (5.4%)	>0.05
Previous use of ACEI/ARB – n. (%)	80 (41.5%)	45 (44.5%)	35 (38.0%)	>0.05
Previous use of statin – n. (%)	38 (19.7%)	16 (15.8%)	22 (23.9%)	>0.05
Previous use of metformin – n. (%)	32 (16.6%)	14 (13.8%)	17 (18.5%)	>0.05
qSOFA = 0	159 (82.4%)	80 (79.0%)	79 (85.9%)	>0.05
qSOFA = 1	34 (17.6%)	21 (21.0%)	13 (14.1%)	
qSOFA = 2	0	0	0	
qSOFA = 3	0	0	0	

Abbreviations: IQR, interquartile range; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CT, computed tomography.

mild (up to 25%); 11–20 points: moderate (26–50%), and >20 points: severe (>50%).

All data were collected in spreadsheets in Microsoft Excel version 365 (Microsoft Corp., Redmon – WA – USA) and the statistical analysis was performed using SAS Guide 4.3 (SAS Institute Inc., Cary – NV – USA).

Descriptive analyses were performed for all variables. Kolmogorov-Smirnov test was used to check if the continuous variables had normal distribution. As the continuous variables did not present a normal distribution, non-parametric tests were used for all variables. For continuous and discrete countable variables, the Wilcoxon Mann–Whitney test and the Kruskal–Wallis test were used to compare two or more categories, respectively. For dichotomous variables, the chi-square test was performed. For all tests, the p-value was calculated within 95% of confidence. Statistical significance was considered when p < 0.05.

The study is in accordance with ethical standards and was approved by local Ethics Committee (National Commission of Ethics in Research/CONEPCAAE 31634420.0.0000.5282/Opinion n. 4.028.151) prior to data collection.

Results

Four hundred and nineteen adult patients were initially screened. From these, 36 (8.6%) had negative RT-PCR for SARS-CoV-2 infection and were excluded from this study. Out of 383 patients, 190 (49.6%) were initially admitted to the intensive care unit (ICU) for severe COVID-19 related ARDS and were also excluded. One hundred and ninety-three patients were consecutively admitted for mild or moderate COVID-19 related ARDS and were included in this study. Of those, 101 (52.3%) used hydroxychloroquine associated with azithromycin (active group) and 92 (47.7%) did not, being considered as the control group. Reasons for not taking hydroxychloroquine combined with azithromycin were: 44 (47.8%) patients had contraindications and 32 (34.8%) refused to take this combination. In 16 (17.4%) patients, this reason was unknown.

Demographic and clinical characteristics are provided in Table 1. The majority of patients were male (117/193; 61%). Median age was 68 years (IQR 47−72) in the total cohort, with 59 years (IQR 47−70) in the active group and 65 years (IQR 47−77) in the control group (p < 0.05). The median BMI was 28.3 kg/m² in the total cohort and both groups had similar median BMI [28 (IQR 25−31) in the active group and 29 (IQR 26−33) in the control group (p > 0.05)]. Hypertension was the most common chronic disease reported, affecting 51.8% (100/193) of the studied population, followed by 29.5% (57) with diabetes mellitus, 15.0% (30) heart disease, 6.7%[13] chronic pulmonary disease, and 5.2%[10] cancer. The frequency of previous comorbidities was not different between groups.

Regarding previous use of medication, angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) use was reported by 41.5% (80/193) of the patients, statins by 39 (19.7%) and metformin by 32 (16.7%) patients, with no significant difference between groups.

Pulmonary CT scan was unavailable in 26 out of 193 patients (exams performed before admission at another facility). Among the 166 CT scans, the extent of pulmonary involvement was considered mild in 60 (36.1%) patients, moderate in 76 (45.8%), and severe in 30 (18.1%) patients (Table 2). Among patients in the active group, 46.2% (36/78) had mild involvement on CT scan, 32 (41.0%) had moderate, and 10 (12.8%) had severe involvement. In the control group, 27.3% (22/86) had mild involvement, 44 (50%) had moderate and 20 (22.7%) had severe involvement. These differences were statistically significant between groups (p = 0.03). However, the median number of affected lung segments of all patients was 11 (IQR 1−20) and there was no difference between groups in that regard.

In terms of biochemical assessment, patients in both groups had similar baseline, peak and nadir values of leukocyte counts, lymphocyte counts, fibrinogen, D-dimer, hepatic enzymes and troponin levels during follow-up, with no statistical difference between groups as shown in Table 3. C-reactive protein (CRP) was lower at baseline in the active group and

Table 2 – Baseline chest computed tomography scans of patients in the active and control groups.

