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Determination of the Effectiveness of Chlorine Dioxide in the Treatment of COVID 19

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Abstract

Introduction: The aim of this review is to determine the Effectiveness of Oral Chlorine Dioxide in the Treatmentof COVID 19.

Methods: Research on the mechanism of action of chlorine dioxide on viruses, on the oral consumption ofwater-solubilized Cl02 and on its toxicity was reviewed; a quasi-experimental investigation wasconducted on the use of oral water-soluble chlorine dioxide in the treatment of 20 patients withactive COVID19 infection, compared to a control group of 20 patients not treated with chlorinedioxide.

Results: To compare the effect in the experimental group versus the control group, a test of comparison of proportions and their confidence intervals was performed for the general symptoms, and for the VAS and Likert criteria, a paired test using the Wilcoxon-Mann-Whitney test (α: 95%) was performed . When comparing the experimental group with the control group on the seventh day after symptom manifestation, a significant difference was found in the experimental group with respect to the control group for the symptoms Fever (p: 0000), Cough (p: 0.0000), Chills (p: 0.0000) and Dyspnea (p: 0.0006). When performing the visual analogous comparison of pain in the control group and in the experimental group, it was found that in all the items that make up the scale decreased significantly in this group with respect to the control group (p: 0.0000; p:00017). On day 14 post-demonstration the difference was greater (p:0.000 ; p:0.0043). When evaluating both groups (Control and Experimental) in the laboratories, a difference was found for the values of the parameters PC Reactive on day 7 (p: 0.0001) and DH Lactate (0.0036), with higher scores for the experimental group; Dimero-D on day 7 (p: 0.0194) and on day 14 (p:0.0029) ; difference was found in all parameters. The results overall (p <0.05) demonstrate the hypothesis that chlorine dioxide is effective in the treatment of COVID19.

Conclusion: Chlorine dioxide is effective in the treatment of COVID19 and the mechanisms of action by which it acts to achieve it are proposed in this work. We recommend doing more research. We recommend conducting double-blind studies and delving into studies of toxicological safety and therapeutic efficacy of chlorine dioxide in pathologies of epidemiological impact in the near future.

Keywords: SARS-CoV-2 • COVID19 • Effectiveness • Chlorine Dioxide.

Introduction

In December 2019, a new respiratory illness emerged in Wuhan, China. The source of this infection was identified as a new coronavirus, related to other coronaviruses that had previously caused outbreaks of Severe Acute Respiratory Syndrome (SARS) between 2002 and 2004 and Middle East Respiratory Syndrome (MERS) in 2012 (National Institutes of Health , 2020). This virus was called "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) and the disease resulting from infection by this virus was called "COVID-19". On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic.

Coronaviruses are a group of enveloped RNA viruses that can damage multiple organ systems. Like other coronaviruses, the SARS-CoV-2 virus is a spherical particle with glycoprotein spikes on its surface. Coronaviruses enter host cells when a region of the spike, known as the "receptor-binding domain," binds to angiotensin-converting enzyme 2 (hACE2) in human cells. The viral membrane then fuses with the host cell membrane, allowing the viral genome to enter the host cell.

Chlorine dioxide (ClO2) has been suggested as a potential agent in the fight against COVID-19 and has been proposed three clinical trials to examine the ability of ClO2 to treat COVID-19. However, this agent is not well known, is not understood and is even demonized in the medical community, we assume that by confusion conceptual with sodium hypochlorite. Therefore, we set out to verify the effectiveness of oral use of the dioxide of chlorine in COVID19 through this study, reviewing in depth the history of ClO2, its safety / toxicity profile and its possible applications in the fight against COVID-19. The objective of this research is to determine if chlorine dioxide is effective in managing covid19 [1-65].

Literature Review

Chlorine Dioxide (ClO_2) Physical and Chemical Properties of Chlorine Dioxide

Chlorine dioxide, ClO_2, is a gas under standard conditions with a molar

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mass of 67.45 g/mol. Typically, ClO_2 gas can be synthesized from the reaction between $NaClO_2$ (sodium chlorite) and C_{l2}, $NaClO_2$ and HOCl, $NaClO_2$, and an acid such as HCl or $H3PO_4$. It is easily soluble in water with a solubility of 3 g / 100 mL https://www.vyphidroasesores.com/.

The reactivity of chlorine dioxide is related to its structure and bond. Chlorine dioxide is a bent symmetric triatomic molecule (C2v point group) with a Cl-O bond length of 147.3 picometers and a bond angle of 117.6 degrees (Figure 1A). ClO2 has an odd number of electrons with 19 valence electrons and therefore, is aparamagnetic radical.Its electronic structure puzzled chemists for a long time because none of the possible structures dandLewisit is very satisfactory for chlorine dioxide [1-10].

The molecular orbital theory reveals that a single electron occupies the highest unoccupied molecular orbital, the p* orbital, which makes the molecule a free radical and explains its reactive nature. The two resonance structures of ClO_2 are shown in figure 1B. The resonance structures of the ClO_2 radical indicate the forms of a double bond between the central Cl atom and an O atom, and a single bond in combination with a 3-electron bond in the other Cl-O bond. The unpaired electron it is shared between the three atoms within the two different resonance structures. Most of the density of a single electron is found in one or another O atom. This unique arrangement provides ClO2 with a single unpaired electron and two reaction centers (O and Cl) on which to react.

When chlorine dioxide dissolves in water, most of it does not hydrolyze: it remains as a dissolved gas in solution. Another part does, and forms both chlorite ion (ClO_{2-}) and chlorate ion (ClO_{3-}). The solubility of chlorine dioxide in water at sea level and at 25°C is close to 3 g / L (≈ 3000 ppm). Its solubility increases at lower temperatures. Therefore, when its concentration is greater than 3 grams per liter, it is common to store it at temperatures close to 5°C. Dissolved in pure water, in a hermetically closed container, in the absence of light, and at a low temperature, it is quite stable although it slowly decomposes into chlorine and oxygen. Chlorides catalyze its decomposition.

