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MAIN ADVERSE REACTIONS IN DRUG THERAPY WITHOUT SCIENTIFIC PROOF USED IN THE TREATMENT OF COVID-19

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Abstract: The new coronavirus pandemic was declared in March 2020 by the World Health Organization (UNASUS 2020). With that, there was a great adherence to the use of medications, without proven clinical efficacy, aiming at the prevention and treatment of this disease. The most used were azithromycin, ivermectin, hydroxychloroquine and chloroquine. Thus, we saw the need to perform an analysis of the adverse effects (AE) of these drugs in the population, in addition to relating them to the doses, time of use, and comorbidities in the population studied. Therefore, an integrative literature review was carried out, aiming to integrate knowledge from research carried out from November 2020 to March 2021, during the pandemic, to elucidate the AE of COVID-19 treatments both early and off-label. With searches in PubMed, BVS and Cochrane, with the descriptors "COVID-19", "hydroxychloroquine", "chloroquine", "azithromycin", "ivermectin", "nitazoxanide", "remdesivir", "adverse effects", "toxic effects " and "off-label". Clinical trial studies and randomized clinical studies, available in English or Portuguese, which had unproven therapy drugs and their AE, were prioritized. Three articles were manually added to the review via active search. Analyzing the number of reactions per 100 participants, it was possible to associate AE with dosage and time, as well as with comorbidities and risk factors for COVID-19. The most relevant disorders were neurological for ivermectin (70%), renal in the association of hydroxychloroquine and azithromycin (69%), followed by gastrointestinal tract disorders for hydroxychloroquine (58%). These drugs have significant AE for hypertensive, diabetic, obese and former smokers with COVID-19. The data showed important AE for the population, demanding greater need to weigh the risks and possible benefits of therapy, and guidance on the risks of self-medication or non-professional recommendations. Furthermore, the adverse effects can be confused with the symptoms of COVID-19, hindering the management of the infection.
Keywords: Toxicity, Therapeutics, COVID-19.

INTRODUCTION

The first coronavirus cases were confirmed in December 2019 in Wuhan, China. On February 26, 2020, in São Paulo, the first case of COVID-19 was confirmed in Brazil1. And then, on March 11, 2020, the World Health Organization declared a pandemic of the new coronavirus (Sars-Cov-2)2.As observed today, April 5, 2021, a total of 332,752 killed by Sars-Cov-2 and 11,436,189 recovered from the disease in Brazil3.

The etiological agent of COVID-19 belongs to the Coronaviridae family. It has positive single-stranded RNA4 and is classified as a beta-coronavirus. This pathogen uses the angiotensin-2 converting enzyme (ACE2) as its receptor for entry into cells. In addition, other proteins are involved in the process of cellular infection by Sars-CoV-2, the S protein (S-spike) located on the virus surface and the serine 2 transmembrane protease (mainly expressed in endothelial cells)5. It is known to have a lethality rate about 10 times greater than seasonal influenza6, however it can cause a range of heterogeneous clinical pictures. From mild and asymptomatic infections to serious and fatal conditions.

The transmission of Sars-cov-2 occurs through droplets of saliva, sneezing, coughing, or phlegm from infected people, contaminated objects or surfaces, in addition to touching contaminated handshakes. After transmission, the incubation period can last from 2 to 14 days, and the commonly expressed symptoms are cough, fever, runny nose, sore throat, difficulty breathing, anosmia, dyspnea, ageusia, decreased appetite, gastrointestinal disturbances, and asthenia7.

In view of the global scenario for COVID-19, a quick solution is being sought to stop the staggering number of deaths. Until May 2020, around 6% of the nearly 7 million cases in the world resulted in death6. In this context, drugs such as azithromycin, ivermectin, hydroxychloroquine and chloroquine were adopted by government officials and by the Ministry of Health in Brazil as standard empirical treatment.

Even with the lack of desired clinical evidence of these drugs, many health professionals continued with the therapeutic approach8. The therapies gained support from the Ministry of Health in the creation of the "KIT COVID", which includes hydroxychloroquine, azithromycin, ivermectin, nitazoxanide and vitamins C, D and zinc for the treatment and prevention of the disease. With that, the population showed great demand for drugs and consequent self-medication. In this sense, the self-medication of a drug cocktail is of concern due to the adverse and even toxic reactions of these drugs. An example of the possible consequences currently observed is drug hepatitis 9.

However, part of the Brazilian population is not aware of the adverse effects that medications can have on their bodies. This majority has the belief that the drug will solve the problem, and they do not have the risks of self-medication.10

Studies claim that drug-associated therapy is more effective than with just one drug, because they can act differently in the action of the virus within our body. They also claim that this therapy can prevent the emergence of possible drug resistance by Sars-Cov-2 11. However, there are studies demonstrating the greater risk of treatment with more than one drug, such as those with synergism on adverse effects.12

Unfortunately, none of these drugs to date have been proven to be effective against COVID-19. Therefore, there is a need to at least weigh the risks and possible benefits to the population. Thus, adverse effects of drugs and the association of those most used for prevention and treatment without proven clinical efficacy emerge amidst the tide of fake news and the population's fear of the covid disease-19.

METHODOLOGY

An integrative literature review was carried out, in order to integrate knowledge from research carried out from November 2020 to March 2021, during the pandemic, to elucidate the adverse effects of both early and off-label treatments of COVID- 19. Six steps were adopted: 1) selection of the research question; 2) definition of inclusion criteria for studies and sample selection; 3) representation of selected studies in tables/charts format, considering all common characteristics; 4) critical analysis of findings, identifying differences and conflicts; 5) interpretation of results and 6) clearly report the evidence found.

For the construction of the guiding question, the PICO method was used, as recommended by Mendes, Silveira and Galvão (2008). The guiding question of the study was "Which adverse effects can be triggered in the treatment without scientifically proven clinical efficacy for symptomatic and asymptomatic patients diagnosed or suspected of having COVID-19". The population selected for study were patients diagnosed or suspected of having COVID-19, symptomatic and asymptomatic, who used any of the treatments without proven efficacy, for the prevention or resolution of the disease. The intervention considered treatment with medications (hydroxychloroquine, chloroquine, ivermectin, remdesivir, azithromycin and nitazoxanide) for the treatment and/or prevention of the disease. The defined control

was the people who received the studied medication versus the group of people who received placebo or standard local treatment. The outcome was the adverse effects found after off-label treatment.

The review was based on searches on the PubMed portal, the VHL and the COCHRANE database. Two searches were performed at PubMed, the first using the keywords "COVID-19", "hydroxychloroquine", "chloroquine", "azithromycin", "ivermectin", "nitazoxanide", "remdesivir", "adverse effects" and " toxic effects". The second with the keywords "off-label", "hydroxychloroquine", "chloroquine", "remdesivir", "ivermectin", "azithromycin". The search carried out on the VHL portal used the keywords: "COVID-19", "off label", "ivermectin", "hydroxychloroquine", "chloroquine", "remdesivir", "azithromycin", "adverse effects", " toxic effects". And the latest search was applied to the Cochrane database with the keywords: "off-label", "hydroxychloroquine", "chloroquine", "ivermectin" and "azithromycin". In all these studies, Booleans AND and OR were used, clinical trial studies and randomized clinical studies, published from May 2020 to March 2021, available in English and Portuguese, were also prioritized.