Characteristic	Total (N = 166)	Active group (N = 78)	Control group (N = 86)	p-Value
Pulmonary CT involvement n. (%)				**<0.05**
Mild (0−25%)	60 (36.1%)	36 (46.2%)	22 (27.3%)	
Moderate (26−50%)	76 (45.8%)	32 (41.0%)	44 (50.0%)	
Severe (>50%)	30 (18.1%)	10 (12.8%)	20 (22.7%)	
Number of affected lung segments – median (IQR)	11 (1−20)	11 (5−18)	11 (8−20)	>0.05

Abbreviations: CT, computed tomography; IQR, interquartile range.

Table 3 – Biochemical assessment at baseline and during hospitalization in the active and control groups.

Variable – median (IQR)	Active group (N = 101)	Control group (N = 92)	Reference value	p-Value
Leukocytes (mm^3)				
Baseline	6000 (4900−7360)	5200 (4400−6950)	4000−11,300	>0.05
Peak	7800 (6300−9900)	7200 (5500−9400)		>0.05
Lymphocytes (mm^3)				
Baseline	1260 (840−1620)	1144 (780−1404)	1000−4800	>0.05
Nadir	1050 (654−1344)	868 (624−1180)		>0.05
Fibrinogen (mg/dL)				
Baseline	497 (401−627)	353 (297−524)	220−496	>0.05
Peak	496 (401−657)	352 (297−524)		>0.05
D-dimer (ng/mL)				
Baseline	758 (463−1236)	753 (520−1227)	<500	>0.05
Peak	1193 (797−1844)	1047 (645−2228)		>0.05
LDH (U/L)				
Baseline	497 (401−627)	273 (221−358)	120−246	>0.05
Peak	346 (287−444)	301 (239−375)		<0.05
Baseline troponin (ng/L)	4 (2−10)	6 (2−13)	<19	>0.05
AST (U/L)				
Baseline	38 (29−61)	45 (36−60)	14−36	>0.05
Peak	49 (40−66)	50 (30−69)		>0.05
ALT (U/L)				
Baseline	31 (19−48)	42 (25−58)	<35 Women	>0.05
Peak	48 (28−71)	38 (23−55)	<50 Men	>0.05
CRP (mg/dL)				
Baseline	6 (3−15)	9 (5−19)	<1	**<0.05**
Peak	16 (6−24)	9 (5−21)		**<0.05**

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 4 – Clinical outcomes in the active and control groups.

Outcome	Total (N = 193)	Active group (N = 101)	Control group (N = 92)	p-Value
Transfer to ICU – n. (%)	44 (22.8%)	25 (25%)	19 (21%)	>0.05
Death – n. (%)	22 (11.4%)	11 (11%)	11 (12%)	>0.05
Duration of niO$_2$ – days – median (IQR)	143 (74.1%)	5 (3−9)	6.5 (3−16)	>0.05
Duration of hospitalization – days – median (IQR)	7 (5−12)	7 (5−11)	8 (5−13)	>0.05

Abbreviations: IQR, interquartile range; ICU, intensive care unit; niO$_2$, non-invasive oxygen therapy.

peaked higher during follow-up compared to the control group. Lactate dehydrogenase (LDH) had also higher values at follow-up in the active group.

There were no significant differences in clinical outcome results between the two groups (Table 4). A total of 44 (22.8%) patients were transferred to ICU as invasive oxygen use was needed: 25 (25%) patients in the active group and 19 (21%) in the control group. Death occurred in 22 cases (11.5%), with 11 deaths in each group. The remaining patients were discharged.

The therapeutic association was well tolerated, with gastrointestinal symptoms occurring in only 8 (7.9%) patients of the active group and in 15 patients (16.0%) of the control group (p = 0.08). Hydroxychloroquine was withdrawn in 7.9% (8/101) patients due to QTc prolongation, with subsequent ECG normalization after withdrawal and no arrythmia reported. Patients in the control group did not have ECG to assess QT interval.

Discussion

We assessed the efficacy of hydroxychloroquine in combination with azithromycin in 101 adult patients with COVID-19 hospitalized for mild to moderate ARDS by comparing data

with 92 similar patients, considered as the control group. No statistical significance was found in clinical and in the majority of biochemical outcomes. Our groups were comparable since the majority of baseline variables analyzed were similar between groups. We only found differences in age, percentage of pulmonary involvement (but not in the number of pulmonary segments affected) and also in baseline CRP, which were all lower in the treatment group. Even in younger patients with milder pneumonia and lower CRP, hydroxychloroquine combined with azithromycin was not effective in these patients hospitalized for mild or moderate COVID-19 related ARDS. In general, this combination was well tolerated, but in almost 8% of treated patients it was withdrawn due to QTc prolongation.

