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Effectiveness of ivermectin for COVID-19: A systematic review

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ABSTRACT

OBJECTIVE

To evaluate the efficacy and safety of ivermectin in the prevention and treatment of COVID-19.

METHODS

This is a systematic review of randomized clinical trials. We searched the electronic databases PubMed (1966-2021), EMBASE (1974-2021) and Clinical Trials (2021) and two evidence megabusers: Turning Research Into Practice (TRIP) database (2021) and Epstemonikos (2021). There was no geographic or language restriction, using DeCS descriptors and terms (Health Sciences Descriptors). The synthesis method involved the combination of similar studies in a narrative review.

RESULTS

463 citations were identified and 2 studies were included, following the inclusion and exclusion criteria. Both studies showed very low quality and reduced sampling.

CONCLUSIONS

The studies completed and published to date do not support the use of ivermectin in the prevention or treatment of COVID-19. It is suggested to carry out new quality clinical trials to elucidate the issue.

DESCRIPTORS

Coronavirus infections, Pneumonia, Ivermectin, COVID-19, Systematic review.

RESUMO

OBJETIVO

Avaliar a eficácia e segurança da ivermectina na prevenção e tratamento da COVID-19.

MÉTODOS

Trata-se de revisão sistemática de ensaios clínicos randomizados. Procedeu-se à busca nas bases eletrônicas de dados PubMed (1966-2021), EMBASE (1974-2021) e Clinical Trials (2021) e em dois megabuscadores de evidências: Turning Research Into Practice (TRIP) database (2021) e Epstemonikos (2021). Não houve restrição geográfica e de idioma, sendo utilizados descritores e termos do DeCS (Descritores em Ciências da Saúde). O método de síntese envolveu a combinação de estudos semelhantes em uma revisão narrativa.

RESULTADOS

Foram identificadas 463 citações e 2 estudos foram incluídos, seguindo os critérios de inclusão e exclusão. Ambos os estudos apresentaram muito baixa qualidade e reduzida amostragem.

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CONCLUSÃO

Os estudos concluídos e publicados até o momento não suportam o uso da ivermectina na prevenção ou tratamento COVID-19. Sugere-se a realização de novos ensaios clínicos de qualidade para elucidação da questão.

DESCRIPTORS

Infecções por coronavírus, Pneumonia, Ivermectina, COVID-19, Revisão sistemática.

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INTRODUCTION

Coronaviruses are part of a broad group of viruses known since the 1960s and which contain RNA (ribonucleic acid) in their genome[1,2].

At the end of 2019, some cases of pneumonia of unknown etiology in China were described.[3] It was found to be a coronavirus, until then not described, of the genus betacoronavirus. It was officially named coronavirus 2 of the severe acute respiratory syndrome (SARS-CoV-2) and the disease, caused by it, was designated as COVID-19[2].

From Asia, COVID-19 quickly spread to Europe and the United States and, later, to South America and Africa, characterizing a pandemic, as decreed by the World Health Organization (WHO) in early 2020. The losses to health and the global economy were and remain evident[3,4,5].

The search for an effective treatment started to centralize the actions of researchers since the onset of the disease. Viral replication inhibitory molecules, protease and protein inhibitors, endocytosis inhibitors, neutralizing antibodies, among many means have been considered and widely studied at this time[6,7].

Among pharmacological strategies, ivermectin, an anti-parasitic agent, has been widely recommended by some health professionals for the prevention and treatment of COVID-19[8].

Ivermectin has been used for many years to treat various infections in mammals. It is a drug described in the late 1970s and approved for use in animals in 1981. It has high lipid solubility, acting against nematodes, arthropods, flaviviruses, mycobacteria and also against malignant cells, although the mechanisms of action against parasites and viruses are not yet fully known, including possible toxic actions for cells[8].

In an in vitro study, it was found that the exposure of the coronavirus that causes COVID-19 to ivermectin generated destruction of almost all viral particles after 48 hours. The drug, according to the study authors, could inhibit the transmission of viral proteins into cells[8].

Ivermectin, in vitro, is able to inhibit import protein (IMP), which compromises viral replication. In addition to this action, in vitro and also in experimental animals, the drug inhibits the production of interleukins, reducing inflammatory activity, at the systemic level and mainly in the lung tissue[9].