In biological systems, ClO_2 can be expected to play an important role as an antiviral / microbial agent through oxidative chemistry.

The therapeutic action of chlorine dioxide is given by its selectivity for pH. It means that this molecule dissociates and releases oxygen when it comes into contact with another acid. When it reacts, it becomes sodium chloride (common salt) and at the same time releases oxygen, which in turn oxidizes (burns) the pathogens (harmful germs) of acidic pH present, converting them into alkaline oxides ("ashes"). Therefore, when chlorine dioxide dissociates, it releases oxygen into the blood, as do erythrocytes (red blood cells) through the same principle (known as the Bohr effect), which is to be selective for acidity. Like blood, chlorine dioxide releases oxygen when it encounters acidity, either from lactic acid or from the acidity of the pathogen. ClO2 is a size-selective antimicrobial agent.

Multicellular tissue has the ability to dissipate this charge and is not affected in the same way. Chlorine dioxide, which is the second strongest disinfectant known after ozone, is much more suitable for use therapeutic since it is also capable of penetrating and eliminating biofilm, which ozone does not do. The great advantage of the therapeutic use of chlorine dioxide is the impossibility of a bacterial resistance to ClO2. Although ozone is stronger in terms antiseptics, its high oxidative potential of 2.07 and its short half-life of only 15 minutes at 25°C with a pH value of 7.0 make it less effective, for *in vivo* therapeutic applications [11-20].

Chlorine Dioxide Antiviral Efficacy

Mechanism of Antiviral Action of ClO_2

ClO_2 exhibits antiviral activity through its oxidative chemistry. A virus consists of an outer shell or shell and an inner nucleic acid core. The viral envelope can be composed of proteins, lipid bilayers, and polysaccharides, and the envelope protects the nucleic acid core, in addition to providing selective binding and receptor cell recognition. Altering or modifying the viral envelope or nucleic acid nucleus will disrupt the modes of viral infection.

In the case of SARS-CoV-2, the carbohydrate envelope encloses it and protects it even more, which makes it more difficult to attack than other viruses. Approximately 70% of the entire surface of the spike protein is coated with glycans; In the case of SARS-CoV-2, sugars are twice as essential. First of all, because they stabilize the spicule in a conformation that allows it to fit with ACE2 receptors on our cells, the process that initiates infection. By removing some glycans from the surface, the spike protein is destabilized and, furthermore, the binding with these receptors is weakened.

A line of research is being developed in post-covid syndrome by one of the authors (B.Bolano), focusing attention on the possibility that Cl02 acts at the level of inflammasomes or even NETosis as a possible explanation for the improvement in the post covid19 syndrome manifested by hundreds of doctors who have reported cases in the world. The relevance and evidence of these findings to the anti-inflammatory mechanism of action of ClO_2 remains unclear at this time.

In order to explore the mechanism of action more deeply, we selected published articles (pubmed, google scholar and other search engines) that describe the action of SARS-CoV-2 in cells, in its interaction with hACE2 and, in In particular, we investigated augmented reality videos or simulation videos based on Silicon, for the three-dimensional representation of the places of action, such as the videos in which the spicular protein and the hACE2 receptor are manipulated, among others, with ChimeraX (UCSF) augmented reality software.

Similarly, we reviewed the structure of the virus spike and drew on the research of Daniel Wrapp and Jason S. McLellan of the University of Texas.

The three-dimensional image of the spicular S glycoprotein of the SARS-CoV-2 betacoronavirus has been seen with electron cryomicroscopy in record time. Thanks to this image with a resolution of 3.5 Å, it is confirmed that this S protein binds to the hACE2 protein of human cells with a higher affinity than that of the SARS-CoV coronavirus. Protein S is the target of the antibodies that immunize us. Its 3D structure allows us to understand why the monoclonal antibodies published against SARS-CoV are not effective against SARS-CoV-2.

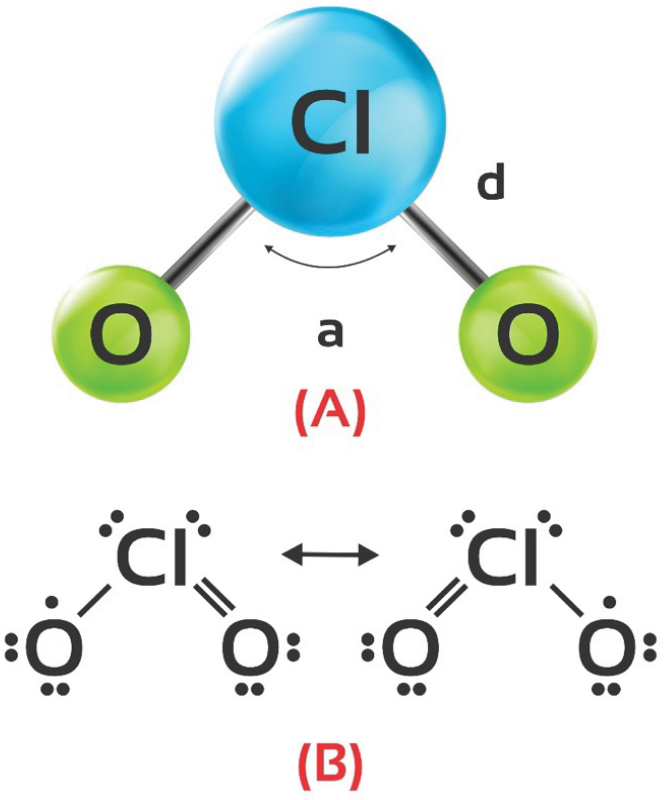

Figure 1: (A). Geometry of the ClO2 molecule with group of points (C2v). The bond angle a is 117.6 O and the length of bond d is 147.3 pm. (B). Two resonance structures of ClO2 are illustrated that reveal the unpaired electron, centered on the Oxygen atom, shared between the three atoms.

