






## ORIGINAL ARTICLE

# CHLORINE DIOXIDE AND CHLORINE DERIVATIVES FOR THE PREVENTION OR TREATMENT OF COVID-19: A SYSTEMATIC REVIEW

Alejandra Burela <sup>1,a</sup>, Akram Hernández-Vásquez <sup>1,b,c</sup>, Daniel Comandé <sup>2,d</sup>,  
Verónica Peralta <sup>1,b,e</sup>, Fabian Fiestas <sup>1,b</sup>

<sup>1</sup> Instituto de Evaluación de Tecnologías en Salud e Investigación - IETSI, EsSalud, Lima, Perú.

<sup>2</sup> Instituto de Efectividad Clínica y Sanitaria (IECS), Buenos Aires, Argentina.

<sup>a</sup> Biologist; <sup>b</sup> Medical Doctor; <sup>c</sup> Master in Management and Public Policy; <sup>d</sup> Degree in Library and Information Science; <sup>e</sup> Specialist in Health Management.

## ABSTRACT

**Objectives:** To systematically review the effectiveness and safety of chlorine dioxide solution and chlorine derivatives used in the prevention or treatment of COVID-19. **Methods:** This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and follows the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions*. A librarian developed and executed the search strategy; it was further reviewed by two of the authors and complemented by manual search. Randomized clinical trials, quasi-experimental studies, cohort studies, case-control studies, cross-sectional studies, and case reports were included; *in vitro* or animal studies were excluded. Abstract and full-text screening according to pre-defined eligibility criteria were performed by two reviewers independently using web application Rayyan QCRI. Disagreements on study selection were resolved by a third reviewer. The systematic review protocol was registered in PROSPERO (CRD42020200641). **Results:** Neither published nor pre-print studies evaluating the use of chlorine dioxide or derivatives on SARS-CoV-2 infection were identified. The only finding was an unpublished observational study registry which has no results released yet. **Conclusions:** To date, there are no scientific evidence to uphold the use of chlorine dioxide or derivatives as preventive or therapeutic agents against COVID-19.

**Keywords:** Chlorine Dioxide; Chlorine Compounds; Prevention and Control; Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19; SARS-CoV-2 infection (Source: MeSH NLM).

## INTRODUCTION

In March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic. The first cases were reported in December 2019 in the Chinese city of Wuhan, and a new type of coronavirus was subsequently identified as the causative agent (SARS-CoV-2) <sup>(1)</sup>. As of August 9, more than 19 million confirmed cases of COVID-19 have been reported worldwide and 471,012 cases and 20,844 deaths caused by this disease have been confirmed in Peru <sup>(2)</sup>.

Person-to-person is the main transmission route, via droplets expelled by an infected person when sneezing, coughing, talking, and even indirectly through fomites. In addition, airborne transmission by aerosol could occur under specific circumstances <sup>(3)</sup>. In mild to moderate cases, symptoms are like a common cold and may or may not result in mild pneumonia; sometimes neurological and gastrointestinal symptoms occur, usually without the need for hospitalization. Dyspnea and hypoxia occur in severe cases, in which more than 50% of the lung tissue is compromised. In these cases, oxygen therapy or mechanical ventilation is required. Critical patients have multiorgan involvement, as well as an intense inflammatory response, and may present sepsis and multiorgan dysfunction syndrome which can lead to death <sup>(4-6)</sup>.

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**Correspondence:** Verónica Victoria Peralta Aguilar; Av. Arenales 1400, Jesús María, Lima, Perú; [veronica.peralta@essalud.gob.pe](mailto:veronica.peralta@essalud.gob.pe)

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There is not enough scientific evidence to support the use of any drug as treatment and/or preventive therapy against SARS-CoV-2<sup>(7,8)</sup>. Now, only symptomatic treatments are available. Thus, because of the lack of established treatment guidelines, different drugs with not enough scientific evidence are used worldwide,<sup>(9)</sup>. In addition, some drugs offered in the Peruvian market, besides not having scientific support for use against COVID-19, lack sanitary authorization to be used in humans as medical treatment<sup>(10)</sup>. However, the distributors and manufacturers of these products assure their effectiveness and safety against COVID-19, as preventive, curative, and symptomatic drugs<sup>(11)</sup>.

The products mentioned previously are chlorine dioxide, sodium chlorite and other chlorine derivatives. Commercially chlorine dioxide is known as CDS (chlorine dioxide solution) and is advertised as a derivative of the compound initially sold as MMS (miracle mineral supplement or mineral miracle solution)<sup>(12)</sup>, which contains sodium chlorite. Sodium chlorite is converted to chlorous acid when mixed in water with an acid, as indicated by its distributors, and then becomes chlorine dioxide. On the other hand, CDS is the chlorine dioxide gas in solution. Chlorine dioxide and other chlorine derivatives (e.g., sodium chlorite, sodium hypochlorite, etc.) are used as disinfecting agents in various industrial processes, due to their strong oxidizing power<sup>(13,14)</sup>. The oxidizing effect ends up denaturing organic compounds, however, this effect is not specific against a particular type of organism.

