



Hydroxicloroquine, What is the Role of the Drug in the Treatment of COVID-19? A Review

**Eliza Miranda Ramos^{1,2*}, Francisco José Mendes dos Reis¹,
Gilberto Gonçalves Facco³, Emerson Luiz Lima Araújo⁴,
Igor Domingos de Souza⁵, Glícia Caroline Andrade Ramos⁶,
Alessandro Carvalho da Fonseca⁷, Iara Barbosa Ramos⁸, Hugo Vieira Ramos⁹
and Valter Aragão do Nascimento¹**

¹*Spectroscopy and Bioinformatics Group Applied to Biodiversity and Health, Faculty of Medicine, Graduate Program in Health and Development in the Midwest Region, Federal University of Mato Grosso do Sul, Campo Grande, Mato Grosso do Sul, Brazil.*

²*Foundation Brazil – CAPES, Brazil.*

³*Graduate Program in Environments and Regional Development, Anhanguera University, UNIDERP, Mato Grosso do Sul, Brazil.*

⁴*Ministry of Health, Secretary of Health Surveillance, Department of Strategic Coordination of Health Surveillance, General Coordination of Public Health Laboratories, Brasília-DF, Brazil.*

⁵*Anhanguera University Center of Campo Grande - MS, Superior Course of Technology in Radiology, Mato Grosso do Sul, Brazil.*

⁶*Secretary of State for Health of the Federal District, Brasília - DF, Brazil.*

⁷*Brazilian Hospital Services Company - EBSERH/Dourados, Mato Grosso do Sul, Brazil.*

⁸*Centro Universitário Anhanguera de Campo Grande - MS, Nursing Course, Mato Grosso do Sul, Brazil.*

⁹*Federal University of Mato Grosso do Sul, Campo Grande, Mato Grosso do Sul, Brazil.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Coronaviruses (COVID-19) is an emerging virus with severe respiratory infection. Despite several efforts, so far there is no medicine to fight it and use it as the ideal treatment. **OBJECTIVES:** This study aims to describe the role of hydroxychloroquine in the treatment of patients with COVID-19 and thus present its benefits in the respective doses. **Methodology:** The methodology used was the systematic review with meta-analysis. **Results:** From the reading of the 75 papers found, only three articles were excluded for not presenting a complete abstract, 65 were excluded for not presenting eligibility according to the inclusion criteria, 01 was excluded for reaching a methodological score below 20 points in Down and Black (1998) and ending the process of inclusion of the articles, only 06 articles were included and included 894 patients. **Conclusion:** Despite the small number of published articles, this meta-analysis found that the use of hydroxychloroquine as an adjunct therapy in the follow-up of COVID-19 in patients with mild to severe clinical signs brings benefits and avoids hospitalization in intensive care.

Keywords: Hydroxychloroquine; COVID-19; extension QT; hospitalization; viremia.

1. INTRODUCTION

The world in recent years has suffered three major epidemiological outbreaks of influenza in the period of 100 years and due to the appearance of these outbreaks it was possible to carry out the genetic and molecular identification of three antigenic virus subtypes differentiated in the groups known in the region, for example, H1N1 or A, H2N2 and CoV [1,2-4].

However, viruses such as coronavirus (CoV) were discovered in 1965 and presented the same severity as found in influenza [5], but advances in research until the mid-1980s on this virus were only recognized through the diagnosis made in the embryonic trachea human infection of a contaminated patient which caused severe respiratory changes in the population in the 1980s and currently COVID-19 has caused a high mortality rate worldwide and has worried health professionals and researchers [5].

In December 2019, COVID-19 was detected in China, in the city of Wuhan [5]. COVID-19 has a very high transmission capacity and its worsening is known as severe acute respiratory syndrome CoV 2 (SARS-CoV-2). However, in early April in Brazil, severe pneumonia caused by COVID-19 (SARS-COV-2) started in populous regions like the city of São Paulo and Rio de Janeiro and, due to the ease of transmission, reached a high level percentage of the Brazilian population and overcame territorial barriers that affect small towns like Guia Lopes da Laguna, in the state of Mato Grosso do Sul [6].

It is worth mentioning that COVID-19 is rapidly transmitted [3,7], which is why it worries health

professionals in the world and the aggravation usually occurs according to the clinical and immunological conditions of patients and patients tend to progress to complications such a viral infections and diseases caused by pneumonia and death [8,9,10].

In Brazil, some researchers are joining forces to fight a COVID-19 pandemic and reducing mortality rates with the use of preventive drugs in the treatment and, recently, the use of hydroxychloroquine was authorized by the Brazilian government [6-12]. Hydroxychloroquine is a drug used for more than 70 years in the treatment of malaria in Brazilian territory and in the last fifteen years it has also been used in Lupus [13,14,15].

In other countries, studies that with hydroxychloroquine showed antiviral activities against other types of endemic viruses, especially the coronavirus, for example, in China in 2020, a study was conducted that demonstrated the use of drugs against various strains of influenza viruses and highlighted the probability of use as a preventive treatment in COVID-19 [16,15,17]. In January 2018, hydroxychloroquine was used as an inhibitor of equine encephalitis virus in Venezuela, which showed beneficial results [18].

Thus, these outstanding studies on the use of hydroxychloroquine in the treatment of auxiliary viral diseases such as broad-spectrum antivirus activities, interfere with the mutation frequency in the viral cell RNA transition, however, this genetic statistics in the host is not performed and, therefore, create a lethal

mechanism in the mutagenic viral process [19,20].

Given the above, a question related to this systematic review with meta-analysis in relation to the use of hydroxychloroquine in COVID-19 is: How does a hydroxychloroquine actually in the treatment of adults with mild symptoms of strains in COVID-19? And does hydroxychloroquine decrease the risk of worsening patients with mild symptoms? Thus, based on these issue, this systematic review with meta-analysis aims to describe the role of hydroxychloroquine in the treatment of COVID-19.

2. METHODOLOGY

Eligibility criteria - The articles chosen to be included in this systematic review and meta-analysis were the studies that presented groups of treatments with a randomized in vivo sample for humans or non-randomized for humans that used hydroxychloroquine as a treatment for COVID-19 in the adult population (12 years to 90 years), and that the control group included randomized or no randomized studies with humans that used other retroviral drugs to treat COVID-19 (Fig. 1). Four independent reviewers located and selected the studies. The doubts were resolved with the fifth reviewer for the final definition of whether or not to include the study in this systematic review and meta-analysis.

