

COVID-19: analysis of pre-exposure antimalarial therapies*COVID-19: análisis de las terapias antipalúdicas previas a la exposición**COVID-19: análise de terapêuticas pré-exposição de antimaláricos***Davi Oliveira Venzel Pego¹**

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Abstract

The aim was to analyze the use of antimalarials in the pre-exposure prophylaxis of COVID-19. This is a literature review, with the approach of analysis of randomized, review and integrative literature reviews. The research was carried out through online access to the PubMed and Google Scholar databases. A total of six articles were used out of a total of 761, selected by different criteria. The articles highlighted the inefficiency of antimalarials, hydroxychloroquine and chloroquine, as a prophylactic measure against pre-exposure to the COVID-19 virus; in addition, they also demonstrated some adverse effects, such as toxicity caused by the continuous use of such drugs. The use of antimalarials has no scientifically proven beneficial effects for the prophylaxis of COVID-19 or its treatment. In this context, the importance of using drugs and other scientifically proven therapeutic or prophylactic procedures for the cause is highlighted.

Descriptors: Therapeutics; Antimalarials; COVID-19; Pre-Exposure; Analysis.

Resumen

El objetivo fue analizar el uso de antipalúdicos en la profilaxis preexposición de COVID-19. Se trata de una revisión bibliográfica, con el enfoque de análisis de literatura aleatorizado, de revisión e integrador. La investigación se realizó a través del acceso en línea a las bases de datos PubMed y Google Scholar. Se utilizaron un total de seis artículos de un total de 761, seleccionados por diferentes criterios. Los artículos evidenciaron la ineficacia de los antipalúdicos, la hidroxicloroquina y la cloroquina, como medida profiláctica frente a la preexposición al virus de la COVID-19, además, también demostraron algunos efectos adversos, como la toxicidad provocada por el uso continuado de tales fármacos. El uso de antipalúdicos no tiene efectos beneficiosos científicamente probados para la profilaxis de la COVID-19 o su tratamiento. En este contexto, se destaca la importancia del uso de fármacos y otros procedimientos terapéuticos o profilácticos científicamente probados para la causa.

Descriptores: Terapéutica; Antipalúdicos; COVID-19; Pre-Exposición; Análisis.

Resumo

Objetivou-se analisar o uso de antimaláricos na profilaxia pré-exposição da COVID-19. Trata-se de uma revisão bibliográfica, com a abordagem de análise de estudos randomizados, revisionais e de revisões integrativas da literatura. A pesquisa foi realizada através do acesso online nas bases de dados do PubMed e Google Acadêmico. Foram utilizados ao todo seis artigos de um total de 761, selecionados por diferentes critérios. Os artigos evidenciaram a ineficiência dos antimaláricos, hidroxicloroquina e cloroquina, como medida profilática à pré-exposição ao vírus da COVID-19, além disso, demonstraram também, alguns efeitos adversos, como a toxicidade provocada pelo uso contínuo de tais medicamentos. O uso de antimaláricos não possui efeitos benéficos cientificamente comprovados para a profilaxia da COVID-19 ou para seu tratamento. Ressalta-se, nesse contexto, a importância da utilização de medicamentos e outros procedimentos terapêuticos ou profiláticos cientificamente comprovados para a causa.

Descriptores: Terapéutica; Antimaláricos; COVID-19; Pré-Exposição; Análise.



Introduction

In December 2019, in the province of Wuhan-China, the first outbreaks of pneumonia and hospitalizations for unknown reasons began. In search of answers to this problem, Huang's research team¹ performed reverse transcriptase reaction tests followed by polymerase chain reaction (RT-PCR) which showed the existence of a viral pathogen, SARS-CoV-2, which causes the disease COVID-19. This viral mechanism, in a few weeks, had spread to countless countries, such as Italy, the United States, France, Brazil, and dozens of other countries. Accordingly, many researches about this virus, until then not cataloged, were carried out in search of a way to contain it in the face of its pilgrimage across the globe.