In this scenario, it is necessary to gather scientific evidence to contrast the widespread claims and the hypothesis in favor of using CDS or MMS as a preventive agent and as a curative or control treatment against COVID-19<sup>(15)</sup>. Therefore, this study aimed to systematically review the efficacy and safety of the use of chlorine dioxide and chlorine derivatives, in the prevention or treatment of COVID-19.

## MATERIALS AND METHODS

For this systematic review we followed the statement of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>(16)</sup> and the Cochrane Manual for systematic reviews of interventions<sup>(17)</sup>. The protocol was registered in PROSPERO with the reference number CRD420200641 ([https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=200641](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=200641)).

### Eligibility criteria

Randomized clinical trials, quasi-experimental studies, cohort studies, case-control studies, cross-sectional studies, and case reports evaluating chlorine dioxide and chlorine derivatives to prevent or treat COVID-19 in people of all

## KEY MESSAGES

**Motivation for the study:** In the absence of an effective medicine to prevent or cure COVID-19, an increasing number of people are ingesting chlorine dioxide or chlorine derivatives, chemical compounds not authorized for human consumption.

**Main findings:** To date, there is no scientific evidence to support the use of chlorine dioxide or chlorine derivatives to prevent or treat COVID-19.

**Implications:** In the absence of evidence, these chemicals cannot be considered effective or safe. That said, the scientific and medical community has expressed concern about the harm that consumption of chlorine dioxide or chlorine derivatives may cause to people.

ages were included. No language or publication status restrictions were applied. Studies on other coronavirus infections (e.g., MERS-CoV, SARS-CoV, etc.) were also considered if no studies on SARS-CoV-2 infections were found. Animal or in vitro studies were excluded.

### Search Strategies

A systematic electronic search for articles published up to July 24, 2020 was conducted in the following databases: PubMed, Embase (Excerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane Library, Web of Science, LILACS (Latin American and Caribbean Literature in the Health Sciences), and SciELO (Scientific Electronic Library Online). A search strategy was initially designed for PubMed and was adapted to the other databases; it combined the terms “coronavirus”, “SARS-CoV-2”, and “Chlorine” with synonyms and other medical descriptors.

A librarian (DC) created the search strategies, which were then validated by two of the authors (AB and AHV). The search terms used for the databases are detailed in the Appendix 1 of the supplementary material. The electronic search was complemented by manual searches of the reference lists of relevant articles to identify possible studies not found in the electronic search (snowball strategy), Google Scholar (first ten pages of results), and pre-print repositories (medRxiv and bioRxiv) using a combination of the following terms: “coronavirus”, “SARS CoV 2”, and “Chlorine”. In addition, we reviewed records from clinical trials in progress or with unpublished data from the China Clinical Trials Registry (ChiCTR), the Netherlands Trials Registry (NTR), ClinicalTrials.gov, and the International

Standardized Randomized Controlled Trial Number (ISRCTN). The search was conducted without restrictions regarding study design, publication status, publication date or language.

### Study selection

In the first stage, results from the electronic and manual search were imported into the reference management software EndNote X9 (license 3061914708). Then, all duplicate records were eliminated following the methodology described by Bramer *et al.* The identified records were evaluated to verify if they complied with the inclusion criteria; those that did not meet the criteria were excluded from the review. Two independent reviewers (AB and AHV) participated in the evaluation of the eligibility of all records by means of the Rayyan web application (<https://rayyan.qcri.org/>)<sup>(19)</sup>. Any disagreements were resolved between the two reviewers, and if no decision could be made, a third reviewer participated in the discussion (VP).

### Extraction and synthesis of results

We planned to report any outcome of using chlorine dioxide and chlorine derivatives to prevent or treat COVID-19, such as the cure rate, resolution time, reduction in the severity of the disease, hospitalization period, mortality rate, adverse events, among others. We also planned to obtain the general characteristics of each study and to evaluate the quality of each one according to the study type. However, no study was found to meet the inclusion criteria for these processes.

### Ethical considerations

The approval of the study by an institutional ethics committee was not required as it was a review of bibliographic databases.

## RESULTS

The search of the databases and other sources included 101 records after removing duplicates. From these 101 records, no published or pre-published studies were identified to have evaluated the use of chlorine dioxide and chlorine derivatives to prevent or treat COVID-19 or other coronavirus infections (Figure 1).