Information sources - The research was carried out in the bibliographic databases in the Cochrane library, PubMed and EMBASE (Elsevier and Lancet). Selected publications included original articles, pre-proof of the accepted and published article since the beginning of February 2020. The following terms were used as a strategy in the search for studies: Hydroxychloroquine, COVID-19, Extension QT, Hospitalization and Viremia. And the search strategy, previously defined as the combination of descriptors in health sciences, was also used, the terms similar to answering the primary outcomes were also used: mortality, prolongation of QT, hospitalizations in intensive care and worsening of the clinical condition (respiratory changes). Variation of these strategies were used according to the requirements of the sources on the platforms used ("AND" or "OR" or "AND NOT") (Fig. 1).

Data Extraction and Analysis - The research was carried out from April 2020, with articles

published from February 2020 to the first half of May and without language restrictions, with a sample equal to or greater than 10 patients and a maximum of 400 patients with group control and treatment in the interval from 18 to 90 years old. So, 75 references were identified in three databases or repositories of scientific evidence. We used the "Rayyan - QCRI" manager for initial screening of titles and abstracts and removal of duplicate articles in the bibliographic survey, carried out by five reviewers [21]. At the end, there were six primary studies that supported the conclusion of this systematic review and meta-analysis (Fig. 1).

Methodological quality and risk of bias - Methodological quality and risk of bias were carried out independently by four reviewers with access to the name of the author, institution and the journal to which the randomized or non-randomized study was published. Disagreements were resolved by consensus [22,21]. The methodological quality assessment was adopted using the Down and Black instrument (1998), this instrument evaluates methodological aspects such as, for example, randomization and blinding of the participants. The risk of bias was assessed using the Cochrane collaboration tool (Table 1 and Table 2) [21].

Meta-analysis - Meta-analysis was performed using Software Manager® 5.3. On continuous outcomes with relative risks for dichotomous data. The weighted average difference was used [22] and the confidence interval established was 95%. In this systematic review and meta-analysis, the heterogeneity examined between the studies was performed using the chi-square test (χ^2) and was quantified by the I² statistic. According to the value of I², heterogeneity was classified as low (<50%), moderate (50-74%) or high (≥75%) [22,21]. The possibility of publication bias was explored by the Egger and Begg tests and the trim-and-fill test for the methods [21].

3. RESULTS

The search for studies for the use of the hydroxychloroquine drug in COVID-19 resulted in 75 articles on the platforms in the Cochrane, PubMed and EMBASE library (Elsevier and Lancet) according to the title and summary (Fig. 1). After reading, three articles were excluded because they did not present the complete summary, 65 were excluded because they did not present eligibility according to the inclusion criteria, 01 was excluded for reaching a

methodological score below 20 points in Down and Black (1998) and ending the process of inclusion of articles. Only 06 articles were included and contemplated 894 patients and most patients in the studies evaluated in this meta-analysis showed clinical signs of relatively mild disease in the admission process (86%) (Fig. 1).

The study by Molina et al. [23] presented a score on the Down and Black instrument equivalent to 23 points, on the other hand, Tang et al. [24] presented a score equivalent to 22 points. The authors Mahévas et al. [25] and Chen et al. [2] had a score equivalent to 20 points and was considered a high risk of bias because they did not use the double-blind methodology. The average of the Down and Black score in this study was 21 points (Table 1). Only in the study by Molina et al. [23] the methods for randomization and for secrecy of allocation of interventions after the randomization process were narrated and 03 included non-randomized studies that used the randomization process performed the narration in the text (Table 1). The

authors Tang et al. [24] and Molina et al. [23] showed a low risk of bias, mainly in the allocation secrecy (in the selection bias of the study participants) and in the random generation of the allocation sequence of the study participants (Chart 1). It is worth mentioning that the confidentiality of allocation is a condition to be considered as risk of bias, because by performing this procedure in a correct methodological way, it is possible to avoid selection bias in the allocation of interventions and thus protect the allocation sequence until the interventions are correctly allocated (Table 1 and Chart 1). The authors of the studies by Chen et al. [2] and Mahévas et al. [25] showed a high risk of bias when considering the outcome incomplete in many participants. There was a considerable loss of follow-up between the control and treatment groups (48.3% in the control group compared to the treatment group) and they also presented a high risk of bias in the blinding criterion of the participants included in the study, mainly in the blinding bias of the results evaluation (Chart 1).