The criteria for selecting the articles were performed in three stages, first by reading the titles, in which if there was no reference to the name of the drugs chosen for the research, or if there were other drugs that were not recommended, they would be excluded. The second stage was performed by reading the abstracts of pre-selected articles, with no mention of adverse effects, which would not be included. Finally, the third stage aimed at the full reading of the articles, those that did not present adverse events derived from drug therapy, without scientifically proven clinical efficacy for COVID-19, were removed from the review. Three articles were manually added to the review via active search. During the review, there was a report on the efficacy of the drug remdesivir against COVID-19, thus, the studies selected by the name of this drug were removed. The complete and detailed description of the articles included and excluded from the review is presented in the flowchart below.

RESULTS

DESCRIPTION OF DISORDERS BY AFFECTED SYSTEMS INSERTED IN THE ADVERSE EFFECTS REACTION CHART

In the table below, each adverse effect reported by studies participants was grouped by systems, thus, our study simplified some of these effects to facilitate the analysis.

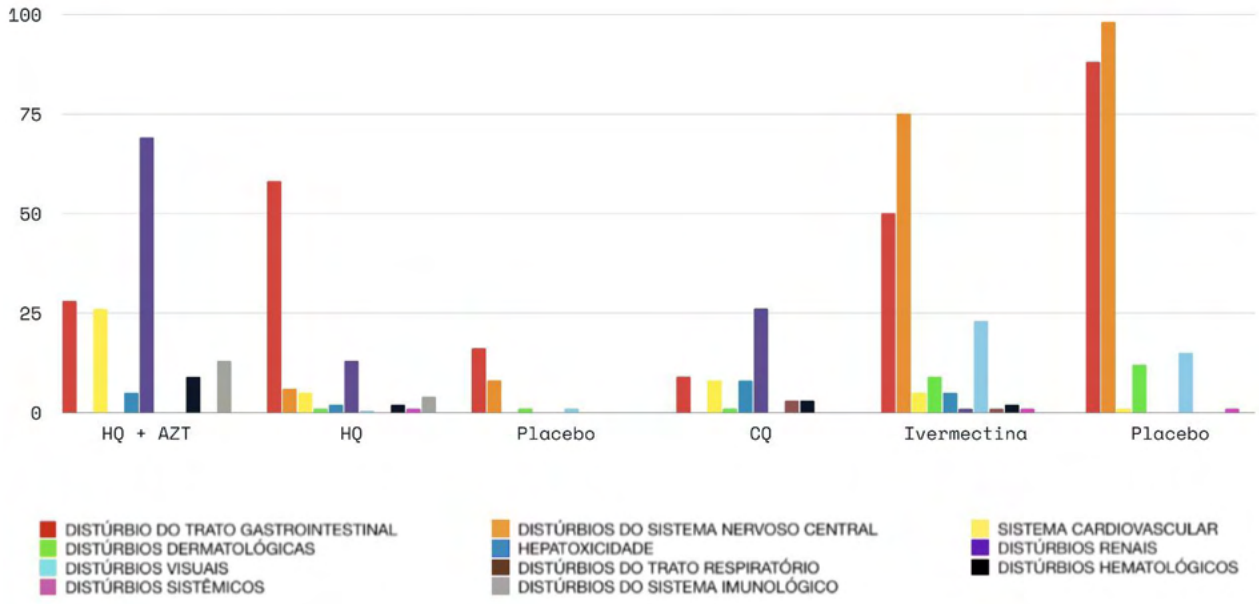
After analyzing the studies, the drugs used and the adverse drug reactions (ADR), the patients who received the same drug were grouped, whether from one study or another, so that a total number of patients who received the drug was obtained. analyzed. Thus, the number of participants who had the same adverse reaction to the drug in question was also grouped. Based on the data obtained through this mathematical analysis, a table and a graph were constructed, where the number of patients who had some adverse effect in the system explained in both schemes, when faced with medication received for therapeutic purposes, are represented.

The first column, in red, represents that 29 people had an advent in the gastrointestinal tract for every 100 people who received Azithromycin along with Hydroxychloroquine. Thus, it is not portrayed whether the same patient had two or more different reactions. But that, 29 reactions were presented for every 100 patients among the 214 who received the therapy. The relevance here becomes explicit as approximately 60 unwanted effects were accounted for by the

Gastrointestinal System Disorders	• Vomiting • Nausea • Abdominal pain • Diarrhea • Gastrointestinal bleeding • Dry mouth
Neurological Disorders	• Dizziness • Confusion • Headache • Tremor • Psychosis • Tinnitus • Nervousness • Irritability • Anxiety • Panic attack
Cardiovascular System Disorders	• Extended QT Interval • Ventricular tachycardia • Edema • Hot flashes and night sweats
Dermatological Disorders	• Rashes or itching • skin discoloration
Hepatotoxicity	• Increased liver transaminases
Kidney Disorders	• Increased creatinine, creatinine phosphokinase, creatine • Acute kidney injury • Acute kidney failure
Visual Disorders	• Blurred vision • Photophobia • Decrease in visual acuity
Respiratory Tract Disorders	• Shortness of breath • Cough • Respiratory failure
Hematological Disorders	• Leukopenia • Thrombocytopenia • Anemia • Hyperbilirubinemia
Systemic Disorders	• Multiple organ failure • Sepsis • Death • Fatigue
Immune System Disorders	• Allergic reactions • Lymphopenia

Incidência das reações adversas por medicamento a cada 100 pacientes

Incidência global das reações adversas em sistemas acometidos por medicamento utilizado em comum entre estudos



NÚMERO DE REAÇÕES ADVERSAS MEDICAMENTOSAS A CADA 100 PACIENTES QUE RECEBERAM O MESMO MEDICAMENTO

DISTÚRBIOS / MEDICAMENTO	TRATO GASTROINTESTINAL	NEUROLÓGICAS	SISTEMA CARDIOVASCULAR	DERMATOLÓGICAS	HEPATOXICIDADE	RENAIS	VISUAIS	TRATO RESPIRATÓRIO	HEMATOLÓGICAS	SISTÊMICAS	SISTEMA IMUNOLÓGICO	SOMATÓRIA DO Nº DE PACIENTES DOS ESTUDOS QUE RECEBERAM O MEDICAMENTO	SOMATÓRIA DO Nº DE PACIENTES DOS ESTUDOS QUE RECEBERAM PLACEBO OU OUTRO MEDICAMENTO
AZITROMICINA + HIDROXICLOROQUINA	29	0	26	0	5	69	0	0	9	0	13	214	
HIDROXICLOROQUINA	58	6	6	1	2	13	0,5	0	2	1	4	798	562
PLACEBO (ESTUDO COM HQ)	16	8	0	1	0	0	1	0	0	0	0		562
CLOROQUINA	10	0	8	1	8	26	0	3	3	0	0	152	
IVERMECTINA	50	70	5	9	5	1	23	1	2	1	0	277	
PLACEBO (ESTUDO COM IVERMECTINA)	88	98	1	12	0	0	15	0	0	1	0		183

participants who received Azithromycin along with Hydroxychloroquine among the studies that presented this intervention. With the aforementioned reasoning and example, the other information provided by the attached graph and table follows.

The most relevant results of the analysis are objectified by renal disorders presented among the therapy with Azithromycin associated with Hydroxychloroquine, gastrointestinal tract reactions due to the use of Hydroxychloroquine, gastrointestinal tract disorders due to the use of ivermectin and, mainly, neurological adverse drug reactions due to the treatment also with ivermectin. That said, in a deeper look, 147 cases of acute renal failure are highlighted, also related to 2 deaths, with concomitant use of Azithromycin and Hydroxychloroquine. With the use of ivermectin, the most observed and outstanding effects were the neurological ones: headache, dizziness and blurred vision.