In a more forceful analysis of the SARS-CoV-2 virus prevention methodologies, the most adopted and most effective measures were the use of masks (PFF2, KN-95 and triple protection), social distancing and hand washing. In contrast to these protection mechanisms, many authorities were hostile and averse to them, bringing, as consequences to this behavior, the elevation of the contamination curve and a subsequent expressiveness of deaths, given the lethal nature of the virus^{2,3}.

In the search for actions and medications to contain the spread of the virus, many of the drugs were studied, such as remdesivir, chloroquine and hydroxychloroquine, the

combination of lopinavir and ritonavir, there was exceptional attention to antimalarial drugs, in this case chloroquine and hydroxychloroquine. However, it is important to point out that the aforementioned antimalarial drugs had a strong media impulse in the face of the decision of countries like Brazil to use them, although without great scientific basis. In general, many dubious decisions were made about the fight against the COVID-19 pandemic, including how to prevent, treat and live⁴.

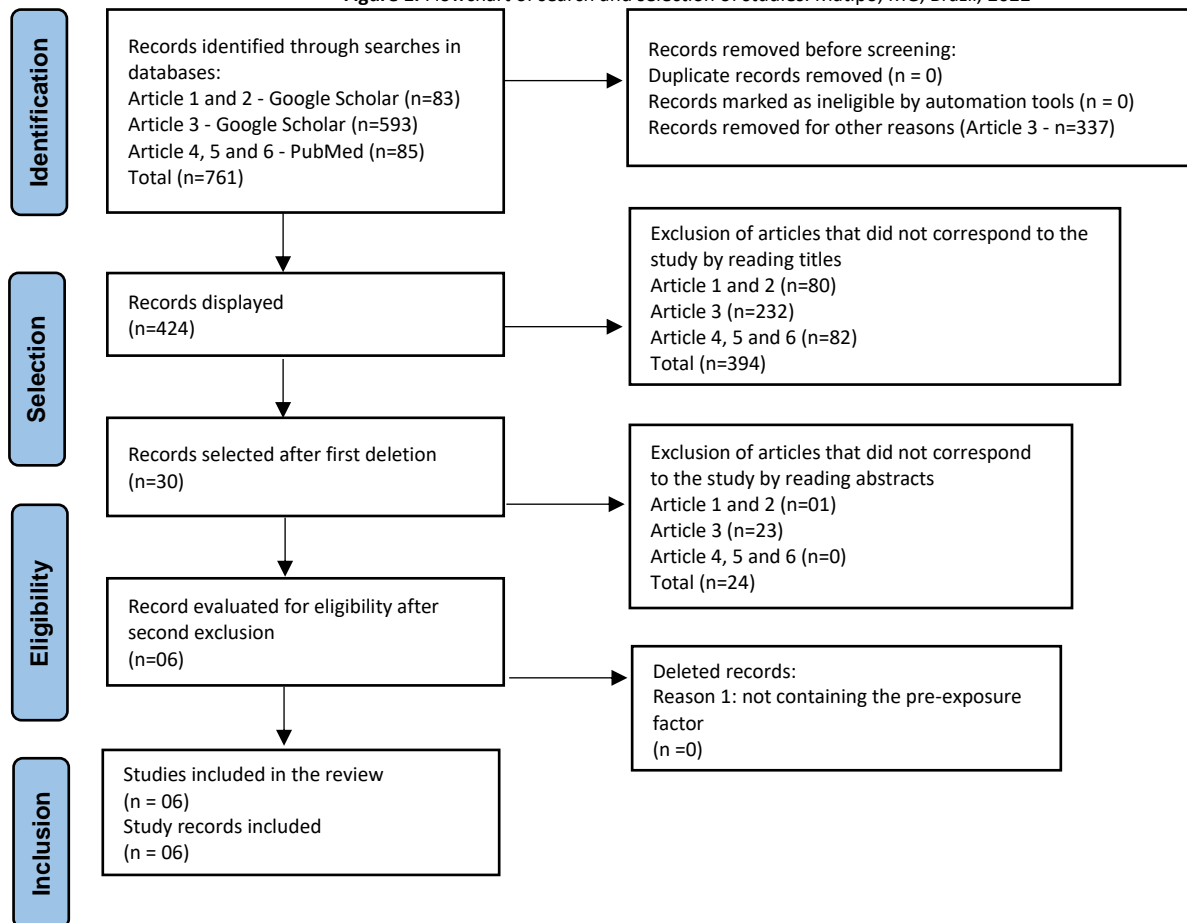
From an anthropological point of view, it is clear that political measures as part of a struggle against a real threat are a strong way of consolidating an influence on collective behavior, considering the authority of figures at the highest level of executive power⁵.