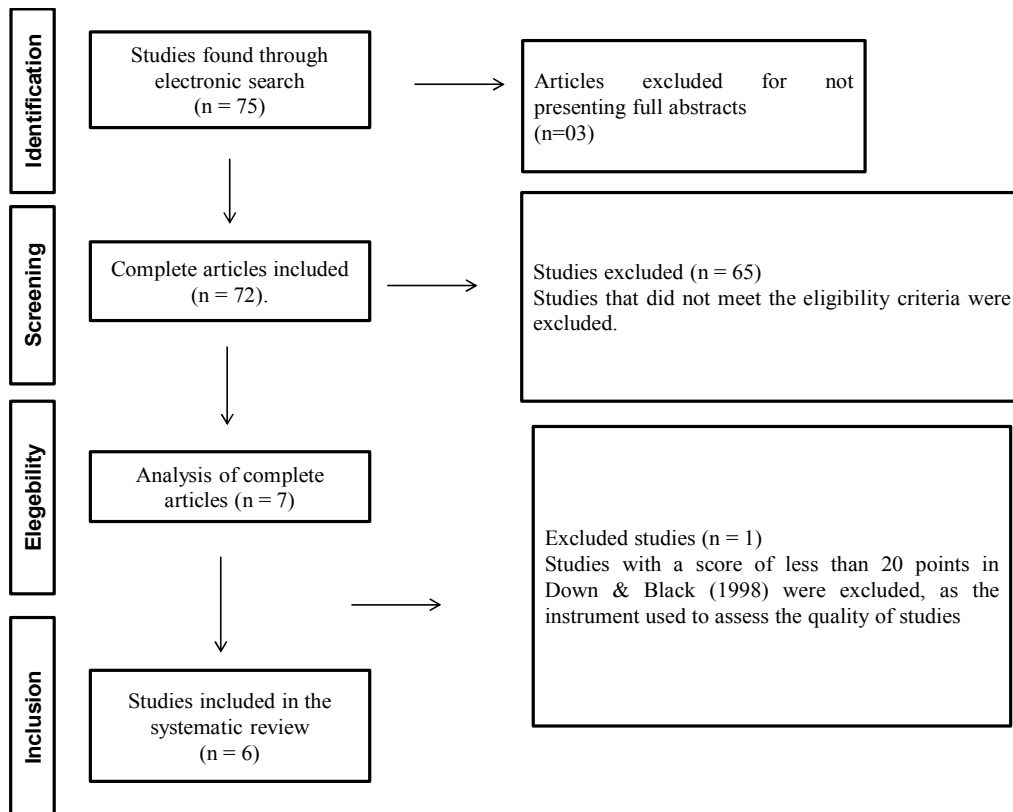


Fig. 1. Flowchart of the selection process for studies included in the systematic review and meta-analysis (PRISMA)

Table 1. Identification and classification of the methodological quality risk of the included studies according to Down and Black (1998)

Article Identification	Reporting (0 – 10)	External validity (0-03)	Internal validity – bias (0–07)	Confusion - bias of selection (0-06)	Power (0 – 5)	Total score
Mahévas, et al. [25]	10	04	04	02	00	20
Chen, et al. [3]	10	04	04	02	00	20
Tang, et al. [24]	10	03	05	03	01	22
Molina, et al. [23]	10	03	05	04	01	23
Gautret, et al. [26]	09	03	04	05	00	21
Gautret, et al. [27]	08	03	05	04	01	21

Source: Sara, H. D.; Black, N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* v.52. p.377–384. 1998

Chart 1. Characterization of the included studies

	Mahévas, et al. [25]	Chen, et al. [3]	Tang, et al. [24]	Molina, et al. [23]	Gautret, et al. [26] (1)	Gautret, et al. [27] (2)
Study location	France	China	China	France	France	France
Sampling and age	With n= 181 patients (Control Group - 97 and Treatment Group - 84) the age of patients included was from 60 years old.	Patient aged over 18 years. With n = 62 (Control Group= 31 and Treatment Group = 31).	Patient older than 46 years, with n = 150 patients (75 control patients and 75 treatment patients).	Patients older than 50 years, with n = 379 (Treatment Group - 221 and Control Group - 158 patients).	Patients over the age of 12 were 42 patients (26 patients in the Treatment group and 16 patients in the Control group).	Patient included from 60 years old. With n = 80 patients (Control Group - 16 patients and Treatment Group - 64 patients).
Inclusion criterion and intervention time	Already show signs of pneumonia and need for oxygenation. The intervention time was 05 days.	Patients with positive laboratory for COVID-19, O2 saturation less than 93% and condition in the hospital room as a mild disease. Patients older than 18 years. 05 day intervention time.	If the patient had a negative conversion to SARS-CoV-2 within 28 days equivalent to the intervention time.	If the patient had a negative conversion to SARS-CoV-2 within 06 days. And the intervention time was 10 days.	If the patient had a negative conversion to SARS-CoV-2 within 6 days. And clinical improvement in temperature, respiratory rate, length of stay and death. The intervention time was 10 days.	If the patient had a negative conversion to SARS-CoV-2 within 5 days.
Treatment group	Hydroxychloroquine with a dose of 600mg was used 48 hours after hospitalization.	Hydroxychloroquine 400 mg was used and received an additional dose of 200 mg on the first day and 5 days.	Hydroxychloroquine used with doses of 800 to 1200 mg in the period of two to three weeks.	600mg of Hydroxychloroquine was used up to 24 hours after laboratory diagnosis and in parallel azithromycin was used within 10 days.	It's used 600 mg of Hydroxychloroquine after 24 hours of laboratory diagnosis and azithromycin within 10 days.	It's used 600mg of hydroxychloroquine up to 24 hours after laboratory diagnosis and in parallel It's used azithromycin for 05 days.
Primary outcome	Transfer to ICU within 7 days after inclusion or death.	It evaluated the time of remission of the cough, time to progress in severe illness, presence of rash and improvement of pneumonia.	It presented a negative conversion to SARS-CoV-2 in the time interval of up to 28 days.	It showed a negative conversion to SARS-CoV-2 within 6 days after starting treatment. And change in QT prolongation with mortality.	It's had a negative viral conversion to SARS-CoV-2 within 6 days and presence of death.	Presence of viral conversion to SARS-CoV-2 within 5 days. He evolved to an aggressive form when needing intensive care.
Risk of bias	High	High	Low	Low	Medium	Medium

This meta-analysis detected that there was a significant difference between the treatment group and the control group in relation to the organism's response to the use of hydroxychloroquine in the follow-up time outcome [25], since the patients who used hydroxychloroquine in the period of 05 days were more likely to achieve beneficial responses compared to patients in the control group (No favorable result) (Fig. 2). The Odds Ratio with 95% confidence interval (IC) to achieve the answer using ($I^2 = 72\%$) [2,26,27,25,23,24]. Regarding the time required in the use of hydroxychloroquine for the outcome follow-up time [3], the meta-analysis detected that there was a significant difference between the control and treatment group, with less response to patients with use equivalent to 10 days, as there was a higher concentration of the dose in the group. Treatment and without the presence of heterogeneity of Odds Ratio of 0.77 (0.19 - 3.19) [25,23]. In addition, in 28 days of treatment the results of the meta-analysis for the primary endpoint follow-up did not occur with statistical significance and showed a high heterogeneity of Odds Ratio of 0.03 (0.00 - 0.27) [24]. The author, Mahévas et al. [25] indicated the significance between the control and treatment groups with a favorable result for the associated treatment in the 05-day period (Fig. 2). This difference with high heterogeneity found in the studies analyzed by Mahévas et al. [25] and Chen et al. [3] can be explained by the fact that the studies included in this meta-analysis are included in the sample analyzed patients with an average laboratory diagnosis of COVID-19 greater than 48 hours and patients with treatment failure, the difference in age is significant and the devaluation in the presence of obesity. In our meta-analysis, it was not possible to use the radiological outcome, as the articles did not indicate standard deviation or other data that used forms of measurement that would allow statistical combination of data [3,25]. On the other hand, when comparing the use of hydroxy-chloroquine associated with azithromycin with monotherapy, the Odds Ratio of (95% IC) is observed with 0.96 (0.64 - 1.41) for loss of follow-up in the follow-up time due to the absence of a favorable result, and this result favors the use of monotherapy [3,26,27,25,23,24] (Fig. 2).