Considering the seriousness of the condition and the lack of therapeutic options, it is reasonable to use compassionate and very careful drugs in cases to be decided by the phisician with the proper documentation and informed consent. In this context, treatments have been described for COVID-19, among which ivermectin therapy, whose effectiveness gap currently prevails and motivated us to make this study. Herein we evaluated the efficacy and safety of ivermectin for the prevention and treatment of COVID-19 in human beings.

METHODS

This is a systematic review of randomized clinical trials. The search was carried out in three electronic databases, being: MEDLINE via PubMed (1966-2021) - www.pubmed.gov, EMBASE (1974-2020) and Clinical Trials (2021) and in two evidence megabusers: Turning Research Into Practice (TRIP) database (2021) and Epistemonikos (2021). There was no date limitation or geographic restriction for the research. The date of the last survey was January 25, 2021.

The official vocabulary identified was extracted from DeCS - Health Sciences Descriptor - http://decs.bvs.br/ and MeSH - Medical Subject Headings - http://www.ncbi.nlm.nih.gov/mesh and the corresponding terms for EMTREE. The descriptors and terms used were: “COVID-19" [Mesh] OR (SARS-CoV2) OR “Ivermectin” OR “Ivermectin”. The methodology adopted for the development of the search strategy followed the Cochrane Handbook, as well as the standardization for high-sensitivity strategies[10].

Only randomized clinical trials (RCTs) and quasi-randomized trials were included in the study, whose participants were adults of both sexes with COVID-19, regardless of the severity and duration of the symptom.

The types of interventions involved a group treated with ivermectin, regardless of dosage or length of treatment, compared to a group treated with any other intervention.

Types of Outcomes
- *Primary*
- clinical improvement
- adverse effects
- *Secondary*
- reduction in number of days in hospital
- reduction in PCR (Polymerase Chain Reaction) positivity time

The citations obtained through the search strategy in the various databases were gathered in a single list, after excluding duplicated citations. The titles and abstracts of all studies were reviewed and those considered to be potentially relevant were selected for full reading. Those who met the selection criteria were included in the review. The entire study selection process was carried out in pairs, by two independent reviewers.

Both, independently, extracted the relevant data from each study selected for inclusion and compared their findings. For each study, information was collected on the characteristics of the study, the participants, interventions and outcomes.

The methodological quality of the included studies was also assessed by two independent researchers, according to the recommendations of the Co-chrane Handbook[10].

Each RCT received a final score for each of six domains, according to the global risk of bias (Table 1), being considered: YES (low risk of bias), UNCLEAR (risk of uncertain bias) or NO (high risk of bias) bias), being:

- Low risk of systematic error or bias: all criteria well described and properly applied;
- Uncertain risk of systematic error or bias: one or more of the first three criteria could not be assessed due to the lack of information for the judgment.
- High risk of systematic error or bias: one or more of the first three criteria improperly applied.

Data analysis was performed by comparing the outcomes of interest between the groups treated with ivermectin and the control. Comparable data were analyzed using Review Manager 5.3 software[11].

As the outcomes under analysis involved dichotomous variables, the difference in risk (DR), the relative risk (RR) and the respective 95% confidence intervals (95% CI) were calculated. The relative risk is the risk ratio between the group undergoing treatment with ivermectin and the control group (placebo or other treatment); a RR greater than 1 is indicative of a favorable outcome. DR is the absolute risk reduction of the group treated with ivermectin in relation to the control.

The unit of analysis was the individual patient.

The table 1 shows the analysis of risk of bias of the Cochrane Collaboration.

Table 1: Analysis of risk of bias of the Cochrane Collaboration[10].

DOMAIN	DESCRIPTION	JUDGMENT
Generation of the randomization sequence	Description of the method used to generate the allocation sequence in sufficient detail to allow whether the assessment will result in comparable groups	Was the allocation sequence generated properly?
Allocation concealment	Description of the method used to hide the allocation sequence in sufficient detail to determine whether the allocation of the intervention could be known between the time of randomization and the administration of the intervention	Was the allocation concealment adequate?
Masking of participants and researchers	Description of all measures used to maintain the masking of participants and researchers until the end of the study. Provides some information if the masking was effective.	Was knowledge of the allocation of the intervention adequately prevented during the study?
Incomplete data on outcomes	Description of all outcome data, including losses and exclusions in the analysis. When there are losses and exclusions, describe the number in each intervention group and reasons.	Were follow-up losses adequately reported and analyzed?
Selective reporting of outcomes	There is the possibility of selective reporting of any of the pre-specified outcomes.	Are the results of the study free of selective reporting of outcomes?
Other sources of bias	Description of any doubts about possible bias not previously analyzed	Is the study apparently free of other problems that can lead to the risk of bias?