Based on this information, we did a study with a doctor in molecular biology from the University of Tsukuba in Japan, in which we sought to build the hypothesis of how chlorine dioxide acts on SARS-CoV-2 (Insignares - Carrione et al , 2020). As a result, we saw that there is an excellent correlation between its structure and its transmission mechanism, as well as the determination of the sites of action of promising substances or drugs in the treatment of covid19 and, however, we have not had the expected results for its rapid control with none of the drugs tested. Bioinformatics is a tool that uses biological data to study biological problems on a wide range of scales, such as evolution, structure, the function and regulation of nucleic acids and proteins with the help of computational methods. In our work in Japan, we carry out in silico analysis, which is a comprehensive quantitative approach that not only provides information on the dynamics of intracellular and intramolecular processes, but ultimately allows us to predict biological behavior from molecular interactions. This was done in our work by focusing on conserved domains, structure, function, and biochemical characteristics to understand the mechanism of action of chlorine dioxide on the spike and SARS-CoV-2 RNA. which is a complete quantitative approach that not only provides information on the dynamics of intracellular and intramolecular processes, but ultimately allows prediction of biological behavior from molecular interactions. This was done in our work by focusing on conserved domains, structure, function, and biochemical characteristics to understand the mechanism of action of chlorine dioxide on the spike and SARS-CoV-2 RNA. which is a complete quantitative approach that not only provides information on the dynamics of intracellular and intramolecular processes, but ultimately allows prediction of biological behavior from molecular interactions. This was done in our work by focusing on conserved domains, structure, function, and biochemical characteristics to understand the mechanism of action of chlorine dioxide on the spike and SARS-CoV-2 RNA (Figure 2).

This type of analysis not only provides information on RNA replication, but also simulates the dynamics of the interrelation between the spike and the hACE2 receptor. The investigation began with the nucleotide sequence of the viral RNA, the open reading frames (ORF's) were determined, which once analyzed, revealed the oxidation of guanine to 8-oxoguanine. The other bases were not modified. The amino acids oxidized by chlorine dioxide are found in the spike, located in the helices, S1, S2, RBD and hACE2, which could explain the almost immediate effect of clinical improvements achieved by dioxide (Insignares - Carrione et al, 2020).

Cysteine, belonging to the group of thiols, is an amino acid up to 50 times more reactive with all microbial systems than the other four amino acids and, therefore, it is impossible for it to create resistance against chlorine dioxide.

The hypothesis proposed by the authors (Insignares - Carrione, 2020) is that the cause of the antiviral effect of chlorine dioxide in SARS-CoV-2 can be explained by its actions on at least five amino acids (Cysteine, tryptophan, tyrosine, proline, hydroxyproline).

Pharmacokinetics

The pharmacokinetics of ClO_2 varies with the route of exposure. Scatina et al. (1984) examined the dermal absorption of a ClO2 preparation applied to the shaved back of rats. The maximum absorption of Cl in plasma was observed after 72 hours and a plasma concentration of 69.4 mcg% Cl was reached. The absorption half-life was calculated as 22.1 hours, which corresponds to a rate constant of 0, 0314 h-1 (Figure 3).

Fridyland and Kagan (1971) measured the degree of ClO2 absorption in the oral cavity of human subjects by rinsing the mouth with water containing predetermined concentrations of ClO2, and then measuring the residual concentrations of ClO2 in the washings. They found that up to 30% of the ClO2 was absorbed.

Safety / Toxicity

The safety / toxicity of ClO2 depends on several variables, including the route of administration (e.g., inhaled, topical, or oral), the state of the molecule (i.e., gaseous or aqueous), the concentration (usually measured in mg / L or ppm for aqueous and ppm or mg / m3 for gaseous), and the duration of exposure. ClO2 gas is toxic at much lower concentrations than aqueous ClO2. Toxicity also increases with the duration of exposure. The fact that ClO2 is less toxic in aqueous form allows the use of this molecule as a safe disinfectant in municipal drinking water, as a disinfectant for drinking water at points of use and as a food disinfectant, among other uses (Figure 4).

Below is a review of studies examining the safety and toxicity of ClO_2.

ClO_2 Solubilized in Water

In vitro studies

Noszticzius et al. (2013) examined the differential effects of ClO_2 on microbes versus humans or animals. They performed perfusion studies using protein membranes and found that the size of the organism exposed to ClO_2 influences the effects of the oxidant. They reported that a low concentration of ClO_2 quickly kills micron-sized organisms while causing little harm to larger organisms, such as humans. The authors suggested that the reasons for this differential effect are: (1) ClO_2 cannot penetrate deeply into the tissues of larger organisms and (2) the circulation of larger organisms provides a constant supply of antioxidants, offering protection against the effects. ClO_2 oxidants.

In vitro studies found that methemoglobin was not formed unless glutathione concentrations in red blood cells were almost completely depleted (Heffernan et al. 1979a).

In vivo Animal Studies

Daniel et al. (1990) exposed rats to ClO2 concentrations of 0, 25, 50, 100 or 200 mg / liter for 90 days. This equates to doses of 11.5 mg / kg / day in males and 14.9 mg / kg / day in females. No exposure-related deaths were reported.

Abdel-Rahman et al (1982b) reported LD50 rates for female rats of 340 to 468 mg / kg and for male rats of 292 to 424 mg / kg after a single gavage dose. Additional reports of LD50 in rats include 94 mg / kg (WHO, 2002), 140 mg / kg (Musil et al., 1963), 292 ppm (National Institute for Occupational Safety and Health, 2014) and> 5,000 mg / kg (US Environmental Protection Agency, 2008). The LD50 in mice has been reported to be> 10,000 mg / kg (Shi et al. 1999).