The influence of the primary outcome, clinical worsening, can be seen in Fig. 3. When using the time-controlled mixed effects model for laboratory diagnosis in COVID-19 over 48 hours, by age, presence of obesity and length of patient

follow-up with COVID-19 it was possible to observe a prevalence of 89% (95% IC with Odds Ratio of 0.24 (0.20 - 0.29)) [3,26,27,25,23,24]. The age range used in the studies was 12 years to 60 years [3,26,27,25,23,24]. To assess the clinical worsening and the influence of temporal follow-up, the evolution of the clinical worsening was estimated for individuals aged 18, 46, 50 and 60 years using the mixed effects model controlled by the average age in the participated in the studies [3,26,27,25,23,24]. In the 46-year-old adults, it is possible to observe through the meta-analysis (Fig. 3) that only in 11.1% there were no clinical complications during the temporal follow-up of COVID-19 (Odds Ratio of 0.65 (0.41 - 1.03) favoring the clinical worsening of the patient being followed up on the use of hydroxy-chloroquine associated with azithromycin and disfavoring monotherapy (Fig. 3) [3,26,27,25,23,24]. However, in adults over the age of 50, only 48.48% (Odds Ratio of 0.14 (0.10 - 0.19) used hydroxychloroquine associated with azithromycin with a dose equivalent to 600 mg/day of hydroxychloroquine in the period of 10 days and a decrease in the clinical worsening that disfavored monotherapy is observed [3,26,27,25,23,24]. On the other hand, in adults over 60 years of age, only 11.6% (Odds Ratio of 0.08 (0.04 - 0.18)) used hydroxychloroquine associated with azithromycin and did not show clinical worsening in the follow-up interval due to 05 days, which reinforced the non-benefit of monotherapy [3,26,27,25,23,24]. However, in this systematic review and meta-analysis, one should consider the great heterogeneity observed and highlight that in this methodological model the use of hydroxychloroquine and azithromycin therapy was adequate in the treatment of COVID-19 with $p < 0.0001$ (Fig. 3) mainly in the age range of 12 years to 50 years [3,26,27,25,23,24].

In the evaluation of the primary result for hydroxychloroquine dosage significantly between the clinical worsening of patients with COVID-19, it was possible to verify that the higher doses (800 to 1200 mg/day) showed a need for hospitalization in an intensive care bed for a longer period. Follow-up time in the treatment of COVID-19 [3,26,27,25,23,24], that is, there is a progressive variation directly related to the dosage as shown in Fig. 4. There was a lower rate of hospitalization in intensive care with the use of 600 mg/day in the follow-up period in the treatment of COVID-19, which can be seen from the statistical differences shown in Fig. 4 [3,26,27,25,23,24].

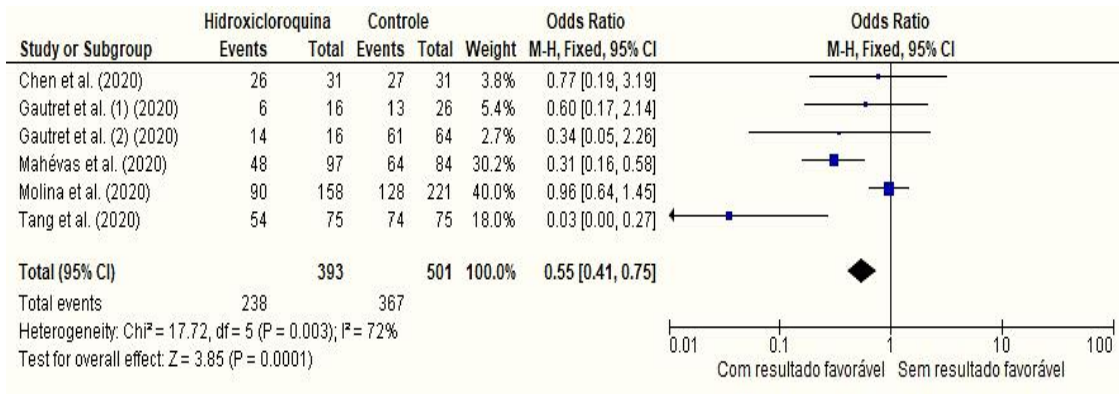


Fig. 2. Meta-analysis of the response to the use of hydroxychloroquine as a result of worsening in the follow-up period

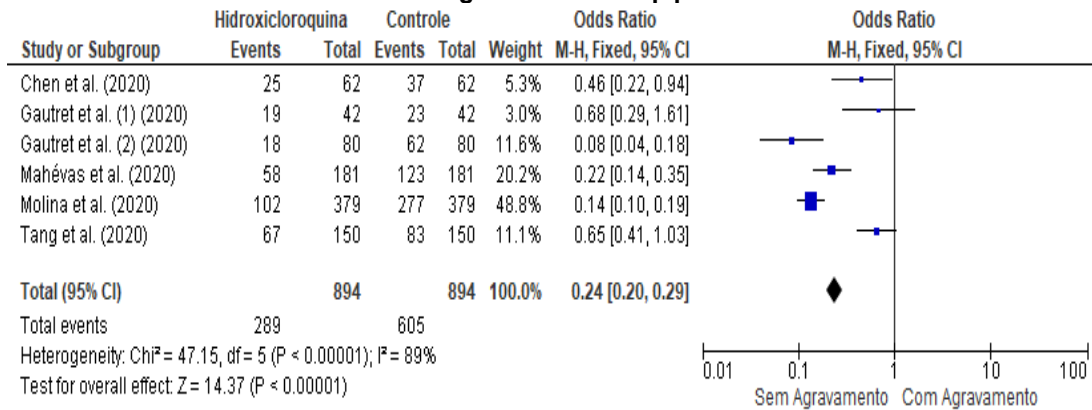


Fig. 3. Response meta-analysis using hydroxychloroquine in the result of clinical worsening with need for bed in intensive care