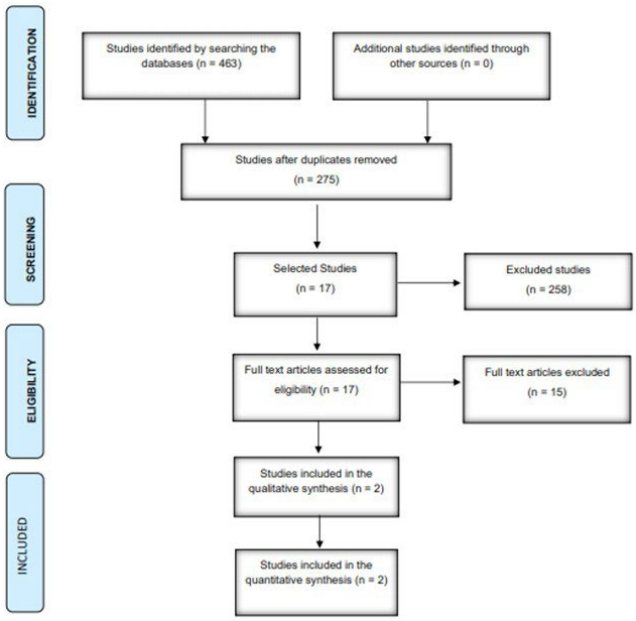
RESULTS

The search strategy recovered in January 2021 a total of 463 citations, 117 in PubMed, 6 in EMBASE, 10 in Clinical Trials, 197 in TRIPDATABASE and 133 in Epstemonikos.

After eliminating duplicate citations (n = 188), 275 unique studies remained. After reading the titles and abstracts of these studies, 258 were excluded for not meeting the selection criteria and 17 were selected for full reading, 2 of which met the inclusion criteria and were included in the review.

The Figure 1 shows the flowchart of the process for identifying studies in electronic databases.

Figure 1: Flowchart of the process for identifying studies in electronic databases.



The characteristics of the included studies are shown in Table 2. And the table 2 shows the bias risk analysis of the included RCTs.

Table 2: Characteristics of the included studies.

Author	Method	Participants	Treatment	Duration	Outcomes
Hashim e cols[12]	Randomized clinical trial	Included: 140 Analyzed: 140 Treated group = 70 Control group = 70	Treated group: 200 mcg / kg / day ivermectin + 100 mg doxycycline Group control: acetinophen 500 mg / day vitamin C 1000 mg (2x / day), zinc 75-125 mg / day vitamin D3 5000 IU / day, azithromycin 250 mg / day dexamethasone 6 mg / day oxygen therapy.	5-10 days	- clinical improvement
Ahmed e cols[13]	Randomized clinical trial	Included: 72 Analyzed: 72 Group 1 = 24 Group 2 = 24 Group 3 = 24	Group 1: ivermectin (12 mg / day / 5 days) Group 2: ivermectin (12 mg / day / 5 days) and doxycycline (200 mg on day 1 and 100 mg / day from the 2nd to the 5th day) Group 3: placebo	5 days	- PCR negative time - length of hospital stay - time to reduce fever and cough

Table 3: Bias risk analysis of the included RCTs.

RISK	Hashim e cols[12]	Ahmed e cols[13]
Randomization sequence	YES	UNCLEAR
Allocation concealment	UNCLEAR	UNCLEAR
Masking of participants and researchers	UNCLEAR	UNCLEAR
Description of losses in follow-up and analysis	YES	YES
Selective reporting of outcomes	YES	YES
Other sources of bias	YES	YES

The trial conducted by Hashin et al.,[12] (Iraq, 2020) evaluated the efficacy of ivermectin, associated with doxycycline in the treatment of COVID-19. The intervention involved two groups: Treated group: patients with COVID-19, mild to moderate (n = 48), severe (n = 11) and critical (n = 11). Control group: patients with mild to moderate degree (n = 48) and critical patients (n = 22) Randomization was performed by sequencing numbered envelopes.