In a study carried out at the University of Querétaro (Mexico) in 2020, researchers challenged the hypothesis that ClO2 decreases viral load and virus-induced mortality in a vertebrate model. To do this, they determined the

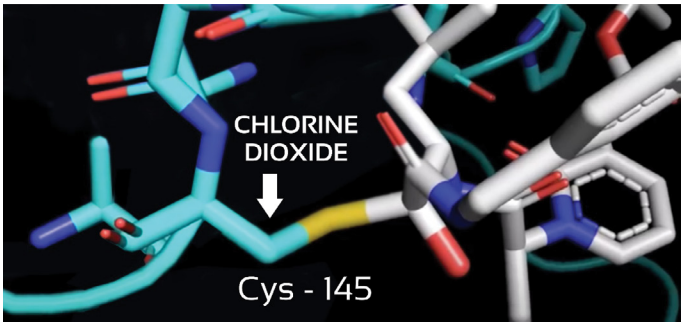

Figure 2: Positions of the amino acid (cysteine) in the structure of the spike, one of the possible sites of action of ClO_2.

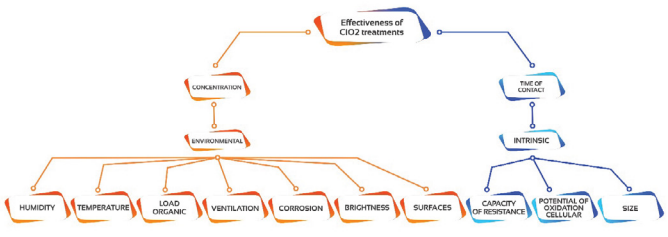

Figure 3: Effectiveness of chlorine dioxide treatment based on concentration and contact time.

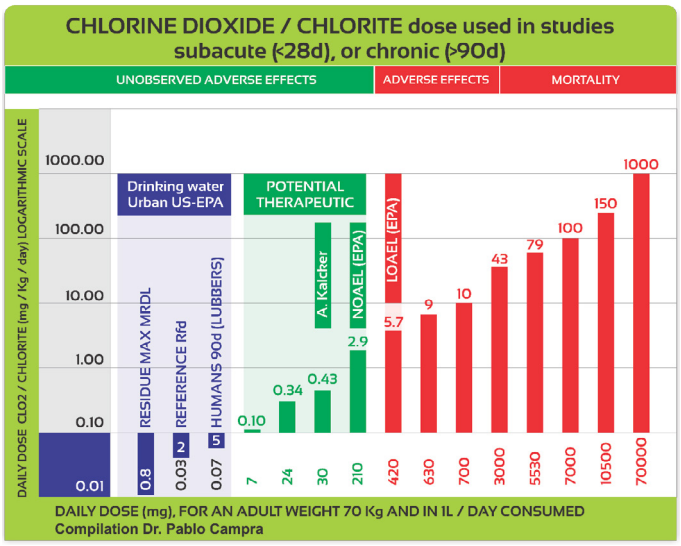

Figure 4: Review of experimental levels of chlorine dioxide / chlorite systemic toxicity. In blue, reference levels for disinfection of drinking water (US-EPA); in green, levels with evidence of therapeutic efficacy at zero toxicity (Refs A Kalcker and E. Insignares Carrione); red: minimum levels of toxicity detection reported in different in vivo studies in animals and humans.

viral load, virus-induced lesions, and mortality in 10-day-old chicken embryos inoculated with 104 EID50 / mL in media of attenuated avian coronavirus (IBV) strains from Massachusetts and Connecticut. ClO2 treatment had a marked impact on IBV infection. Specifically, viral titers were 2.4 times lower and mortality was reduced by half in infected embryos that were treated with ClO2. The infection caused developmental abnormalities, regardless of treatment. Lesions typical of IBV infections were observed in all inoculated embryos, but severity tended to be significantly less in ClO2-treated embryos. They found no gross or microscopic evidence of toxicity caused by ClO2 at the doses used in this case. The study concludes that ClO2 could be a safe and viable way to treat and mitigate the effects of avian coronavirus infections, and raises the possibility that similar effects may be observed in other organisms. (Xóchitl Zambrano-Estrada et al, 2020).

Water Solubilized Chlorine Dioxide (CDS) in Human and Animal Studies

The studies by Lubbers et al. (1982, 1984a) at the Ohio State University School of Medicine evaluated the short-term toxicity of drinking ClO2. In the first study (Lubbers et al. 1982), a group of 10 healthy adult males drank 1,000 ml (divided into two 500 ml portions, 4 hours apart) of a gradually increasing dose of ClO2. The study included a series of six sequences of 3 days each in which subjects drank 0.1, 1.0, 5.0, 10.0, 18.0, and 24.0 mg / L of a ClO2 solution. (0.34 mg / kg, assuming a reference body weight of 70 kg). . In the second study (Lubbers et al., 1984a) groups of 10 adult males received 500 ml of distilled water containing 0 or 5 mg / L ClO2 (0.04 mg / kg-day assuming a reference body weight of 70 kg) for 12 weeks.

In a comparative study of hyperpure chlorine dioxide with two other irrigants regarding the viability of periodontal ligament stem cells (PLDSCs), cell viability experiments demonstrated that the application of ClO2 does not lead to a significant decrease in the viability of PLDSCs. in the concentrations used to kill microbes. In contrast, traditional irrigants, H2O2 and CHX are highly toxic to PDLSCs. The aging of PLDSC cultures (passages 3 vs. 7) has characteristic effects on their responsiveness to these agents, since the increased expression of the mesenchymal stem cell markers becomes decreased. They conclude that although the active ingredients of mouthwashes (H2O2,

Oral ingestion of ClO_2 solubilized in water.