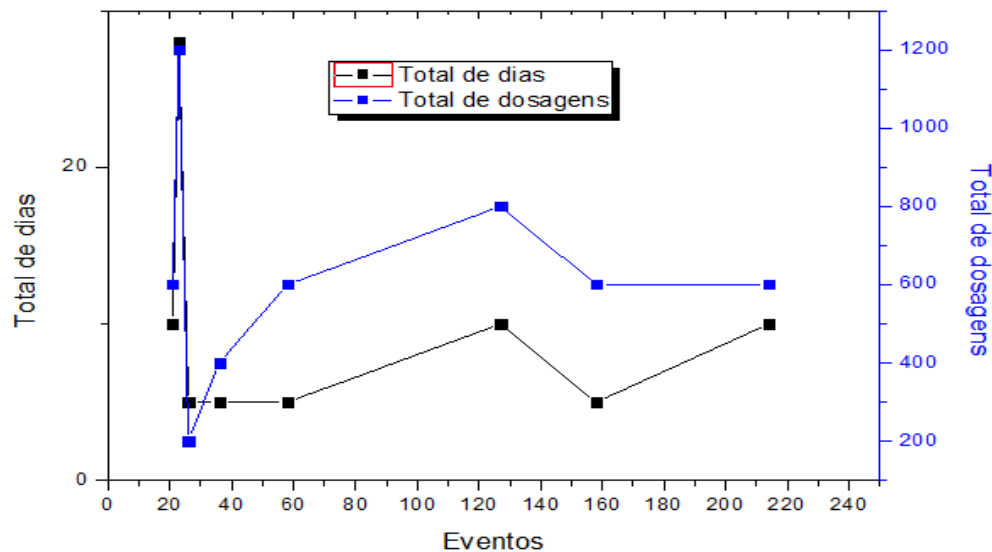


Fig. 4. Hydroxychloroquine in clinical aggravation requiring bed in the intensive care unit

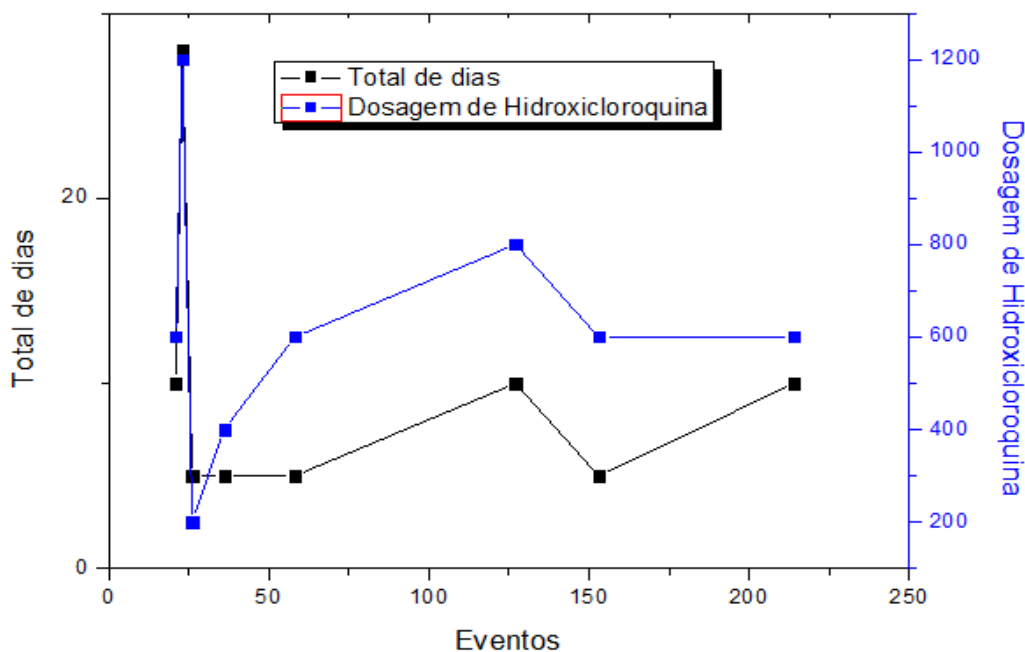


Fig. 5. Hydroxychloroquine in reducing viremia in the clinical worsening outcome

However, we found that despite the use of hydroxychloroquine dosage ranging from 200 to 600 mg/day associated with azithromycin, the primary result in need of an intensive care bed resulted in a decrease in the 10-day follow-up interval (Fig. 4) [3,26,27,25,23,24]. In other words, in this meta-analysis it can be considered that the great heterogeneity found disadvantages the use of monotherapy in the treatment of COVID-19, since the median graphic value does not under go significant changes for the benefit in the treatment observed in Fig. 4 [3,26,27,25, 23,24]. Clinical trials that used a dosage of 200 to 600 mg/day of hydroxychloroquine with small sample, and selected in a non-random manner were favorable in the use of hydroxychloroquine associated with azithromycin in the follow-up interval of 05 to 10 days compared to the control group with monotherapy, however it was not possible to conclude the favorable results in studies with a larger sample in a longer follow-up period, in this case, 28 days (Fig. 4) [3,26,27,25,23,24].

The association of hydroxychloroquine 400 mg/day with an additional dose of 200 mg/day in the first 03 days and 500 mg of azithromycin showed promising results in worsening the follow-up of COVID-19 and avoiding the need for an intensive care bed as shown in Fig. 4 [3,26,27,25,23,24].