DESCRIPTION OF ALL TABLES SEPARATED BY MEDICINE AND STUDY

AZITROMICINA (AZT) + HIDROXICLOROQUINA (HQ)

STUDY 1

""Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomized clinical trial" was published in 2020, a work by Furtado, Berwanger , et al. Involving 447 adults. At the end of the study, 214 were counted in the group that received azithromycin and hydroxychloroquine, and 183 in the control group that received only hydroxychloroquine. In the group treated with azithromycin there were 18 smokers (8%), 126 hypertensive (59%), 81 diabetic (38%), 14 with heart failure (6%), 10 with previous stroke (5%), 8 patients with cardiac infarction (4%), 12 with COPD (6%), 10 with active cancer (5%), and 26 with renal failure (12%). While in the control group there were 18 smokers (10%), 115 hypertensive (63%), 71 diabetics (39%), 9 with heart failure (5%), 5 with previous stroke (3%), 9 with cardiac infarction (5%), 12 with COPD (6%), 4 with active cancer (2%), and 18 with kidney failure (10%). Of the group that received the antibiotic in question, 47 had QTc interval prolongation (22%), 61 gastrointestinal intolerance (28%), 8 relevant ventricular arrhythmias (4%), 147 acute kidney failures (69%) and 2 deaths due to renal failure (1%). 10 showed a decrease in the number of leukocytes (5%), 27 a decrease in the number of lymphocytes (13%), 10 in platelets (5%), and 10 showed an increase in the amount of bilirubin (5%). While in the control group 42 cases of prolonged QTc interval (23%), 48 gastrointestinal intolerance (26%), 5 relevant ventricular arrhythmias (3%), 103 acute renal failure (56%) and 3 deaths due to renal failure were reported (2%), 4 showed a decrease in the number of leukocytes (2%), 21 a decrease in the number of lymphocytes (11%), 8 in platelets (4%), and 6 showed an increase in the amount of bilirubin (3%). In both groups there was a similar percentage of patients who required dialysis (39% and 34% respectively) or cardiac resuscitation (7% of both groups). In this work, no limitations were reported.

HYDROXYCHLOROQUINE

STUDY 2

Developed in the USA by D.R. Boulware, M.R. Pullen, et al, the study titled "A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19" was published in the New England Journal of Medicine. In this study, tested positive or symptomatic patients were excluded from the study, considering that the objective was to test hydroxychloroquine for the prevention

of COVID-19. 821 people were included in the randomized clinical trial, of which 414 received hydroxychloroquine and 407 placebo. In the group receiving hydroxychloroquine treatment, 31 people had previously had asthma (7.5%), 51 had hypertension (12.3%), and 12 had diabetes (2.9%). While in the placebo group, 31 randomized had asthma (7.6%), 48 hypertension (11.8%), and 16 diabetes (3.9%). The number of patients who had confirmation of COVID-19 after intervention with hydroxychloroquine or placebo in the study was similar, as was the number of patients who had symptoms of infection or were hospitalized. The most reported adverse effects were nausea in 22.9% of those taking HQ (80/349), and diarrhea, abdominal discomfort and vomiting in 23% (81/349). Neurological reactions were observed in 5.4% of patients treated with hydroxychloroquine (19/349). Still, 13 had headache (4%), 3 had visual changes (1%), 4 skin reactions (1%), and 1 allergic reaction (0.2%). While using placebo, 27 cases of nausea were presented among 351 people (7.7%), and 15 cases of diarrhea (4%), abdominal discomfort or vomiting. Also 13 neurological reactions (4%) and 8 cases of headache (2%). The work did not mention limitations.

STUDY 3

""Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19" was published in Annals of internal medicine, a randomized trial produced by Skipper, Pastick, et al. In this study, 491 patients were randomized, of which 423 contributed. Also, 81% of the 423 had laboratory confirmation of Covid-19. After division into groups, symptoms of infection were noted after 14 days of treatment in 24% (49/201) of those who received hydroxychloroquine, against 30% (59/194) of those who received placebo. Adverse drug reactions were observed in 43% (92 of 212) of participants who were treated with hydroxychloroquine, while in the placebo group 22% (46 of 211). Both groups had 1 death each. It is concluded that there were no significant contributions with the treatment via hydroxychloroquine. When comparing with the placebo group, it was seen that treatment with hydroxychloroquine was prevalent in adverse reactions, with nausea and diarrhea, abdominal discomfort and vomiting being more reported. 138 of the 212 patients manifested Covid-19 symptoms through cough, 84 fever, 65 difficulty breathing, 116 headache, 116 fatigue and 100 myalgia among those who underwent drug treatment. Of the participants in this group, 23 (11%) were hypertensive, 8 (4%) diabetic, 28 (13%) asthmatic and 8 (4%) smokers. The numbers were very similar to the placebo group. Adverse effects from hydroxychloroquine were seen in 43% of participants who received it, versus 22% of those who took the placebo regimen. Thus, 66 people (31.1%) out of 212 reported nausea or stomach pain, 50 (23.6%) reported abdominal pain, diarrhea or vomiting, neurological disorders (nervousness, irritability, dizziness, or vertigo) 20 (9.4 %), dermatological disorders 6 (2.8%), tinnitus 8 (3.8%), allergic reaction 5 (2.4%), changes in vision 4 (1.9%), hot flashes and night sweats 2 (0.9%), headache 2 (0.9%). While in the placebo group 26 (12.3%) people reported nausea or stomach pain, 20 (9.5%) reported abdominal pain, diarrhea or vomiting, neurological disorders (nervousness, irritability, dizziness, or vertigo) 13 (6 .2%), dermatological disorders 2 (1%), tinnitus 5 (2.4%), changes in vision 5 (2.4%), dry mouth 1 (0.5%), racing heart, anxiety and heart attack. panic 1 (0.5%). The limitation found by study arises from the shortage of tests for Covid-19 in the US at the time of the work.

STUDY 4

A randomized clinical trial by Galan, Santos, Asato, et al, which was published in Pathogens and Global Health in 2021, suggests a lack of efficacy against covid-19 for the three drugs in question, given the similar mortality observed between the treated groups. There was no use of placebo. 168 patients participated in the trial, 54 of whom were relocated to hydroxychloroquine, 61 to chloroquine, and 53 to ivermectin. 37.5% of the 168 patients were obese, 43.4% had SAH, 28.1% diabetes mellitus, and 5.3% reported previous lung disease. Arrhythmia as an adverse effect was not presented among participants, and hematological and hepatic adverse reactions did not differ between groups. Mortality was similar in the three groups, being 22.2% in the one who received HCQ. In this group, an increase in G1/G2 liver transaminases was observed in 15.2% of the participants, G3/G4 liver transaminases in 10.2%, anemia in 5.5%, and leukopenia in 5.5%. Being over 60 years old or having diabetes mellitus were shown to be risk factors for higher mortality. The onset of diarrhea prior to hospital admission was associated with lower mortality compared to those without this symptom. No limitations were reported.

CHLOROCINE (CQ)

STUDY 5

In April 2020, the clinical study of HUANG, M. et al., evaluating the efficacy and safety of chloroquine in 22 hospitalized and COVID-19-positive patients with moderate to severe disease was released. Of these, 10 were treated with 500 mg of chloroquine orally twice a day for 10 days and the control group with Lopinavir/Ritonavir 400/100 mg orally twice a day for 10 days. Within analysis group 3 were classified as having severe COVID-19 and the others as having moderate disease. The most common adverse event was vomiting (50%) observed in 5 patients. Other effects were: abdominal pain (10%), nausea (40%), diarrhea (50%), rash or itching (10%), cough (40%) and shortness of breath (1%). No serious adverse events or discontinuation of chloroquine were reported during the treatment period. As for the comorbidities reported in the chloroquine group, smokers (20%), hypertensive (10%) and diabetes (10%) were observed. The authors classified the small sample size as a limitation of study.