The only study conducted for the use of water-solubilized ClO2 (CDS) ingested by oral route is our present study carried out in a multicenter clinical trial in various countries from central and South America (https://clinicaltrials.gov/ct2/show/NCT0434374). Statistics of Bolivia where the use of water-solubilized ClO2 for the prevention and treatment of COVID-19 was approved by law in early August 2020, demonstrate a marked reduction in cases and deaths in that country. The highest peak recorded in Bolivia was epidemiological week 29 (10,939 cases), with cases falling to 670 in epidemiological week 45, (representing a 93% decrease). The case-fatality rate decreased from 8% to 4.5% in epidemiological week 36, coinciding with the massive use of dioxide in the population without it being possible to affirm with certainty that dioxide is responsible for this decrease. (https://snis.minsalud.gob.bo/). From a peak of 2,031 daily cases on August 20, 2020, cases dropped to 147 daily cases on October 21, 2020, representing a 93% decrease. Daily deaths decreased from a peak of 132 on September 3, 2020 to 24 deaths on October 21, 2020, with an 82% decrease in mortality. (https://www.covid19.onl/country/bolivia).

While there was a rebound in cases from epidemiological week 49 to 53, mortality remained relatively low. Some doctors linked to our research group (in Bolivia more than 220 doctors) provide feedback that the population reduced the consumption of dioxide and that could be a possible explanation for the peak, and the increase in the consumption of chlorine dioxide again reduced the peak to the previous levels, maintaining a reduced comparative mortality (personal communications) (Figure 5).

In summary, while in other countries the plateau was maintained, in Bolivia it fell, attributing this decrease (as a possible explanation) to preventive measures, the consumption of chlorine dioxide and the massive use of traditional medicine as a possible explanation.

Dose

In vitro and *in vivo* studies demonstrate that low doses of water-solubilized ClO2 exhibit potent and rapid antiviral activity against a wide range of viruses. In a study on drinking water in the Netherlands, Jin et al. (2013) found that treatment with ClO2 at concentrations of 0.5 ppm for 25 minutes, or 1.5 ppm for 10 minutes, or 2 ppm for 5 minutes achieved at least a 4 log reduction of enterovirus. Schijven et al (2019) demonstrated that municipal drinking water treated with ClO2 (0.1 ppm in summer and 0.05 ppm in winter) significantly reduced adenovirus levels to levels that are considered safe for drinking water.

Alvarez and O'Brien (1982) found a ClO2 concentration of 40 ppm added to wastewater seeded with SARS-CoV that completely inactivated the SARS-CoV in 30 minutes.

The dose used in this research is 30 mg per day for 21 days, which is well below the NOAEL, or in the worst case the same as the NOAEL reported in previous studies in animals, as we discussed in previous lines. .

Materials and Methods

Figure 5: The death rate of the Coronavirus in Latin America.

To make the greatest search for scientific information on chlorine dioxide, sand they searched Google Scholar, PubMed (Medline), LILACS, Cochrane Library, Science, Scielo, MedScape, looking for articles in English and Spanish, which would contain search terms chlorine dioxide, virus, SARS-CoV-2, coronavirus, oxidant, water purification, "Chlorine dioxide" OR "Chlorine dioxide protocol" OR Chlorine dioxide AND virus; Chlorine dioxide AND SARS-COV-2; OR "COVID-19 drug treatment" OR "spike glycoprotein, COVID-19 virus" OR "severe acute respiratory syndrome coronavirus 2" OR "COVID-19" OR "2019-nCoV" OR "SARS-CoV-2" O "2019 new coronavirus "OR" 2019 coronavirus disease "OR (pneumonia).

Additionally, a Google search was conducted using these same search terms. The articles selected for inclusion consisted of publications related to the potential use of ClO2 as prevention or treatment of COVID-19, on the beneficial aspects and possible effects of maleficence or toxicity of the substance. All retrieved articles were screened and a subset of relevant abstracts was selected for further evaluation. The bibliographies of these articles were then searched for additional references. The final articles selected for inclusion in this review consisted of articles examining historical uses, chemistry, toxicity, antimicrobial and virucid ClO2, previous investigations in animals in vitro and in vivo, and research in humans. The registries of www.clinicaltrials.gov and those of the WHO International Clinical Registry Platform (ICTRP) were reviewed to identify ongoing or unpublished clinical trials.

From the search results, we selected those that referred to the virucidal action of chlorine dioxide on various microorganisms, in particular on viruses and, among them, SARS-CoV-2 or SARS-CoV.

On the other hand, we selected articles that describe the action of SARS-CoV-2 in cells, in its interaction with ACE2 and, in particular, we investigated augmented reality videos or simulation videos based on Silico, for three-dimensional representation. De sites of action such as videos in which the spicular protein and the ACE2 receptor (37) are manipulated, among others, with the ChimeraX (UCSF) augmented reality software.

Similarly, we reviewed the structure of the virus spike and relied on the research of Daniel Wrapp and Jason S. McLellan of the University of Texas, information with which, in a parallel study, we were able to hypothesize how chlorine dioxide acts on SAR-CoV-2.

With the information needed to conclude that chlorine dioxide was beneficent and that its use in the COVID19 pandemic is turned in an immense possibility to control it based on the scientific foundations revealed in previous investigations, and above all, that it was not maleficent for patients, we take the decision to carry out the investigation for determine if it was effective orally in the treatment of COVID19.

We decided to carry out a phase **IIa** design given the urgency to verify a option effective, fast and economical treatment that could be implemented quickly worldwide, which is why we opted for a quasi-experimental clinical trial.

The NCBI (National Center for Biotechnology Information) for Medline and Pubmed databases recently included the concept of ECE (Quasi Experimental Studies) under the MeSH term "Non-Randomized Controlled Trials as Topic" (NCBI, 2015).