The studies included in this systematic review and randomized or non-randomized meta-analysis classified from low to high risk of bias with considerable average population sampling in short-term follow-up (interval from 05 to 10 days) showed favorable results in relation to the decrease in viremia in the clinical worsening of the patient with COVID-19 (Fig. 5) [3,26,27,25, 23,24]. According to Fig. 5, clinical trials with small samples evaluated within 10 days of treatment follow-up, when compared to the control group, showed a favorable result in the reduction of viremia evaluated in the studies by PCR (Fig. 4 and Fig. 5) [3,26,27,25,23,24]. The results regarding the increase in the follow-up time (28 days) and the increase in the dosage (800 to 1200 mg/day of hydroxychloroquine) related to the decrease in viremia were clearly discordant, as the study by Tang et al. [24] found that viral clearance occurred up to 28 days after the start of treatment and in low quality. However, it is possible to verify in Fig. 5 that the hydroxychloroquine associated with azithromycin brings clinical benefits with decreased risk of hospitalization in an intensive care bed due to the reduction of the viral load in a statistically significant variation (Fig. 5) [3,26,27,25,23,24]. From the comparison of the treatment group in the 10-day follow-up with the control group, it is possible to verify the cure from the point of view of viral load detected in patients, this reflects a

synergistic effect with the use of both hydroxychloroquine and azithromycin, that is, both drugs (Fig. 5) [3,26,27,25,23,24].

In this study of systematic review and meta-analysis, a total of 894 patients with mild to severe clinical characteristics were included. Critically ill patients needed hospitalization in an intensive care bed as shown in Fig. 2, and about 2.6% required the use of mechanical ventilation in the hospitals of Wuhan and Paris before death (Table 2) [3,26,27,25,23,24]. All the 894 patients received hydroxychloroquine as monotherapy or associated with azithromycin during follow-up treatment of COVID-19 [3,26,27,25,23,24]. In the primary endpoint mortality, it is possible to conclude in Table 1 that studies with a dose equivalent to 800-1200 mg/day of hydroxychloroquine showed a 6.6% increase in death when compared to the control group, and the length of hospital stay in bed. Intensive therapy before the patient's death, which was equivalent to 15 days when compared to the group that performed the use of hydroxychloroquine and azithromycin with a dose variation of 200 to 600 mg/day of

hydroxychloroquine and thus, an average difference was found in the variation of 2.4% mortality (Table 1) [3,26,27,25,23,24]. In other words, this study demonstrates that the initial basic treatment of hydroxychloroquine with azithromycin in patients with mild signs after 24 hours of laboratory diagnosis is promising in reducing the mortality of patients with COVID-19 due to the decrease in worsening in the follow-up period in the treatment of patient (Table 2) [3,26,27,25,23,24].

All the 894 patients included in this systematic review and meta-analysis, a total of 124 (13.8%) patients had QT prolongation and no electrocardiographic abnormalities (Table 2) [3,26,27,25,23,24]. In Table 2, the study by Tang et al. [24], finds that the patient older than 46 years has a higher incidence of stretching in the QT interval and without changes in the electrocardiogram (Table 3) in the follow-up period for treatment of COVID-19 and the study by Gautret et al. [27] (2) reinforces that patients over 60 years old develop QT prolongation without electrocardiographic changes (8.7%) (Table 3) [3,26,27,25,23,24].

Table 2. Hydroxychloroquine in the outcome clinical worsening in mortality

Article	Mortality			Hydroxychloroquine dosage (mg)
	Events	Total patients	n%	
Tang, et al. [24]	10	150	6,6	1200
Tang, et al. [24]	01	150	0,66	800
Molina, et al. [23]	01	379	0,26	600
Gautret, et al. [26] (1)	01	42	2,38	600
Gautret, et al. [27] (2)	01	80	1,25	600
Mahévas, et al. [25]	09	181	4,9	600
Chen, et al. [2]	01	31	3,2	400
Chen, et al. [3]	01	31	3,2	200

Table 3. Hydroxychloroquine in the QT prolongation outcome

Article	QT extension			Hydroxychloroquine dosage (mg)
	Events	Total patients	n%	
Tang, et al. [24]	92	150	61,3	1200
Tang, et al. [24]	12	150	8,1	800
Mahévas, et al. [25]	07	181	4,6	600
Molina, et al. [23]	01	379	0,26	600
Gautret, et al. [26] (1)	01	42	2,38	600
Gautret, et al. [27] (2)	07	80	8,7	600
Chen, et al. [2]	03	31	2,1	400
Chen, et al. [3]	01	31	3,2	200

4. DISCUSSION

COVID-19 is an emerging outbreak caused by SARS-CoV-2 and has easy contagious characteristics that result in an increasing number of infected individuals in regions such as China, France and currently in Brazil [28,6]. The promising result of using hydroxychloroquine alone or in combination with azithromycin has become a very controversial issue in the scientific world [29]. We report the results of 894 patients with COVID-19 treated with hydroxychloroquine or associated with azithromycin in the mild to severe phase up to 48 hours after laboratory diagnosis [3,26,27,25,23,24]. So far there is no specific drug to treat COVID-19 [29]. In this systematic review and meta-analysis, the COVID-19 severity spectrum varies from mild to severe symptoms, for example, respiratory distress [3,26,27,25,23,24].

The articles included in this systematic review and meta-analysis evaluated patients who received at least five days to twenty eight days of treatment with hydroxychloroquine as monotherapy or associated with azithromycin [3,26,27,25,23,24]. Most patients in the studies evaluated in this meta-analysis had clinical signs of relatively mild disease in the admission process (86%) [3,26,27,25,23,24].

The methodological conditions of this systematic review and meta-analysis showed that the treatment was associated with a low proportion of patients with worsening of the disease, that is, only 124 patients (13.8%) were transferred to intensive care and with a low incidence of deaths in this population sample (n = 24 patients with death) [3,26,27,25,23,24]. In this systematic review and meta-analysis we have the hypothesis of the use of hydroxychloroquine associated with azithromycin that may be promising in the treatment of COVID-19 [3,26,27,25,23,24]. Some in vitro studies have verified the efficacy of hydroxychloroquine in the treatment of COVID-19, in this case, the etiological agent SARS-CoV-2 [30].

In the world, today there is no safe and effective medicine to face the disease, and hydroxychloroquine can be a therapeutic alternative, and it is a medication that has been used for more than 70 years and is relatively safe [8,15,30]. But there are opposing opinions in the Brazilian scientific academy that must be analyzed, as well as the high number of drug interactions, in this case, of the serious patients of COVID-19, mainly in hospitalization [8,30].