Additionally, as a result of the review of clinical trial records, a single study was identified in ClinicalTrials.gov (NCT04343742) entitled "Determination of the Effectiveness of Oral Chlorine Dioxide in the Treatment of COVID 19"; it was registered as an observational study that plans to include 20 Colombian participants to evaluate the efficacy of oral chlorine dioxide in the treatment of patients with COVID-19 infection<sup>(20)</sup>.

## DISCUSSION

Based on the results of the systematic review, no published or unpublished scientific evidence has evaluated the use of chlorine dioxide or chlorine derivatives as a preventive or therapeutic agent against COVID-19 administered by respiratory, oral, or parenteral route. Only one study was identified as observational in ClinicalTrials.gov and has no results to date. Likewise, due to the recent occurrence of this type of coronavirus, the search was expanded to include other types of coronavirus, for which no evidence was identified either. This lack of evidence has also been reported by the Instituto Nacional de Salud del Perú in a technical document of evidence synthesis<sup>(21)</sup>.

Prior to the emergence of the COVID-19 pandemic, the use of chlorine products was already commercialized in some European countries and the United States. Specifically, sodium chlorite, under the name of MMS, whose distributors claimed that after mixing with an acid, it had antimicrobial, antiviral and antibacterial effects, and was supposed to be a treatment for various unrelated diseases, such as autism spectrum disorder, neoplasms, hepatitis and HIV/AIDS<sup>(22)</sup>. There are several communications before and after the current COVID-19 pandemic issued by regulatory entities, whose purpose is to denounce and demand the withdrawal of this product from the market within those countries<sup>(23-25)</sup>.

However, within the Americas, chlorine dioxide and sodium chlorite have continued to be offered with special relevance due to the SARS-CoV-2 pandemic; their use is promoted not only as a treatment for the previously mentioned diseases, but also as a preventive and treatment agent for SARS CoV 2 infection. The Pan American Health Organization (PAHO)<sup>(26)</sup> does not recommend the use of chlorine dioxide or sodium chlorite by oral or parenteral route in patients suspected or diagnosed with COVID-19. It also mentions that it should not be used in any other type of illness, since there is no evidence of its efficacy; on the contrary, the ingestion or inhalation of these products would generate serious adverse effects. The U.S. Food and Drug Administration (FDA) has received reports of adverse events caused by these products, including respiratory failure due to methemoglobinemia, cardiac arrhythmia due to prolongation of the QT interval, hypotension due to hydro-electrolyte imbalance, acute liver failure, hemolytic anemia, vomiting, and severe acute diarrhea<sup>(24,27)</sup>.

The concept of "first do no harm" is a fundamental principle in health and in life. As previously mentioned, chlorine dioxide and chlorine derivatives are routinely used in industrial