STUDY 6

A randomized clinical trial carried out in Brazil, Manaus, in April 2020 by BORBA, et al 2020, analyzed 81 hospitalized patients suspected of COVID-19, administering 600 mg of chloroquine twice daily for ten days in the high-dose group, and 450mg of QC twice a day plus a placebo a day, on the first day, and 450mg/day for four days, then only placebo for five days, in the low-dose group, therefore, it is noted that the use of QC in this last group it was only five days. Participants from both groups presented as adverse effects. In the low dose group there was a decrease in hemoglobin (22.2%), increase in creatine phosphokinase (31.6%), creatinine (46.7%), creatinine phosphokinase-MB (23.1%), QT interval corrected by Fridericia method > 500 ms (11.1%). In the high dose group there was also a decrease in hemoglobin (19.2%), increase in creatine phosphokinase (50%), increase in creatinine (39.1%), creatinine phosphokinase-MB (53.8%), corrected QT interval by the Fridericia method > 500ms (18.9%), and ventricular tachycardia (2.7%). 11 of 73 (15%) patients had a QTc interval prolongation greater than 500 ms, and one patient had rhabdomyolysis and the drug was withdrawn. Furthermore, the authors state that in the higher-dose group there were more toxic effects and increased lethality, mainly affecting the prolongation of the QTc interval

(11.1% in the low-dose group versus 18.9% in the higher-dose group). As for the most prevalent comorbidities manifested were hypertension (low dose 37%, high dose group 53.6%), alcohol use disorder (low dose 30.8%, high dose group 24%) and diabetes (low dose 18 .5%, high-dose group 32.1%), others mentioned were asthma, chronic kidney disease, with rheumatic diseases, tuberculosis and liver disease in the low-dose group. In the high-dose group there were more people with heart disease and had one patient with HIV/AIDS. Also regarding this group, patients with previous heart disease and other comorbidities had higher lethality, with 39% compared to 15% in the low-dose group. The limitations identified by the study were the small sample size, a single-center design, absence of a placebo control group, and lack of exclusion criteria based on the QTc interval at the beginning of the study.

IVERMECTINA

STUDY 4

Still on the study by Galan, Santos, Asato, et al, for the ivermectin group, 14 mg of ivermectin were administered once on day 0 added to a placebo tablet. On days 1 and 2 one tablet per day of ivermectin, and on days 3 and 4 one tablet of placebo per day. The total dose of the drug was 42 mg. For patients with body weight below 55 kg, the dose of ivermectin was adjusted to 10 mg per dose. In the group there were 35% obese patients, 37.6% as ex-smokers, 31.2% active smokers, 56% regular use of alcohol, 30.4% with systemic arterial hypertension, 31.1% diabetes. Diabetes was associated with an increase in mortality of 32.8%. Also, moderate to severe obesity, with a BMI cut-off level above 33 kg/m2, was related to an increase in mortality of 32.5%. Compared to those without these conditions, these numbers are significant. Other comorbidities in the clinical trial were not related to an increase in adverse reactions. The most prevalent adverse event reported for this group was 26.4% hepatotoxicity. As for serious cardiac, hematological or hepatic effects, they were not observed because the dose used is considered safe. The study did not observe any significant difference in treatment with these drugs in terms of reduced need for supplemental oxygen, admission to the ICU, invasive ventilation, or death in hospitalized patients with severe COVID-19. It did not have limitations.

STUDY 7

In the study by CHACCOUR, et al, 2021, the use of ivermectin was analyzed aiming its efficacy in a single dose of 400mcg/kg aiming at reducing the transmission of the virus in 24 randomized participants who presented symptoms of COVID-19 or with positive PCR, through a randomized, double-blind clinical trial carried out in Spain. The study did not include participants with comorbidities or risk factors in the study, and the sample for analysis was separated into 12 people for the ivermectin group and another 12 for the placebo group. The prevalent adverse effects were symptoms of dizziness, blurred vision and confusion. However, symptom accounting was done by treatment days, reported by patients daily for 28 days. The same symptom can be counted more than once by the same patient, different from other studies. Because of this, it was not possible to analyze these results as data from other studies. The clinical trial showed 15 adverse effects, 7 in the analysis group and 8 in the placebo group, reported by 10 participants, 5 in the ivermectin group and 5 in the placebo group. There were no reports of severe adverse events. As for the limitations, the study emphasized a careful interpretation of the results as it focused not on the drug's efficacy, but on a potential use for COVID-19 and, as a result, the low number of participants

was explained, as well as the recruitment of individuals. mildly affected and without risk factors, medicated within the first 48 hours of the onset of fever or cough. Another limitation was the quantification of the viral load due to the heterogeneity of the samples.

STUDY 8

Another randomized, double-blind clinical trial, now looking at the effect of ivermectin related to duration of symptoms in adults with mild COVID-19, published in March 2021, in Colombia, by López-Medina, et al, 2021, enrolled 398 participants symptomatic, with mild infection, separating them into 200 in the ivermectin groups and 198 in the placebo, with a dose of 300μg/kg per day of the drug in solution for 5 days. Most of the sample had no comorbidity (79%), however, some individuals with hypertension, diabetes, thyroid disease, cardiovascular disease, smokers and some other coexisting condition were observed. In 154 patients who were in the ivermectin group mentioned adverse events (77%), 2 patients in the group reported serious adverse events, with 15 patients in that group discontinuing treatment due to the events. The most common effects in the ivermectin group were headache 104 patients (52%) followed by dizziness 68 (34%), diarrhea 52 (26%), nausea 46 (23%), abdominal pain 36 (18%), blurred vision 23 (11.5%), tremor 13 (6.5%), skin discoloration 13 (6.5%), rash 12 (6%). In the placebo group, 111 (56%) had headache, 68 (34.3%) dizziness, 65 (32.8%) diarrhea, 47 (23.7%) nausea, 49 (24.7%) abdominal pain, 19 (9.6%) rash, 23 (11.6%) blurred vision. The most common serious adverse event was multiple organ failure, in 4 patients, present in both the placebo and drug-treated groups. Effects in the placebo group of 198 participants were headache in 111 patients (56.1%), dizziness in 68 (34.3%), diarrhea in 65 (32.8%), nausea in 47 (23.7%), pain abdominal 49 (24.7%), photophobia 4 (2%), blurred vision 23 (11.6%), decreased visual acuity 2 (1%), tremor 6 (3%), skin discoloration 4 (2%), rash 19 (9.6%), among other reactions with less frequency noted. In the placebo group, 111 (56%) had headache, 68 (34.3%) dizziness, 65 (32.8%) diarrhea, 47 (23.7%) nausea, 49 (24.7%) abdominal pain, 19 (9.6%) rash, 23 (11.6%) blurred vision. Regarding the limitations presented by the authors, the study started and within 6 weeks it had to readjust its original design and its primary outcome, due to the low incidence of clinical deterioration presented by the study sample. Despite having good potency for detecting the hazard ratio (hazard ratio) for resolving symptoms in the groups analyzed, affirming the possibility of having been meager in detecting a smaller reduction. The clinical trial did not include virological evaluations, however, the clinical characteristics analyzed implicitly demonstrate viral activity. Another limitation presented was that the use of placebo in the first 65 participants had a difference in smell and taste than ivermectin, however there was no distinction between the results compared at the end of the analysis. The authors mention the use of an 8-category ordinal scale, which requires participant self-report in the early stages, favoring subjectivity. Another aspect raised was that they did not collect plasma levels of ivermectin. Finally, the fact that the study sample is younger may imply different results from an older population.