Once the research protocol was done, it was decided to register it in clinicaltrials.gov which was accepted on April 7, 2020 under the number NCT 04343742. The design was made international multicenter in order to have a faster collection of the sample and in the future, to have a much larger and more representative sample. The same protocol was presented in eleven American countries and in Spain for approval. Unfortunately, drug control entities in all countries generated warnings and even bans on its use for human consumption that made it difficult for ethics committees to approve the protocol. In Bolivia the law was approved No. 1351 of 2020 that authorized the elaboration, commercialization, supply and consented use of the CDS chlorine dioxide solution as prevention and treatment in the face of the coronavirus pandemic (COVID 19); The ethics committee endorsed by the Bolivian Ministry of Health was legally constituted, which approved this multicenter research protocol of international scope, retro-prospective, made up of five (5) universities (Technical University of Oruro, Public University of El Alto, Universidad Mayor de San Simón, Gabriel René Moreno Autonomous University and Yacuiba Technical Institute "Gran Chaco") which in turn, through its scientific and ethical clinical research committees, are doing their own research on chlorine dioxide for use in different applications [20-35].

Data collection and registration

Data collection and recording was carried out by recording demographic and symptomatic data and by means of observation scales based on visual analogue scale (VAS) and laboratory parameters organized by Likert scale for better evaluation and comparability. Thus, the instruments or formats were built, which were recorded in software specially designed for research with the following characteristics:

An electronic form in a WEB environment was specially designed for the registration of information required in the investigation through PCs, smartphones and tablets.

The application was developed by the company SCORPII SAS in 2020, with the following functionality:

- Registration of the contact information and basic profile of the investigating physician, who identifies the location of the medical center where the patient was treated for the first time and records their contact details and socio-cultural profile.
- File of the letter of informed consent for the use of an investigational substance, signed by each patient.
- Registration of the information on the patient's initial diagnostic clinical history.
- Record of the patient's follow-up clinical history in relation to his symptoms, pain scale (VAS) and assessment with the Likert scale of the laboratory reports made on day 0, 7, 14 and 21.
- In relation to the security conditions, the registered information does not have options to make changes or adjustments to the registered information by the investigating physicians, guaranteeing the authenticity, integrity and confidentiality of the information. Each researcher has access to the application through the authentication of their email and password, in such a way that they are solely responsible for the registration of information on each of their patients.
- Generation of information consolidation reports for statistical analysis,

a function of access exclusively by the research director, without options for modifying the database of records made by investigating physicians.

That is, the instruments made it possible to collect and record the results from the performance of semiological, clinical and laboratory examinations at the beginning of the study treatment of the experimental group and the control group, as well as after 7, 14 and 21 days.

In addition to demographic data, the following are measured:

Semiological: red eyes, fever, cough, expectoration, asthenia / adynamia, chills, vomiting, dyspnea, nasal congestion.

The VAS criteria (The visual analog scale or VAS) for pain it is a straight line in which one end means no pain and the other end means the worst pain imaginable. The patient marks a point on the line that matches the amount of pain felt) and the variables investigated. They are: sore throat, head, chest, general myalgic type, affectation due to low back pain.

Likert criteria (The Likert scale is an *ordinal* scale using 5 levels) grouped paraclinical exams. The variables investigated are lymphocytes, leukocytes, platelets, C-reactive protein, Lactate dehydrogenase, AST, -D-dimer and lactate in oximetry.

The instruments made it possible to collect and record the results from the performance of semiological examinations, assessment of painful symptoms (VAS) and laboratory (LIKERT) at the beginning of the treatment under study (or baseline) as well as after 7, 14 and 21 days .

Analysis and Interpretation of the Data

It is carried out according to the established variables, with the support of the IBM - SPSS Statistics software; the data of the experimental and control groups were analyzed, the general symptoms by means of a comparison of proportions test and their confidence intervals, and the VAS and Likert criteria by means of a paired test using the Wilcoxon - Mann - Whitney test α: 95%).

Population

The experimental population to which the multicenter study was directed consisted of a group of patients with active infection with COVID-19 , in various medical centers in Bolivia (14 patients) , most of them in the southern clinic in La Paz, Bolivia , Peru (two patients) and Ecuador (four patients) for a total of twenty (20) patients. The control population consisted of eight (8) patients from Ecuador, seven (7) patients from Bolivia, three (3) from Mexico and two (2) from Peru, for a total of twenty (20) patients.

Patients

The selection of the treatment or experimental group was made based on patients with active COVID19 infection, who were with positive RT-PCR, symptomatic in intervals from 3 to 7 days, which were not in the resolution phase, who were proposed to be voluntary research subjects. Control group patients chose not to be chlorine dioxide treatment subjects. Similarly, simultaneity was applied, which means that patients were obtained in the same period of time in which the cases arose. Viral load was not determined due to costs, technical and logistical difficulties of the reference laboratories in Mexico, Bolivia, Peru and Ecuador.

Number of Patients

Twenty patients (n = 20) for the experimental group and 20 patients (n = 20) for the control group were included in the study. A one-to-one relationship per center was not maintained and they were presented randomly according to a probabilistic sample design.

Acceptance Criteria in the Study

The following inclusion criteria were used: Covid 19 RT-PCR positive, characteristic symptoms of Covid-19: fever, odynophagia, respiratory distress, aged between 18 and 80 years.

Exclusion Criteria

Covid 19 RT-PCR negative, IV / VI renal failure, congestive heart failure, patients who consume anticoagulants in particular warfarin sodium.

Duration of Treatment per Patient

The observation period per patient in the experimental group was (21) twenty-one days. In the control group it was fourteen (14) days. A review was carried out at the beginning, at 7, 14 and 21 days in the experimental group; in the control group at the beginning, at 7 and 14 days. Post-protocol clinical follow-ups (day 22 onwards) were not included in the experimental group and neither in the control group. It is important to note that there was clinical follow-up by the research staff in most of the patients treated and not treated with chlorine dioxide, observing resolution completeness of symptoms in the treated group. As an empirical observation, the researchers' report that patients who consumed chlorine dioxide as a treatment for COVID19, substantially reduced post-COVID19 symptoms compared to patients with the disease, not treated with dioxide.