In this meta-analysis it was possible to verify that the mortality rate was 2.6% of the total sample (894 patients) [3,26,27,25,23,24]. The included studies used hydroxychloroquine care and the association of hydroxychloroquine with azithromycin and other immunomodulatory antiviral drugs that are used to treat more severe patients in intensive care in other viral diseases such as Mers-CoV [3,26,27,25,23,24] a virus that causes Middle East Respiratory Syndrome of the coronavirus Family [3,26,27,25,23,24]. But the ultimate goal of the studies was to decrease viral replication and whether the organism had a favorable immune response to illness and worsening by COVID-19 [8,30,31].

It is from the epidemiological statistical data found in this meta-analysis that it was possible to identify this hypothesis. It has been promisingly established that treatment with hydroxychloroquine associated with azithromycin increases the quality of survival of patients with mild signs and, in the case of critically ill patients, reduces the probability of death statistically significantly (3.25%) (Table 01) [8,30,31].

It was found in these studies that doses greater than 25 mg/kg and with administration time greater than 20 days, that they cause serious damage to the patient being treated with COVID-19 with severe clinical signs [3,26,27,25,23,24]. For example, the included studies did not exclude patients with myasthenia gravis, porphyria cutanea tarda, multiple sclerosis, treatment for cancer, liver disease, AIDS, psoriasis and other dermatological conditions, or the studies did not report whether precaution was taken in administering doses to patients with kidney, liver or heart failure, severe gastrointestinal disorders, glucose-6-phosphate dehydrogenase deficiency or the presence of neurological changes or specific care in patients with pre-existing diseases such as diabetes [3,26,27,25,23,24]. Carrying out these inclusion criteria in the research period with the drug is to safely build a flowchart in the study that respects the narrow safety margin of this drug in order to avoid increasing the percentage of deaths related to the risk of bias during the methodological process of the study [3,26,27,25,23,24]. In malaria, the dose of the drug used for treatment is relatively safe and is used only for three days [3,26,27,25,23,24]. Usually the usual dose for the treatment of malaria in the plasmodium species is 25 mg/kg and its administration is done in three days, with the first dose being equivalent to 600 mg/day, on

the second day 300 mg/day and on the third 300 mg/day and has been used to treat children and pregnant women [8,30,31].

In malaria, studies that associate hydroxychloroquine to azithromycin as an intermittent preventive treatment regimen demonstrate a higher frequency of adverse events when compared with other regimens that associate sulfadoxine primetamine [8,3,26,27, 25,23,24]. Still the protocols used in Brazil for the treatment of hepatic amebiasis bring doses for adults of 600 mg/day on the first and second days and 300 mg/day for two to three weeks [8, 9,10]. It is reinforced that until now there is no specific drug treatment for COVID-19.

Based on a study developed by a group from the "Department of Science and Technology of Guangdong Province and Health Commission of Guangdong, it was through this study that it was possible to recommend the use of hydroxychloroquine in order to bring promising results to the treatment of patients with SARS-CoV- 2 [32].

The scientific basis is that some in vitro studies have shown that chloroquine phosphate can inhibit the viral replication of several coronaviruses with an inhibitory concentration close to that established during the treatment of acute malaria [30].

Hydroxychloroquine inhibits viral replication by reducing terminal glycosylation at angiotensin-converting enzyme 2 (ACE2) receptors specifically on the vero E6 cell surface and affects the binding of SARS-CoV-2 and ACE2 receptors [25,15,30,31].

But the authors included in this meta-analysis in Chinese clinical practice during the SARS-CoV-2 epidemic period that brought consensus on the use of hydroxychloroquine in the treatment of pneumonia, highlighted that the patients included in this meta-analysis were considered critical with COVID-19 when treated with hydroxychloroquine associated with azithromycin showed an antiviral response even though their life was lost [26,27, 33]. The studies of this systematic review and meta-analysis with a medium sample, but considered small in relation to the severity and exponentially increase of the affected population, were promising and need randomized studies with a larger sample [3,26,27,25,23,24].

Hydroxychloroquine had an immunomodulatory effect through the inhibition of lysosomal

activation of dendritic cells that resulted in suppression antigens for the receptor, in the key lock form of the TRL that enhanced the secretion of IL-1, IFN-1 and TNF and thus, the response. An excessive amount of cytokines that decreased the immune activation triggered by the disease process was characterized in this process with a decrease in the sampling worsening (Fig. 3) [26,27,23-25]. Hydroxychloroquine is a drug with anti-inflammatory and antiviral properties and in these articles its immune modulating role stands out by inhibiting receptor binding and membranous fusion. These two steps are essential for the virus to enter the cell and acts on the glycosylation process of the angiotensin-converting enzyme 2 (ACE2) and thus, the endosomal fusion is blocked, which will stop the virus from replicating in the host cell [12,25,24].

Hydroxychloroquine is able to significantly raise the endosomal pH and thus stop the action of proteases capable of activating the endosome to initiate the viral endocytosis process [3,26,27,25, 23,24]. Therefore, the ideal dose of hydroxychloroquine associated with azithromycin and with a load of 400 mg/day twice daily is administered orally, with a maintenance dose of 200 mg / day administered at least twice a day for a maximum period of 5 days (Fig. 2) [8,34,4].

COVID-19 patients have shown a reduction in the percentage of lymphocyte in peripheral and lymphatic tissues [25]. However, there is a development of a large amount of lymphocytic infiltration in the lung tissue, as well as in other organs that can lead to cardiac damage [2,3,29,26]. The authors in this systematic review and meta-analysis proved that hydroxychloroquine is associated with reduced viral load and viral disappearance visible in the clinic by decreasing lymphocytic infiltration in lung tissue in individuals with COVID-19 and the impact of its action is increased by adding azithromycin [3,26,27,25,23,24].

The hydroxychloroquine associated with azithromycin brings favorable results in the exacerbation of pneumonia, a complication that causes death, visible in the improvement of the pulmonary image and in obtaining negative results for the aggravation of the disease [3,26,27,25,23,24]. Hydroxychloroquine has brought favorable results to the treatment for pneumonia, who it can present higher concentrations in the lung tissue and thus decrease respiratory worsening, that is, it decreases the lymphocytic infiltration in the lung

tissue that leads to cardiac damage [35,26, 27,36].