DOSE AND RAM RELATIONSHIP

AZITHROMYCIN

The article referring to Azithromycin does not allow associating dose to adverse reactions, as no other trials that addressed azithromycin therapy were found during the search for articles for this study.

STUDY NUMBER	TREATMENT TIME	ADMINISTRATED DOSE	ADVERSE EFFECTS
2 - BOULWARE, D. R.; PULLEN, M. F.; BANGDIWALA, A. S.; et al. 2020.	5 DAYS	Within 4 days after exposure, participants received 800 mg of hydroxychloroquine (4 tablets) once, followed by 600 mg (3 tablets) over 6 to 8 hours, then 600 mg (3 tablets) daily for an additional 4 days. Participants who had intestinal problems were able to divide the daily dose into 2 or 3. Oral hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for another 4 days) or masked placebo Hydroxychloroquine 400 mg twice on day 0, and once a day from day 1 to 4, total dose 2.4 g; Or Chloroquine: 450 mg, 2 times on day 0, and once daily from day 1 to day 4, total dose 2.7 g; Or ivermectin 14 mg once on day 0 plus one placebo tablet and once daily from day 1 to day 2 plus one placebo tablet daily from day 3 to 4, total dose: 42 mg. For patients with body weight below 55 kg, the dose of ivermectin was adjusted to 10 mg per dose.	Sample: 349 (HQ) • Disorders of the gastrointestinal system: 164 (47%) • Neurological disorders: 40 (11.4%) • Visual disturbances: 3 (0.8%) • Dermatological disorders: 4 (1.1%) • Immune System Disorders: 1 (0.2%) • Systemic disorders 1 (0.3%) Sample: 212 • Disorders of the gastrointestinal system: 116 (54.7%) • Neurological disorders (14.1%) • Disorders of the cardiovascular system 2 (0.9%) • Visual disorders 4 (1.9%) • Dermatological disorders 6 (2.8%) • Immune system disorders 5 (2.4%)
3 - SKIPPER, C. P.; PASTICK, K. A.; ENGEN, N. W.; et al. 2020.	5 DAYS		•
4 - GALAN, L. E. B.; SANTOS, N. M.; ASATO, M. S.; et al. 2021.	5 DAYS HQ and CQ 3 DAYS OF IVRMECTIN		Amostra grupo HQ: 54 • Hepatotoxicidade: 13 (24,1%) • Distúrbios hematológicos: 6 (11,1%) Sample QC group: 61 • Hepatotoxicity: 13 (21.3%) • Hematological disorders: 5 (8.2%) Sample ivermectin group: 53 • Hepatotoxicity: 14 (26.4%) • Hematological disorders: 5 (9.4%)
6 - BORBA, M. G. S.; VAL, F. F. A.; SAMPAIO, V. S.; et al. 2020.	5 DAYS, low dose group.	Low-dose group: 450mg chloroquine twice + 1 placebo daily on the first day, 450mg/day for 4 days, then placebo for 5 days.	Low dose group: 40 • Hematological disorders: 9 (22.5%) • Disorders of the cardiovascular system: 4 (10%) • Kidney disorders: 40 (100%) Creatinine Increase 46.7% Increase in creatine phosphokinase 31.6% Increased creatinine phosphokinase-MB 23.1%

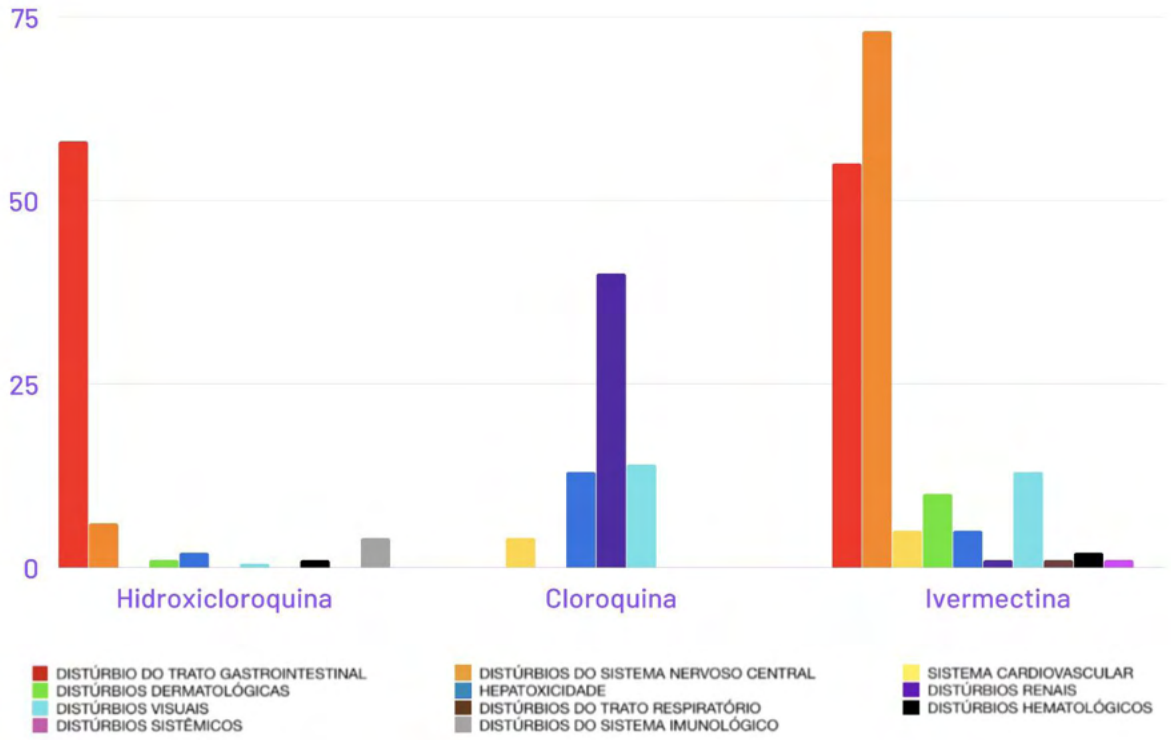
8 - López-Medina, E.; López, P.; Hurtado, I. C.; et al. 2021	5 DAYS	0,3 mg/kg per day of ivermectin in solution for 5 days	Sample:200 • Disorders of the gastrointestinal system: 139 (69.5%) • Neurological disorders: 185 (92.5%) • Disorders of the cardiovascular system: 4 (2%) • Dermatological disorders: 25 (12.5%) • Kidney disorders:2 (1%) • Visual disturbances: 17% • Respiratory tract disorders: 2 (1%) • Systemic disorders: 3 (1.5%)