Total duration of the study

The study began in July 2020 and concluded in December 2020.

Assignment of study medication

Each patient received, in order of admission to the study, a consecutive patient number (odd numbers were selected) and the corresponding study medication. The allocation of this medication was made prior to the start of the study, by means of a computer generated list of vials produced for the purpose of the research. The patients received the chlorine dioxide base preparation at 3,000 ppm, produced by electrolysis with ultrapure chlorine dioxide generating equipment, brand medalab www.cl02.com with precise written instructions on how to prepare, drink and preserve dilutions. The chemists of the research team controlled the standardization of the water used for the base preparation of the dioxide at 3000 ppm, as well as the water used for diluting and drinking; the controlled variables were: conditions and characteristics of the preparation process, standardized characteristics of the container, use of standardized Merck 28% sodium chlorite, standardized sterile double-distilled water, buffered at pH 7 and chlorine dioxide concentration at 3,000 p.p.m.

The control group received anti-inflammatory treatment (ibuprofen at doses between 200 and 400 mg every 8 hours), antibiotics (azithromycin 500 mg daily for 5 days), antihistamines (hydroxyzine x 5 mg every 12 hours), corticosteroids (generally 40 mg of methylprednisolone every 12 hours for 3 days and then 20 mg every 12 hours for 3 days) and supportive measures. The experimental group did not receive this treatment.

Dosage and Routes of Administration

The medication used is chlorine dioxide 3000 ppm in x 120 cc bottles marked with a planned label and administered according to the standard established in the research protocol.

Chlorine Dioxide Administration Protocols used:

Initial protocol, loading or protocol (F): 10 ml of chlorine dioxide 3000 ppm is added to 1 liter of water, and the liter is taken in two hours, divided into eight (8) equal doses. Then it is administered.

Maintenance protocol: (C) 10 ml of chlorine dioxide 3000 ppm is added to 1 liter of water, and the liter is given to drink divided into ten (10) equal doses, during the day, every hour.

The medication is manages orally dissolved in the mouth, at least 60 minutes before or after a meal. There were no remnants or shortages in the medication delivered and the original protocol were strictly adhered to. There is no abandonment of treatment.

Results

Preliminary analysis of the parameters at study entry

The characteristics of the patients in the experimental group at the time

of admission, after verification of the positive RT-PCR, generated the following data: By sex: 13 male patients (65%) and 7 female (35%).

The ages range between 36 years the minimum and 72 years the maximum. The average age for men is 47.6 years and for women 58 years of age. The general average age is 53.2 years.

A parallel instrument was designed to record possible adverse effects of chlorine dioxide where the data of each patient and their adherence process are placed. In two patients, a slight sensation of gastritis was registered, 7 days after treatment, temporary, which resolved without intervention and did not require stopping the medication (Figure 6).

Characteristics of the control group

The characteristics of the patients in the control group at the time of admission after verification of the positive RT-PCR generated the following data: By sex: 10 male patients (50%) and 10 female (50%).

The ages range between 44 years the minimum and 69 years the maximum. The average age for men is 55.6 years and for women 52 years of age. The general average age is 54.5 years (Figure 7).

Result of the comparison of the Experimental versus Control Group by means of a comparison of proportions test and their confidence intervals and Wilcoxon – Mann – Whitney test (α: 95%)

To evaluate the effectiveness of the ClO_2, the results of each of the items were compared by means of a comparison of proportions test and their confidence intervals (general symptoms) and a Wilcoxon – Mann – Whitney test (α: 95%)(VAS and Likert) of the data obtained from the Experimental Group compared with the Control group in the Cohort points of Onset of Symptoms, 7 and 14 days after the first symptomatic manifestation.

Below we present the comparisons between the groups, for general symptoms, VAS and Likert (Table 1).

Regarding general symptoms, on the day of onset of general symptoms, both groups (Control and Experimental) were the same for most of the items (p > 0.05). However, for the Chills the Experimental group had a higher Average Range (25.5) than that of the Control Group (15.5) (p : 0,0001). These results confirm that in general for general symptoms, both groups had a similar behavior.

When making the comparison on the seventh day post symptom manifestation, a significant difference was found in the Experimental group with respect to the control group for Symptoms Fever (p: 0000), Cough (p: 0.000), Chills (p: 0.000) and Dyspnea (p: 0.0006). At day 14 in the symptoms that had not disappeared, the difference was very significant, decreasing its manifestations in the Experimental group (Table 2).

For the VAS Scale, at the time of symptom manifestation, both groups reported the same subjective assessment of pain. When performing the same visual analogue comparison of pain in the control group and in the experimental group, it was found that all the items that make up the scale decreased significantly in this group with respect to the Control group on day 7 (p: 0,0000 ; p:0,0017). The only painful symptom that remained similar was low back pain (P: 0,9633). On day 14 post manifestation the difference was greater (p: 0.000 ; P: 0,0043 y P: 0,0067) (Table 3).

When evaluating both groups (Control and Experimental), a difference was found for the values for the PC Reactive parameters (p: 0.0398) and Lactate DH (0.0422), the scores being higher for the experimental group; no difference was found in the rest of the parameters. When comparing the groups at 7 days post-initial manifestation, only the Lymphocytes and Leukocytes showed no difference between groups (p> 0.05), the other parameters significantly decreased in the Experimental group with respect to the Control.(p:0,0001; p: 0,0036 ; p: 0,0403; p: 0,0194; p: 0,0003). At day 14, all the biochemical parameters had decreased significantly in the experimental group with respect to the Control group (p < 0,05).