Based on the above, this article aims to analyze the use of antimalarials in the pre-exposure prophylaxis of COVID19, in order to bring to light the real prophylactic potential of antimalarial drugs in patients not infected with the disease COVID-19.

Methodology

The present study is a literature review article and with the approach of analysis of randomized, review and integrative literature review, which were selected within the PubMed and Google Scholar platform. A total of six articles were used out of a total of 761, selected by different criteria.

Figure 1. Flowchart of search and selection of studies. Matipó, MG, Brazil, 2022



As articles one and two were selected by Google Scholar, the Boolean operators "AND" and those described were used: "COVID-19", "Antimalarials" and "Prophylaxis".

No filter was included to exclude the research. The total result was 83 articles, of which only three were selected, after reading the title and abstract, the others were excluded



for presenting the theme in a shallow and ineffective way of the subject addressed.

Article three, which was also found by the Google Scholar platform, used the descriptors: "Antimalarials" and "COVID-19". When using the Portuguese language filter, a total of 256 articles were found, which through the analysis of the title, 232 were eliminated. Then, when reading the abstracts of the 24 selected, 23 did not correspond properly to the subject.

Articles four, five and six found on the PubMed website used the following filters: randomized article, publications of up to five years (2017 to 2022), in English and Portuguese and free publications. In addition, the selection was also filtered through Boolean operators "AND" and the descriptions used to perform the search were: "COVID-19", "Hydroxychloroquine" and "Prophylaxis". After analyzing the site, a total of 85 articles appeared, of which 82 were excluded by reading the titles, the remaining three were used in the study.

The review and critical analysis of the selected articles passed through the sieve of the theme to be addressed, thus avoiding deviations in the subject treated, being selected only articles that contemplate a prophylactic measure with antimalarials in non-infected patients or with an inexpressive viral load for the manifestation or detection of this pathogen. The guiding question was established based on anthroposocial studies and analyzes of the health situation and the policy to combat COVID-19 in Brazil, aiming

to establish a clear dialogue regarding the effectiveness of antimalarial medications, especially establishing the question "What is the effectiveness of the prophylactic treatment of COVID-19 with antimalarials?"

As exclusion criteria, texts that did not contain the descriptors "pre-exposure" and those that did not include the descriptor "antimalarials" were removed. It is also worth mentioning the addition of exclusion criteria by titles, being that, articles that did not have the theme pre-exposure prophylaxis to COVID-19 and/or that the focus was not this. As a source of pertinent analysis of the facts, articles that included randomized clinical trials (RCTs), integrative literature reviews and revision articles on the topic addressed were mostly used. These parameters are used for a clearer and cleaner analysis of the central theme.

Results

Of the articles analyzed, all presented unsatisfactory or negative results regarding the use of antimalarial drugs in the fight against COVID-19, above all, a rate of illness from secondary causes due to medication intake was also presented. In short, the evaluated articles are quite clear about the inefficiency presented by this group of drugs in the viral fight.

Six articles were collected for study, of which it is intended to analyze when the methodology applied, the objectives outlined by them, results obtained and the conclusions presented.