TABLE OF TREATMENT IN UP TO 5 DAYS RELATED TO ADVERSE EFFECTS

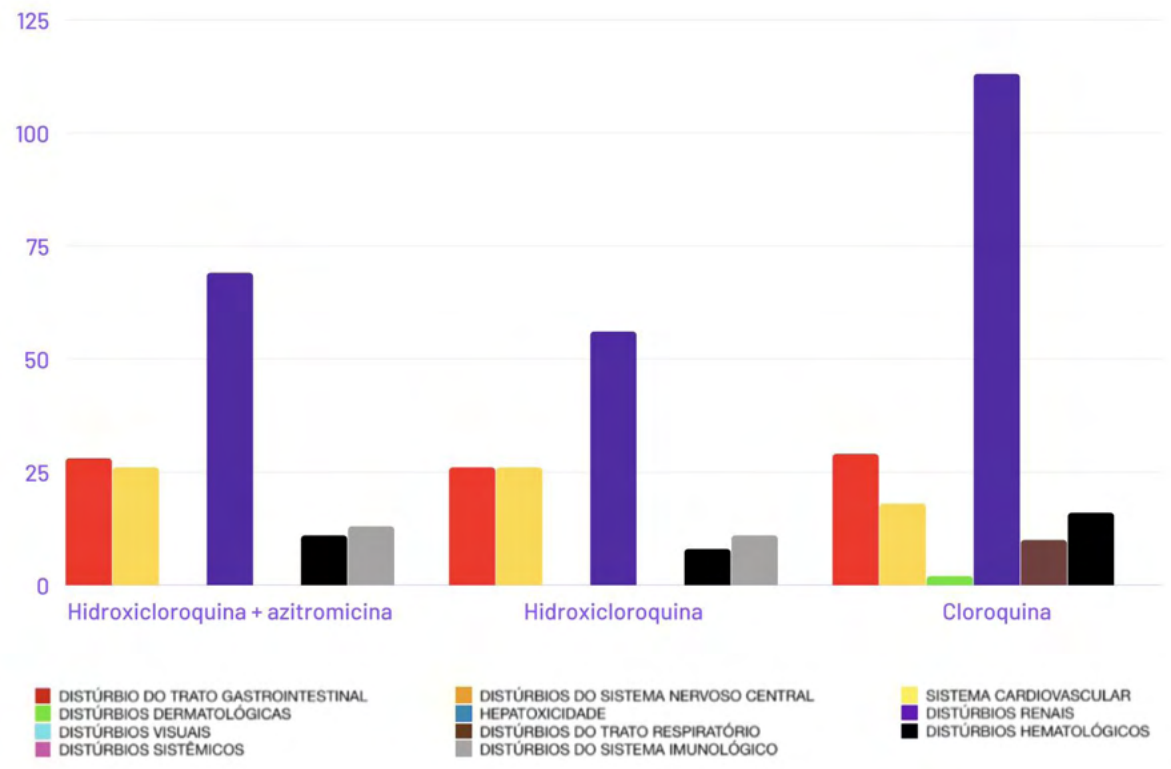
STUDY NUMBER	TREATMENT TIME	ADMINISTRATED DOSE	ADVERSE EFFECTS
1 - FURTADO, R. H. M.; BERWANGER, OT.; FONSECA, A. T.; et al. 2020.	10 DAYS	Group that received azithromycin - 500mg/day administered orally or nasogastric or intravenously, for 10 days. Control group received standard treatment without macrolides. As there was a recommendation by Brazilian authorities to treat all severe patients of COVID-19 with hydroxychloroquine or chloroquine, the study adopted these two drugs for both groups, in the dosage: 400 mg twice a day orally or nasogastric route for 10 days .	Sample: 214 (AZI + HQ) • Cardiovascular System Disorders: 55 (25.7%) • Disorders of the Gastrointestinal System: 61 (28.5%) • Kidney Disorders: 147 (68.7%) • Hematological disorders: 24 (11.2%) • Immune System Disorders: 27 (12%) Sample: 183 (HQ) • Cardiovascular System Disorders: 47 (25.7%) • Disorders of the Gastrointestinal System: 48 (26.2%) • Kidney Disorders: 103 (56.3%) • Hematological disorders: 15 (8.2%) • Immune System Disorders: 21 (11.5%) Sample: 10 • Disorders of the gastrointestinal system: 15 (1.5%) • Dermatological disorders: 1 (10%) • Respiratory tract disorders 5 (50%)
5 - HUANG, M.; TANG, T.; PANG, P.; et al. 2020.	10 DAYS	500 mg oral chloroquine twice daily for 10 days.	
6 - BORBA, M. G. S.; VAL, F. F. A.; SAMPAIO, V. S.; et al. 2020.	10 DAYS, high dose group	High dose group: 600 mg chloroquine twice daily for 10 days.	High dose group (41) • Hematological disorders: 8 (19.5%) • Disorders of the cardiovascular system: 9 (22%) • Kidney disorders: Creatinine increase: 16 (39.1%) Increased creatine phosphokinase: 20 (50%) Increased creatinine phosphokinase-MB: 22 (53.8%)

TREATMENT CHART IN MORE THAN 5 DAYS RELATED TO ADVERSE EFFECTS

Treatment for over 5 days



Treatment for over 5 days



HYDROXYCHLOROQUINE

Concerning the treatment with hydroxychloroquine, we had three studies that performed the therapy for 5 days, the one by Boulware et al (2020), Skipper et al (2020) and Galan et al (2021). The first two studies used the same drug dosage and the most relevant disorders were in the gastrointestinal tract, with 46.1% reported by Boulware et al (2020) and 26.4% in the study by SKIPPER, C. P.; et al. On the other hand, Galan et al (2021) administered a dose of hydroxychloroquine sulfate of 400 mg twice on day 0 and once a day on days 1 to 4. Since the dose was smaller, the hepatotoxic effects stood out (24.1%) and hematological (11.1%), which were not observed in the first two studies mentioned. Furtado et al (2020) demonstrated that with the administration of the drug for 10 days, with the same dosage as in the study by Galan; et al (800 mg per day) showed more kidney disorders (56.3%), followed by gastrointestinal system disorders 26.2% and cardiovascular system disorders 25.7%.

CHLOROCINE

In Borba's study; et al, it was noted that the administration of 450 mg of chloroquine twice on the first day of treatment, combined with a placebo and followed by 450 mg/day for the remaining 4 days, was associated with more kidney disorders (elevation of creatinine 46.7 %) and hematological 22.5%. The same dosage (450 mg), in another study (GALAN, et al, 2021) demonstrated a greater hepatotoxic effect (24.1%) and some cases of hematological disorders persisted (11.1%). Huang et al (2020) also addressed chloroquine in their article, but the administration was 500mg twice a day for 10 days, and this study showed more adverse reactions related to the respiratory tract (50% of the number of patients in the sample) . Borba et al (2020), on the other hand, administered 600mg of the drug twice a day for the same period and obtained as the most prominent adverse events disorders of the cardiovascular and renal system (elevation of creatine phosphokinase (50%) and increase of creatinine phosphokinase-MB 53, 8%).

IVERMECTINA

The study by Galan et al (2021) used 14 mg of ivermectin once on day 0 plus one placebo tablet and one tablet per day from day 1 to day 2 plus one placebo tablet per day from day 3 to 4, full dose of 42 mg, demonstrated some effects in the participants, such as hepatotoxicity (26.4%) and hematological disorders (9.4%). In the article by López-Medina et al (2021), 0.3 mg/kg per day of ivermectin in solution was administered for 5 days, showing more neurological effects (92.5%), followed by disorders of the gastrointestinal tract (69, 5%), visual (17%) and dermatological (12.5%). It is noticed that the longer treatment, 2 days more, may have affected other systems, and regarding the dose, the lower dosage showed hepatotoxic effects and the greatest neurological effects.

In the study which presented a therapeutic approach through the combination of Azithromycin and Hydroxychloroquine, a similar prevalence of hypertensive and renal adverse effects was observed, which may suggest the influence of the comorbidity reported with the affected renal system. In addition, other studies also reported the presence of participants with renal impairment at a similar rate, but when faced with another therapeutic scheme, they did not highlight renal impairment as with the use of associated antibiotics. Other studies did not suggest a possible association by analyzing the numbers presented. The most common comorbidities were hypertension, diabetes, lung diseases and use of tobacco and alcohol substances.