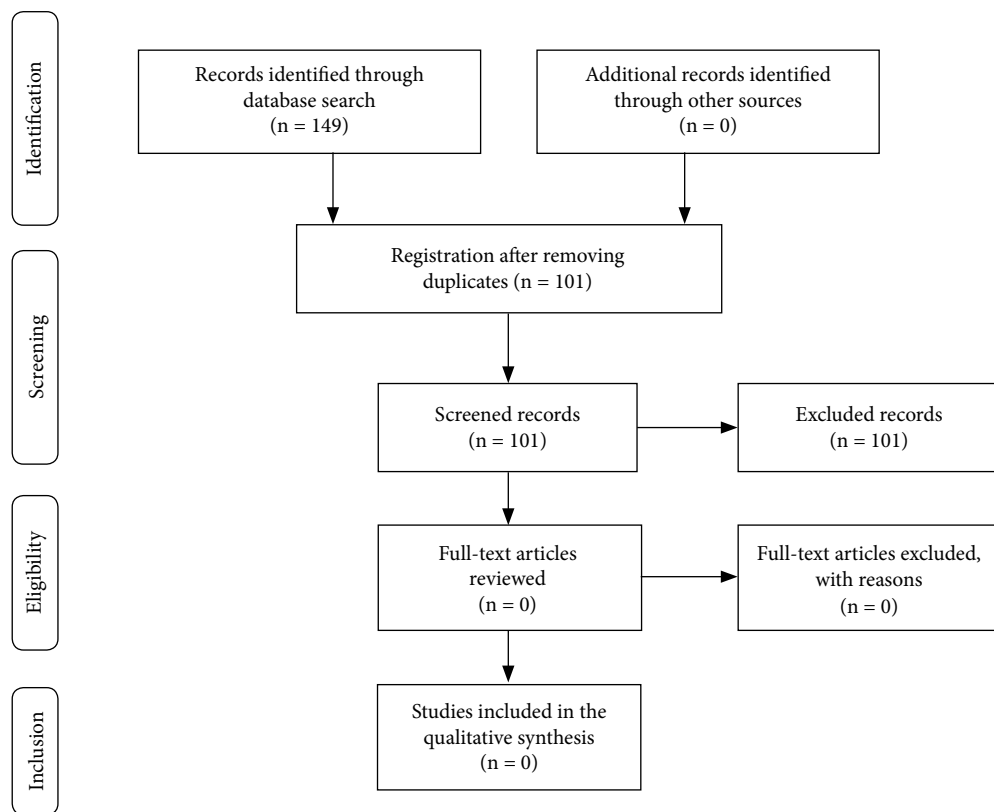


Figure 1. Flow diagram of study selection according to the PRISMA statement

processes, for example, in the purification of water for human consumption. It should be noted that the health effects of a substance will always depend on the dose, duration and form of exposure, the presence of other substances, personal characteristics and habits, and the individual's health status<sup>(13)</sup>. That is why there are maximum permitted limits for the amount of chlorine dioxide and chlorite per volume of water in the drinking water treatment process. However, the products offered to prevent and treat COVID-19, in addition to not having scientific evidence of their effectiveness, lack sanitary registration, so it is not possible to standardize a maximum dose that at least ensures that such substance can be safe in order to prevent adverse events. It has been observed that the concentrations of these products exceed the maximum limits allowed in drinking water in countries where chlorine dioxide or sodium chlorite have been marketed as therapeutic agents<sup>(23)</sup>. In other words, these products marketed as preventive agents or treatments by oral or parenteral route not only do not have clinical scientific evidence that has demonstrated benefit for any type of disease but could also cause serious harm.

In Peru, the Dirección General de Medicamentos, Insumos y Drogas released a statement against the use of these substances to treat any disease, such as COVID-19, warned that the promotion and commercialization of these types of

products is illegal and reported that their consumption could cause potentially fatal damage<sup>(10)</sup>.

The purpose of this research was to try to identify any published or to-be-published scientific study regarding the efficacy and safety of the administration by respiratory, oral, or parenteral route of chlorine dioxide, sodium chlorite or chlorine derivatives. Therefore, as demonstrated in the results of this systematic review, no academic, research or health entity in the world has seen reasonable to study the potential preventive or therapeutic effects of these substances, attributed by its distributors, despite the fact that to date there is a therapeutic void regarding treatment for COVID-19.

To spread arguments trying to use an apparent scientific language can cause confusion for the consumer, therefore, it is necessary to understand the mechanism of action of oxidizing agents, such as chlorine dioxide, sodium chlorite, sodium hypochlorite, among others. These substances serve as disinfectants since they can oxidize other compounds by means of an oxidation-reduction reaction (also known as REDOX), in which the oxidizing agent is reduced by gaining electrons, while the reducing agent is oxidized by losing electrons<sup>(28)</sup>. This oxidizing effect denatures the organic compounds<sup>(14,29)</sup>. However, its effect is not specific to a particular organism, since all living organisms are composed of organic molecules,

our cells, like other microorganisms, are also affected<sup>(30)</sup>.

The use of products that have not been proven to be safe and effective against COVID-19 not only poses a potential health risk to those who use them, but also to the entire population. When a false sense of security is generated, due to the supposed unproven beneficial effect of the product, prevention and control measures against COVID-19 that have been proven to be effective may be abandoned, such as the use of masks, social distancing, hand hygiene and respiratory etiquette<sup>(3,31)</sup>. Therefore, it is a collective duty to be responsible for the prevention and control measures that each individual uses.

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Although a thorough review of the literature was conducted, there may be additional sources in other bibliographic databases or regional repositories. However, this study included the largest and most important databases in the biomedical area, gray literature and pre-print repository, without applying any restriction to the inclusion of studies according to design,

publication status, date or language of publication, as long as they were conducted in humans.

It is concluded that currently, there is no scientific evidence to support the use of chlorine dioxide or chlorine derivatives to prevent or treat COVID-19. This is possibly due to the fact that there would be no biological plausibility or preliminary clinical evidence to support the development of coherent hypotheses for the use of chlorine dioxide or chlorine derivatives as therapeutic or preventive agents, and to the concern of the medical community about the toxicity of these products.

**Authorship contributions:** FF, AB and AHV conceived the idea of the review. DC conducted the searches and validated them with AB and AHV. AB and AHV were responsible for the selection of studies and wrote the first draft of the review. VP coordinated the elaboration of the review. All authors critically reviewed the manuscript, approved the final version and assume responsibility for all aspects of the article.

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**Conflicts of interest:** VP and FF are members of the IETSI. Also, AB and AHV are external consultants to the institute. AHV is a member of the editorial committee of the *Revista Peruana de Medicina Experimental y Salud Pública (RPMESP)* and did not participate in any stage of the editorial process after the submission of this article. DC declares not to have any conflict of interest.

**Supplementary material:** Available in the electronic version of the RPMESP.

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