The use of azithromycin, a common antimicrobial used in the Brazilian health system, showed an increase in the benefit of respiratory viral infection by preventing a bacterial worsening [8, 3,26,27,25,23,24]. However, with the result of this meta-analysis it is possible to verify that the use of higher doses (800 to 1200 mg) of hydroxychloroquine, will induce cardiotoxicity and death [3,26,27,25,23,24]. The Chinese study including patients who evolved to pneumonia associated with SARS-CoV-2, showed that hydroxychloroquine was superior in the control group in the primary outcome for worsening pneumonia as well [3,26,27,25,23,24] and the increasing the need for bed use in intensive care. It is noteworthy that this conclusion was reached with viral negative and the duration of the disease [2,3,23,24].

However, the doses used of hydroxychloroquine in this systematic review and meta-analysis are the same used in the treatment of inflammatory diseases such as Lupus and Venezuelan encephalitis, and therefore hydroxychloroquine for patients diagnosed with COVID-19 actually more hypothetically as an immunomodulators and anti-inflammatory and not as indirect viral agent [3,26,27,25,23,24]. Patients who presented death as the primary outcome in the studies included in this systematic review and meta-analysis were considered patients with more severe clinical signs at the beginning of the follow-up for the treatment of COVID-19 when compared to patients with mild clinical signs and already under going treatment with hydroxychloroquine [3,26,27,25,23,24].

It should be note that in these included studies, patients who did not adhere to the prescribed treatment were not excluded since the intake of drug therapy was not controlled [3,26,27,25, 23,24]. However, due to the risk of adverse effects in previous studies on malaria, strict control of the blood level of hydroxychloroquine in treated patients is recommended, in order that the dosage of the medication will be adapted appropriately for the patient being followed up [8, 11,3]. As already described in previous studies, mainly those included in this meta-analysis, it was confirmed that older patients with COVID-19 have a significant increase in adverse effects, such as QT prolongation [3,26,27,25,23,24]. In addition, elderly patients treated with COVID-19 started follow-up for treatment in studies late and

already had clinical or radiological signs of pneumonia [3,26,27,25,23,24] and the prognosis evolved to consequences such as death [3,26,27,25,23,24]. It should be noted that randomized or non-randomized studies carried out in the pandemic develop limitations, as health services are being overloaded. The data is being passed on incomplete in relation to some patients [3,26,27,25,23,24].

In some health institutions, computed tomography and serum levels of the drug in the blood are not being available to patients, and generally these results when sent are outside the "golden hour" of care [3,26,27,25,23,24]. Therefore, in the outcome of QT prolongation, in patients who received azithromycin simultaneously, they had an increased risk of developing QT prolongation and sudden death during the follow-up of COVID-19 treatment [3,26,27,25,23,24]. In this systematic review we found an increase in QT prolongation with a prevalence of 13.8%, which were asymptomatic from the cardiac point of view. It should be noted that the use of azithromycin may imply this anomaly and the fact that it reverses in patients who with draw the drug can be considered hydroxychloroquine not directly related to the process of cardiac worsening [3,26,27,25,23,24].

These cardiac changes could not be considered caused by the dose or the time of use of hydroxychloroquine, and this can occur with drugs similar to quinidine [4], for example, an idiosyncratic that is directly related to the types of sodium and potassium channels and are genetically determined, in this case, in the gene polymorphisms that affects drug metabolism [3, 3,26,27,25,23,24].

In summary, this systematic review and meta-analysis study demonstrated that hydroxychloroquine significantly reduces the risk of death for patients with initial treatment within 48 hours after the diagnosis of COVID-19 [3,26,27,25,23,24] and that it does not present significant toxicity in its mechanism of action and this mechanism must be mediated by the inhibition of inflammatory cytokines, in addition to showing, according to the results in Fig. 5, the ability to decrease viral replication [3,26,27,25, 23,24].

As a conclusion, it is necessary to elaborate randomized, no randomized, double-blind and large-scale clinical studies for the treatment of COVID-19 with hydroxychloroquine, however,

the use of hydroxychloroquine for patients in early stage should be considered when using safety records through the long history of its use in the treatment of infections such as malaria where there is a greater need for investigation and drug administration and thus must be performed safely for the patient [3,26,27,25,23, 24]. To ensure safety for patients with COVID-19 in the interim period awaiting urgent randomized studies, the results of the benefits attributed to hydroxychloroquine in this meta-analysis in the treatment of COVID-19. It is suggested that this treatment should be prescribed to the patient safely through protocols and flowcharts with initial cardiac assessment in or patients, in the case with daily electrocardiogram and in critically ill patients in intensive care, monitoring of residual blood concentration should be performed two times [26,27,23-25]. Restricted attention must be driven by contraindications and possible interactions with concomitant medications used to monitor treatment in COVID-19, for example, in diabetic patients [28,37,6,8, 11]. For better analysis, it is necessary to redirect the existing drugs and evaluate their benefit in controlled trials with a large sample in Brazilian territory in the constraints of a pandemic [3,26, 27,25,23,24].

5. CONCLUSION

Scientific evidence in the treatment of COVID-19 is being constructed in general, but they are limited and divergent as to the role of hydroxychloroquine in the follow-up of patients with COVID-19. This systematic review with meta-analysis found that the use of hydroxychloroquine as an adjunct therapy in the follow-up of COVID-19 in patients with mild clinical signs brings promising responses by decreasing the worsening. In critically ill patients, the response helps to decrease the length of hospital stay in intensive care, but there is a need for further scientific research involving a larger number of patients with randomized, double-blind studies that can be used to evaluate its effectiveness in combating COVID-19. Therefore, the accessible and preliminary scientific evidence is of low methodological quality and care must be taken when interpreting its results. It is possible to conclude in this meta-analysis that the clinical and laboratory demographic variables in the use of hydroxychloroquine have internal validity affected by factors that cause confusion and important biases in the study design, for example, in the data collection regarding the aggravation and

need for bed in therapy of the patient in the electronic process of obtaining the data. The studies did not take into account the epidemiological particularities of the studied populations and the multicentre generalization in the sampling was used and this method causes bias in the result. Therefore, this meta-analysis used a reduced sampling in order to decrease the legal issue in the clinical safety of the results, the rigorous statistical methodology demonstrated that hydroxychloroquine in patients with COVID-19 with mild signs is not statistically associated with the possibility of death, however the use of hydroxychloroquine with azithromycin is associated with QT prolongation.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the authors.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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