The most reported comorbidities and risk factors in studies that used hydroxychloroquine

STUDY NUMBER	RAM BY AFFECTED SYSTEM	BASE DISEASES PRESENTED IN THE STUDY AND OTHER RISK FACTORS	NOTES
1 - FURTADO, R. H. M.; BERWANGER, OT.; FONSECA, A. T.; et al. 2020.	Sample: 214 azithromycin + HQ • Cardiovascular System Disorders: 55 (25.7%) • Disorders of the Gastrointestinal System: 61 (28.5%) • Kidney Disorders*: 147 (68.7%) • Hematological disorders: 24 (11.2%) Immune System Disorders: 27 (12%) Sample: 183 HQ • Cardiovascular System Disorders: 47 (25.7%) • Disorders of the Gastrointestinal System: 48 (26.2%) • Kidney Disorders*: 103 (56.3%) • Hematological disorders: 15 (8.2%) Immune System Disorders: 21 (11.5%)	Sample: 214 azithromycin + HQ • Smokers 18 (8%) • Hypertensive 126 (58%) • Diabetics 81 (37%) • Heart failure 14 (6%) • Previous stroke 10 (4%) • Patients with cardiac infarction 8 (3%) • Dpoc 12 (5%) • Active Cancer 10 (4%) • Kidney failure 26 (12%) Sample: 183 HQ • Smokers 18 (9%) • Hypertensive 115 (62%) • Diabetics 71 (38%) • Heart failure 9 (4%) • Previous stroke 5 (2%) • With cardiac infarction 9 (4%) • COPD 12 (6%) • Active Cancer 4 (2%) With kidney failure 18 (9%)	Acute kidney failure 147 (68%) associated with 2 deaths
2 - BOULWARE, D. R.; PULLEN, M. F.; BANGDIWALA, A. S.; et al. 2020.	Sample: 349 HQ • Disorders of the gastrointestinal system: 164 (47%) • Neurological disorders: 40 (11.4%) • Visual disturbances: 3 (0.8%) • Dermatological disorders: 4 (1.1%) • Immune System Disorders: 1 (0.2%) Systemic Disorders 1 (0,3%)	Total sample: 414 • Hypertension 51 (12.3%) • Asthma 31 (7.5%) • Diabetes 12 (2.9%) • Smoker 15 (3.6%)	The total sample of patients randomized to treatment with hydroxychloroquine was 414, of which 349 reported having used it.

3 - SKIPPER, C. P.; PASTICK, K. A.; ENGEN, N. W.; et al. 2020.	Sample HQ group: 212 • Disorders of the gastrointestinal system: 116 (54.7%) • Neurological disorders (14.1%) • Disorders of the cardiovascular system 2 (0.9%) • Visual disorders 4 (1.9%) • Dermatological disorders 6 (2.8%) • Immune system disorders 5 (2.4%) HQ group sample: 54 • Hepatotoxicity: 13 (24.1%) • Hematological disorders: 6 (11.1%) Sample QC group: 61 • Hepatotoxicity: 13 (21.3%) • Hematological disorders: 5 (8.2%) Sample ivermectin group: 53 • Hepatotoxicity: 14 (26.4%) • Hematological disorders: 5 (9.4%)	Sample HQ group: 212 • Hypertensive 23 (10%) • Diabetics 8 (3%) • Asthmatics 28 (13%) • Smokers 8(3%). Total sample: 168 Obese (BMI> 30 kg/m2): 63 • Group HQ 21 (33.3%) • CQ Group 20 (32%) • Ivermectin Group 22 (35%) Ex-smoker: 69 • Group HQ 26 (37.6%) • CQ Group 17 (24.6%) • Ivermectin 26 group (37.6%) Active smokers: 16 • Group HQ 3 (18.7%) • QC Group 8 (50%) • Ivermectin 5 group (31.2%) Regular use of alcohol: 25 • Group HQ 6 (24%) • QC Group 5 (20%) • Ivermectin 14 group (56%) Systemic arterial hypertension: 69 • Group HQ 24 (34.8%) • CQ Group 24 (34.8%) • Ivermectin 21 Group (30.4%) Diabetes mellitus: 45 • HQ Group 13 (28.9%) • CQ Group 18 (40%) • Ivermectin 14 group (31.1%) Previous chronic lung disease: 9 • Group HQ 3 (33.3%) • CQ Group 4 (44.4%) • Ivermectin 2 group (22.2%) Chronic kidney failure: 4 • HQ Group 0 (0%) • QC Group 2 (50%) • Ivermectin 2 group (50%) Cancer: 5 • Group HQ 2 (40%) • QC Group 1 (20%) • Ivermectin 2 group (40%)	
4 - GALAN, L. E. B.; SANTOS, N. M.; ASATO, M. S.; et al. 2021.			Associated with diabetes: increased risk factor for mortality of 32.8% Associated with moderate to severe obesity BMI>33 kg/m2: higher mortality (32.5%) compared to those without this condition, almost doubling the risk of death.

5 - HUANG, M.; TANG, T.; PANG, P.; et al. 2020.	QC Group: 10 • Disorders of the gastrointestinal system: 15 (1.5%) • Dermatological disorders: 1 (10%) • Respiratory tract disorders 5 (50%)	QC Group: 10 • Smokers 2 (20%) • Hypertension 1 (10%) • Diabetes 1 (10%)	
6 - BORBA, M. G. S.; VAL, F. F. A.; SAMPAIO, V. S.; et al. 2020.	Low Dosage Group, CQ: 40 • Hematological disorders: 9 (22.5%) • Disorders of the cardiovascular system: 4 (10%) • Kidney disorders: 40 (100%) High dose group (41) • Hematological disorders: 8 (19.5%) • Disorders of the cardiovascular system: 9 (22%) • Kidney disorders: Creatinine increase: 16 (39.1%) Increased creatine phosphokinase: 20 (50%) Increased creatinine phosphokinase-MB: 22 (53.8%)	Low Dosage Group, CQ: 40 • Ex smoker 12.5% • Smoker 12.5% • Hypertension 37% • Diabetes 18.5% • Alcohol use disorder 30.8% • Heart disease 0% • Asthma 3.8% • Chronic kidney disease 3.8% • Rheumatic diseases 11.1% • Liver disease 7.4% • Tuberculosis 7.4% • HIV/AIDS 0% High dose groups (41): • Former smoker 33.3% • Smoker 4.2% • Hypertension 53.6% • Diabetes 32.1% • Alcohol use disorder 24% • Heart disease 17.9% • Asthma 10.7% • Chronic kidney disease 10.7% • Rheumatic diseases 0% • Liver diseases 0% • Tuberculosis 0% HIV/AIDS 3.6%	
8 - López-Medina, E.; López, P.; Hurtado, I. C.; et al. 2021	Sample ivermectin group: 200 Disorders of the gastrointestinal system:139 (69,5%) Neurological disorders: 185 (92.5%) Disorders of the cardiovascular system: 4 (2%) Dermatological disorders: 25 (12.5%) Kidney disorders:2 (1%) Visual disturbances: 17% Respiratory tract disorders: 2 (1%) Systemic disorders:3 (1,5%)	Sample ivermectin group: 200 • Current smoker 3 (1.5%) • Obesity 37 (18.5%) • Hypertension 28 (14%) • Diabetes 10 (5%) • Thyroid disease 7 (3.5%) • Cardiovascular disease 4 (2%) Any other coexisting condition 44 (22%)	15 patients in this group discontinued treatment due to the effects.

TABLE OF RELATIONSHIP BETWEEN RAM AND BASIC DISEASES AND OTHER RISK FACTORS PRESENTED IN THE STUDY

were hypertension, diabetes, asthma, former smokers, previous chronic lung disease, and cancer. As for the most prevalent adverse effects, they were gastrointestinal disorders, kidney disorders and even hepatotoxicity. Thus, these comorbidities may be associated with the ease of development of these adverse effects.