In other studies, several protocols of hydroxychloroquine administration have been used for mild, moderate and severe cases. In a quaternary center, 811 patients with moderate to severe COVID-19, defined as resting oxygen saturation of less than 94%, were treated with hydroxychloroquine in combination with azithromycin for five days and 565 were not treated.[20] Although hydroxychloroquine-treated patients were more severely ill at baseline than the control group, authors did not find differences between both groups regarding intubation or death in this observational study. Moreover, in a similar retrospective study done at a French university hospital, authors studied lower doses of hydroxychloroquine alone in mild, moderate and severe COVID-19. No significant reduction of the risk of unfavorable outcomes (death, transfer to ICU) was observed with hydroxychloroquine in comparison to standard care.[21]

Furthermore, in an impressive large multicenter retrospective study that included 2541 patients, authors analyzed if hydroxychloroquine alone or in combination with azithromycin, or neither drug, was associated with in-hospital mortality in patients with COVID-19. Some patients had severe COVID-19 needing intensive care treatment. In this study, hydroxychloroquine was used as prescribed at our hospital, but azithromycin dose was lower than that used in our study. The combination of hydroxychloroquine + azithromycin was reserved for patients with severe COVID-19 and minimal cardiac risk factors. They found that hydroxychloroquine alone or in association with azithromycin was associated with reduction in COVID-19 mortality with respiratory failure as the primary cause of death.[22] However, this has not been confirmed in subsequent clinical trials.

In the COALITION II trial, patients received treatment with hydroxychloroquine (400 mg twice daily for 10 days) in different Brazilian hospitals for severe COVID-19. Authors found that hydroxychloroquine associated with azithromycin did not improve clinical outcomes compared to standard treatment in severe COVID-19.[23] Moreover, in the RECOVERY trial, with 1561 patients hospitalized with COVID-19, authors found that hydroxychloroquine at high doses was not associated with reduction in 28-day mortality, but was associated with worse outcomes (increased length of hospital stay and progression to invasive mechanical ventilation and death).[24] These findings, along with other studies, indicated that hydroxychloroquine was not effective for hospitalized patients with severe COVID-19, even prescribed in different doses.[25] But discussion regarding its use in patients with milder SARS-CoV-2 infection remained in course in different countries.

In our study, exclusively focused on patients admitted for mild to moderate COVID-19 related ARDS, with baseline qSOFA 0 or 1 and not requiring invasive oxygen therapy, hydroxychloroquine plus azithromycin use was neither associated with lower mortality nor lower need of invasive oxygen therapy, lower transfer rate to ICU or lower duration of hospitalization. The only baseline significant differences between our study groups were lower median age, lower percentage of pulmonary involvement (with no difference in the number of affected lung segments) and lower CRP in the active group, which could ameliorate the results of the active treatment. But this was not seen. Similar results were found in an open-label, multicenter, randomized, controlled trial, entitled COALITION COVID-19 BRAZIL I. In this trial, authors assessed whether hydroxychloroquine, alone or in combination with azithromycin, would be effective in improving clinical status in the same levels of disease severity (mild to moderate), but with more time of active treatment (seven days).[26] They did not find any significant difference in clinical outcomes among groups. They found more frequent adverse events in patients who received hydroxychloroquine, either in combination or alone, regarding QTc prolongation and increase in liver-enzyme levels compared to patients who did not receive either medication. In our study, we did not find any difference regarding liver enzyme levels, but we found greater CRP and LDH peak values during follow-up, which suggested more systemic inflammation in the course of the disease in the active group. Our findings are also consistent with recent published meta-analyses assessing the outcomes of COVID-19 patients treated with hydroxychloroquine as monotherapy or combined with azithromycin that showed no benefit in mild to moderate disease.[27–29]

The study has some limitations such as its retrospective nature and smaller sample size compared to other studies, but has the strength of having homogeneous groups regarding baseline variables, including comorbidities and previous medications used, not evaluated in other studies, which had permitted a fair comparison between them, with better reliability of our findings. Also, we used a clear standardized protocol for treatment and all patients were from a single center in a single health system, in which the same medical teams had treated the patients.

In conclusion, the use of hydroxychloroquine combined with azithromycin showed no benefits when compared to the standard care, based on clinical and biochemical outcomes in adult patients hospitalized for mild to moderate COVID-19 related ARDS and was associated with few non-severe adverse events.

Funding

Conflict of interest

The authors declare no conflicts of interest.

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