Chart 1. Synoptic table. Matipó, MG, Brazil, 2022

Title	Year	Methodology	Objective	Results	Conclusions
A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of COVID-19	2020	Randomized clinical trial	Seek evidence that corroborates the use of hydroxychloroquine as a prophylactic treatment for COVID-19.	Hydroxychloroquine was not associated with a lower incidence of SARS-CoV-2 transmission than usual care (18.7% and 17.8%, respectively).	Pre-exposure therapy with hydroxychloroquine did not prevent SARS-CoV-2 infection.
Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers	2020	Randomized, double-blind, placebo-controlled clinical trial	Evaluate the effectiveness of using hydroxychloroquine as prophylaxis against pre-exposure of health professionals to patients infected with COVID-19, in order to prevent the transmission of SARS-CoV-2.	Compared to participants who received placebo and those randomized to receive hydroxychloroquine, there was no significant difference in infection levels. In addition, although the clinical trial was terminated early, mild adverse events were more common in participants who used hydroxychloroquine compared to those who received placebo.	Although the use of hydroxychloroquine was limited by the early termination of the trial, there was no clinical benefit of daily administration of hydroxychloroquine as pre-exposure prophylaxis among randomized healthcare providers.
Hydroxychloroquine as Pre-exposure Prophylaxis for Coronavirus Disease 2019 (COVID-19) in Healthcare Workers: A Randomized Trial	2020	Double-blind, placebo-controlled randomized clinical trial	Analyze positive or negative indications of the use of hydroxychloroquine as pre-exposure prophylaxis to the SARS-CoV-2 virus that causes COVID-19.	In health professionals, of whom 79% are directly exposed to the new coronavirus, the use of hydroxychloroquine dosage once or twice a week triggered a rate of 27% and 28% events/persons per year, respectively, while the one with the placebo use was a rate of 38%, which demonstrates that such prophylaxis does not present a significant reduction.	Hydroxychloroquine was not effective in reducing the transmission of COVID-19 among healthcare individuals exposed to the virus.
Cloroquina e hidroxicloroquina associado ao zinco e/ou azitromicina na COVID-19	2020	Literature review	Show the uses of CQ and HCQ, the mechanisms proposed as anti-COVID-19 alone or in association with azithromycin or zinc and the controversies in the studies.	The association of CQ/HCQ with Zn 2+ proved to be harmful, since the interaction with Zn2+ significantly increases the cytotoxicity of CQ. Furthermore, the combination significantly amplified the apoptotic process due to the exacerbated influx of Zn 2+ into the cell interior.	The results presented so far are dubious and insufficient to support the use of CQ and HCQ as the first-choice treatment for COVID-19 cases, due to their short safety window and high toxicity.



Análise de possíveis intoxicações resultantes do uso indiscriminado de ivermectina e hidroxicloroquina durante a pandemia de COVID-19	2022	Literature review	Highlight, through empirical and current analyses, the risks associated with the indiscriminate use of ivermectin and hydroxychloroquine as therapeutics against COVID-19, highlighting the toxicity effects of these drugs.	There are still no conclusive studies that support the hypothesis that ivermectin is effective in the treatment of COVID-19.	The "COVID Kit", especially when it comes to ivermectin and hydroxychloroquine, can be potentially toxic to the human body.
Análise de hidroxicloroquina e possíveis benefícios no tratamento da COVID-19	2020	Literature review	Reflect on the benefits of using chloroquine and hydroxychloroquine in the prevention and treatment of COVID-19.	The benefits of using chloroquine and hydroxychloroquine in the treatment of COVID-19 were discussed, showing a significant antiviral effect, in view of their therapeutic action against SARS-CoV-2. Likewise, it was important to highlight the side effects of these drugs in patients infected by the virus, including the high toxicity caused by their continuous use.	Despite some favorable results from treatments using chloroquine and hydroxychloroquine in those infected with SARS-CoV-2, it is concluded that, at the date of publication of the article, there is no scientifically effective prophylactic and therapeutic drug for COVID-19.