In the study by Galan, et al (2021), an association was found between the number of diabetic patients and an increase in the risk factor for mortality (32.8%), in addition to moderate to severe obesity related to higher mortality (32.5%). In the article by Borba, et al (2020), participants in the low dose group (CK) had hypertension, followed by alcohol use disorder, as comorbidity, which may be related to the adverse events of kidney disorders, the largest reported effect. In the same study, the high-dose group prevailed over hypertension and diabetes with a possible link between the most listed adverse reactions, kidney disorders, such as increased creatinine phosphokinase-MB and creatinine phosphokinase, and cardiovascular disorders.

As for the studies related to ivermectin, more comorbidities and risk factors such as obesity, ex-smokers, alcohol use, hypertension and diabetes were presented, with the probability of being connected with adverse reactions described as neurological, gastrointestinal, dermatological, visual disorders and hepatotoxicity.

The study by Chaccour et al, number 7 (TABLE 2), was taken from the tables comparing treatment time, dose and adverse effects (TABLE 4, 5), and from the table listing comorbidities, risk factors and adverse events (TABLE 6), as it did not detail such effects by patients as in other studies, but because of the reported amount of adverse effects presented per days of treatment, moreover, the study did not present patients with comorbidities. Because of this, we were not able to account for the adverse effects of the article, for both drug and placebo reactions, for this analysis.

Other limitations: there were no other studies with therapeutic approach by azithromycin to have a comparison effect between studies and data, and some studies had few patients.

DISCUSSION

In view of the analysis of the results, with numbers always brought in the form of number of reactions per 100 participants, it was possible to evidence that the adverse effects had a possible association with time and dosage, as well as with comorbidities and some risk factors for the COVID-19. The disorders that most stood out were neurological for ivermectin, renal in the association of hydroxychloroquine and azithromycin, followed by gastrointestinal tract disorders for hydroxychloroquine, the latter stood out for having been reported in three of the four studies with this chemical intervention. This information may lead to reflection on the possibility of confusing these symptoms with those of COVID-19 infection. In this scenario, it is necessary to better analyze the distribution of the drug to patients who already face a situation of alteration in the functioning of the gastrointestinal tract due to the infection.

Regarding the treatment of up to 5 days with hydroxychloroquine, it was possible to observe that the existence of gastrointestinal system disorders was more prevalent. In the study by GALAN, et al, 2021, more cases of hepatotoxicity were observed compared to studies that performed therapy in 10 days, where there were more reports of kidney disorders. As for the 5-day treatment of chloroquine, a prevalence of hepatotoxicity and kidney disorders was noted. For 10 days, the patients reported kidney, respiratory and cardiovascular disorders. In therapy

with ivermectin for 5 days, many cases of neurological and gastrointestinal system disorders were highlighted. It can be observed that the 5-day treatments had more adverse effects such as disorders in the gastrointestinal and renal tracts, and the 10-day therapies had a prevalence of renal disorders in all analyzed drugs.

The doses used and the time applied by the studies showed different adverse effects in some treatments, such as, for example, hydroxychloroquine at a lower dose highlighted hepatotoxicity and hematological disorders, whereas the same dose in a period of 10 days showed more renal adverse reactions. When using chloroquine at a lower dose, the prevalent adverse reactions were hematological and hepatotoxicity, while at the highest dose the prevalent effects were respiratory disorders and cardiovascular system disorders, in addition to the renal disorders that emerged in both dosages. When analyzing the dose of 14 mg of ivermectin, hepatotoxicity was evidenced, and when administered 0.3 mg/kg, neurological and gastrointestinal effects predominated.

The possible relationships between comorbidities and risk factors with adverse effects were that the study that addressed therapy with azithromycin and hydroxychloroquine had more hypertensive and more reports of kidney disorders. In the study with hydroxychloroquine, there was a predominance of patients with hypertension, diabetes, asthma, former smokers, previous chronic lung disease and cancer, which may be related to the significant amount of gastrointestinal and renal events and even hepatotoxicity. With chloroquine, most patients were hypertensive and the most reported disorders were renal. In the study with ivermectin, the comorbidities that appeared were obesity, history of smoking, alcoholism, hypertension and diabetes, and the prevalent drug reactions were neurological, gastrointestinal, dermatological, visual and hepatotoxicity disorders. Thus, adverse effects arising from therapies with azithromycin associated with hydroxychloroquine, hydroxychloroquine, and chloroquine suggested a relationship with hypertension and kidney disorders, instigating a better analysis of this possible correlation.

There are demonstrations about the risk of treatment with more than one drug, such as the use of chloroquine or hydroxychloroquine added to azithromycin, which have synergism on cardiac adverse effects. (BORBA, VAL, SAMPAIO, et al. 2020). In view of the association of azithromycin with hydroxychloroquine, slightly higher numbers of adverse reactions on the cardiovascular and renal systems emerged, compared to isolated therapies with the second drug. It may also represent a relationship with previous accidents or underlying diseases, such as heart failure, stroke, heart infarction or previous kidney failure.

The occurrence of acute kidney failure in the study by FURTADO et al proved to be relevant after the start of off-label therapeutic intervention, represented by 147 cases, associated with 2 deaths. The data underscore a greater need to weigh the risks and possible benefits of therapy. From therapy with the drug ivermectin a large number of adverse reactions emerged. Among them, those from the gastrointestinal system stand out by number, and fifteen withdrew from treatment due to unwanted reactions. The study by CHACCOUR, et al showed impairment of visual acuity due to the use of the drug, and in the study by Galan, et al, it was possible to observe the existence of hepatotoxicity, points that may draw more attention in the indiscriminate use of this drug.

When comparing the therapies with drugs in a study with a placebo group or

another drug, it was seen that, in study 2, in which treatment with hydroxychloroquine was addressed, both groups had similar adverse reactions, being more prevalent in the one that received hydroxychloroquine. In addition, it was noted that there were visual changes present only in the use of the drug and possibly related to it. In study 3, also with hydroxychloroquine, it was observed that events such as allergic reaction, hot flashes, night sweats and headache were related only to the group with hydroxychloroquine. Nausea or stomach pain, abdominal pain, diarrhea or vomiting were the most reported reactions, but present in both groups. Study 5 looked at chloroquine, where a skin rash or itching in one participant was only in the drug group. As for ivermectin, study 7 showed that the confounding symptom was not presented in the placebo group. Finally, study 8, also on the latter drug, had a greater number of reports of tremor and skin discoloration while using the drug, in addition to gastrointestinal bleeding in two participants that was not reported in the placebo group.

The analysis of studies on adverse reactions due to treatment without proven efficacy for COVID-19 was complex, as some of the articles studied did not thoroughly divide the adverse effects of the disease progression state, as well as patient comorbidities, making exact correlation difficult. adverse events of the drug against the disease, and this fact can be considered one of our limitations.

CONCLUSION

It was possible to infer that the use of drugs without proven clinical efficacy (azithromycin, hydroxychloroquine, chloroquine and ivermectin) have significant adverse effects for the population, especially for hypertensive, diabetic, obese and former smokers with COVID-19. The need for safe information for drug treatment is highlighted, going against advertising that does not indicate the important dangers to listeners, and the indiscriminate use through self-medication or recommendations by professionals outside the health area. It is necessary for the physician to analyze during the anamnesis about the comorbidities and risk factors of the patient with COVID-19, and the possible relationships that can be developed with adverse drug events, to better assess the risk and benefit of these treatments without clinical support scientific. In addition to taking greater care with the development of worrisome reactions due to the indiscriminate use of drugs propagated as an effective treatment. Furthermore, adverse effects, considering the adoption of these drugs on a large scale, can be confused with symptoms of COVID-19, hindering the management of signs and symptoms of the infection.

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