The treated group used 200 mcg / kg of ivermectin in a single daily dose and 100 mg of doxycycline every 12 hours for a period of 5 to 10 days. The Control Group was treated with acetinophen 500 mg, vitamin C 1000 mg (2x / day), zinc 75-125 mg / day, vitamin D3 5000 IU / day, azithromycin 250 mg / day for 5 days, dexamethasone 6 mg / day and oxygen therapy. The outcome of the analysis was clinical improvement.

The authors described a shorter recovery time in the treated group (M = 10.61 ± 5.3 days versus 17.9 ± 6.8 days; p ‹0.05). There was no difference for (9% in the treated group and 11% in the control group; p ›0.05). The mortality rate was zero in both groups for mild cases; in critically ill patients: 18.2% (2/11) in the treated group and 27.27% (6/22) in the control group - p = 0.052.

The authors concluded that patients treated with ivermectin and doxycycline may have shorter recovery times and lower mortality rates in critically ill patients, although 18.2% of these participants in the treated group died.

The study conducted by Ahmed (Bangladesh, 2020) aimed to determine the time for negative CRP in patients with COVID-19 treated with ivermectin and the safety of the drug, reduction in hospitalization time and time to reduce fever and cough.

The authors found no shorter hospital stay in patients with COVID-19 treated with ivermectin: mean (in days) of 9.7 (95% CI: 8.1-11.0) in the ivermectin group; 10.1 (95% CI: 8.5-11.8) in the ivermectin + doxycycline group and 9.6 (95% CI: 7.7-11.7) in the placebo group - p = 0.93. The average duration of viral clearance detected in the PCR was 9.7 (95% CI: 7.8-11.8; p = 0.02) days in the group treated with ivermectin; 11.5 (95% CI: 9.8-13.2; p = 0.27) in the ivermectin + doxycycline group and 12.7 (95% CI: 11.3-14.2) in the placebo group. There was no reduction in the number of days of fever (p = 0.35) and cough (p = 0.18) after treatment.

The authors considered the need for further studies in view of the low sample size.

None of the included studies identified adverse events.

DISCUSSÃO

Since the end of 2019, when the virus appeared, the evidence based on clinical practice has already promoted important foundations related to clinical manifestations. Initial studies, at a pace never seen before, allowed the devel-opment of vaccines in less than a year. However, the need for prevention goes hand in hand with the need for treatment of the affected and therapies, medi-cated or not, have started to emerge and be described as potentially effective in recent literature.

Many treatments started to be considered. The use of ivermectin, either for the prevention or treatment of COVID-19, has foundations in in vitro studies and in animal experimentation studies. These showed inhibitory activity in coronavirus replication, with anti-inflammatory activity also described. In this context, in fact, there are several studies in favor of ivermectin for the preven-tion and treatment of COVID-19[8].

However, it is necessary to clarify that the in vitro response does not al-ways reproduce in vivo and in humans, and the therapeutic basis must involve the ability of the treatment to bring more benefits than harm.

The screening in the databases showed a large number of publications related to COVID-19 involving ivermectin, but only 2 randomized clinical trials.

Both studies (Hashim et al.12 And Ahmed et al13) have very low quality and small sampling.

It is clear that the level of evidence for the use of ivermectin, whether in the context of prevention or for the treatment of COVID-19 in humans, is ex-tremely limited.

In view of society's interest, covering aspects linked to public health and impacts on the global economy, governments should encourage the realization of studies that clarify the issue.

It is recommended to conduct clinical trials with good sampling and crite-ria for patient inclusion, randomization and allocation to well-delineated and described groups. The parameterized description of results also facilitates sys-tematic reviews in search of the best evidence. It should be noted that clinical trials are based on CONSORT (Consolidated Standards of Reporting Trials).

CONCLUSION

There is no scientific evidence of the effectiveness of ivermectin in humans for preventing or treating Covid-19. There are only 2 completed randomized clinical trials with very low quality and reduced sampling. Currently, therapy is based on in vitro studies and studies on experimental animals. We recommended new good quality randomized clinical trials to elucidate the question.

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