The antimalarials, Chloroquine and Hydroxychloroquine, evaluated as a possible prophylactic measure of COVID-19, were chosen for this determination due to their previously researched antiviral effects on other types of coronavirus, including SARS-CoV-1. In addition, chloroquine is a drug of vast production in the drug industry, which demonstrates high resource availability, and therefore relatively low production cost. Analyzing the data described in the table above, due to its effectiveness in determining the efficacy of drugs and vaccines, it can be seen that the randomized, double-blind, placebo-controlled clinical trial was the most used to corroborate the research carried out. Through this methodology, we sought to understand to what extent the use of such drugs is effective in preventing COVID-19, especially in health professionals, who are more exposed to the virus. After the investigation carried out, many results were obtained, including the high toxicity caused by the continuous use of such drugs and their ineffectiveness as prophylaxis against pre-exposure to the virus, since there was no significant difference in the levels of infection between the participants actually medicated and the control group participants.

Discussion

Hydroxychloroquine (HCQ), an antimalarial drug with anti-inflammatory properties, and also used as an immunomodulator in cases of rheumatologic diseases, such as systemic lupus erythematosus (SLE), being easily accessible to the population, is widely disseminated and easily accessible, favoring the abuse of its use, even under mandatory medical prescription. In view of the SARS-CoV-2 virus pandemic, which started in 2019, much has been discussed about the effectiveness of this drug for the treatment of this viral infection. Among the discussions held are the side effects of this medication, and the political influence that permeates it⁶⁻⁹.

The use of chloroquine (CQ) and HCQ is related to a series of adverse effects, including: itching, nausea, dizziness, headache, loss of appetite, diarrhea and fever. In addition, CQ and HCQ can also predispose patients to severe arrhythmias by causing the suppression of the sinoatrial

node, generating disturbances in the conduction of electrical impulses causing heart failure. Such interferences trigger a stretch in the cardiac QT interval, increasing the risk of myocardial problems. This elevation depends on the drug concentration used, increasing by 6 milliseconds (ms) after a 600 mg dose and 28 ms after a 1200 mg dose¹⁰.

Although there are discussions whether the doses administered are essential for the occurrence of side effects, the misuse of hydroxychloroquine can cause severe side effects and health problems that, in more severe cases, lead to death. According to this fact, the indiscriminate use of these antimalarial drugs can be characterized by the administration of the drug in people with COVID-19, since, during the pandemic, among the Brazilian population, there was a behavior of self-medication, which is a drug in study status for this current comorbidity^{11,12}.

Despite the long use of CQ in the treatment of malaria and its safe administration to patients, there are still risks such as muscular retinopathy and cardiomyopathy, which are associated with the safe ocular dose of hydroxychloroquine and abrupt adverse effects of chloroquine, respectively¹³.

When dealing with the clinical pharmacology of HCQ, more specifically its cardiovascular performance, it is evident that conduction disorders and heart failure have been reported with antimalarial drugs, but both complications are very rare with HCQ. Regarding the side effects and contraindications presented by CQ and HCQ, the ototoxic effect of chloroquine has led to its use being reduced because it is subject to toxicity and side effects such as skin hyperpigmentation and retinopathy. Above all, it is emphasized about the necessary protocol for the use of QC, its use requires periodic ophthalmological supervision, and the levels of liver enzymes are periodically evaluated in order to detect, early, signs of liver toxicity¹³⁻¹⁵.

Even after debates and research, there are many controversies regarding the use of this medication. Political pressure for the use of these compounds by various governments in several countries, including Brazil, generated approval for their use, although studies have



shown controversial and confusing results regarding their use.

not have scientifically proven beneficial effects for the prophylaxis of COVID-19 or for its treatment. Above all, the importance of searching for truthful information for the use of medicines is emphasized, being necessary, in this scenario, to avoid merely political therapeutic indications with rare or non-existent scientific basis.

Conclusion

In view of the studies analyzed and the results obtained, it was concluded that the use of antimalarials does

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