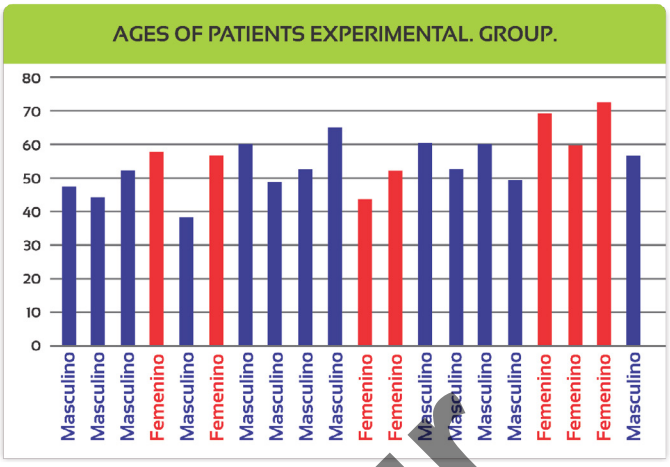

Figure 6: Ages of Patients Experimental Group.

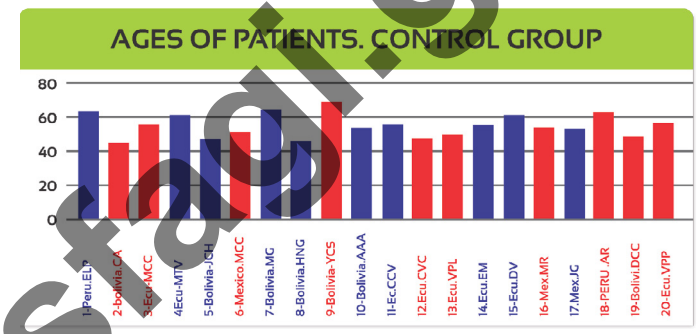

Figure 7: Ages of Patients. Control group.

The results overall (p < 0.05) demonstrate the hypothesis that chlorine dioxide is effective in the treatment of COVID19.

Permanence of the intervention

As we noted in previous lines, the design of the protocol did not include post-intervention follow-up beyond day 21, which was the limit that we set ourselves from the beginning. As a non-parameterized observational annotation, we can share that the group of researchers did clinical follow-up of the patients until approximately two months after the onset of the disease, verifying a satisfactory evolution with very few post-covid symptoms. Some of the patients noted some mild spinal discomfort and some degree of chronic fatigue.

Discussion and Recommendations

This research has focused on studying the effectiveness of the use of chlorine dioxide in patients with COVID19, by measuring before and after treatment, present clinical symptoms and laboratory variables based on standardized and accepted scales in research (VAS and Likert) of an experimental group compared to a control group.

Regarding the research question whether chlorine dioxide could effectively reduce morbidity and mortality in COVID19, the confirmatory significant statistical validation by the U test of Wilcoxon – Mann – Whitney test (α: 95%) in the experimental and control groups reveal this and confirm the hypothesis that chlorine dioxide is effective in the treatment of covid19.

This phase IIa clinical trial is the preliminary phase for the realization of an upcoming phase IIb, double-blind randomized study, where we can have a sample of 400 patients, a purpose in which we are already working.

The main advantage of the design we chose is that it is a simple and inexpensive study to carry out (the authors did not receive any external funding and the costs were paid directly and personally by them) than a clinical trial

Table 1: Result of the comparison of the Control Group versus the Experimental Group by means of a comparison of proportions test and their confidence intervals for General Symptoms.

Syntom	Group	Day 0 n (%) | *P*-value		Day 7 n (%) | *P*-value		Day 14 n (%) | *P*-value	
Fever	Ctrl	18 (90%)	0,3160	14 (70%)	0,0000	12 (60%)	0,0000
	Exp	17 (85%)		0 (0%)		0 (0%)	
Cough	Ctrl	20 (100%)	0,0680	18 (90%)	0,0000	18 (90%)	0,0000
	Exp	18 (90%)		6 (30%)		6 (30%)	
Asthenia Adynamia	Ctrl	18 (90%)	0,1015	20 (100%)	0,0000	20 (100%)	NA
	Exp	15 (75%)		2 (10%)		0 (0%)	
Expectoration	Ctrl	7 (35%)	0,1405	3 (15%)	0,0301	0 (0%)	NA
	Exp	4 (20%)		0 (0%)		0 (0%)	
Chills	Ctrl	17 (85%)	0,0001	10 (50%)	0,0000	4 (20%)	0,0127
	Exp	7 (35%)		0 (0%)		0 (0%)	
Vomit	Ctrl	1 (5%)	0,1524	0 (0%)	NA	0 (0%)	NA
	Exp	0 (0%)		0 (0%)		0 (0%)	
Dysnea	Ctrl	18 (90%)	0,5000	16 (80%)	0,0006	12 (60%)	0,0005
	Exp	18 (90%)		7 (35%)		3 (15%)	
Nasal Congestion	Ctrl	5 (25%)	0,2438	2 (10%)	0,0680	0 (0%)	NA
	Exp	7 (35%)		0 (0%)		0 (0%)	

Table 2: Result of the comparison of the Control Group versus the Experimental Group through a Wilcoxon – Mann – Whitney test (α: 95%) for the VAS Scale.

VAS Scale	Group	Day 0 median (IC) | *P*-value		Day 7 median (IC) | *P*-value		Day 14 median (IC) | *P*-value	
Throat pain	Ctrl	3,1 IC ± 0,6	0,9670	2,1 IC ± 0,4	0,0000	1,3 IC ± 0,3	0,0000
	Exp	3,2 IC ± 0,9		0,0 IC ± 0,0		0,0 IC ± 0,0	
Headache	Ctrl	2,9 IC ± 0,5	0,2665	2,9 IC ± 0,4	0,0000	2,5 IC ± 0,4	0,0000
	Exp	2,6 IC ± 0,8		0,5 IC ± 0,2		0,4 IC ± 0,2	
Chest pain	Ctrl	0,6 IC ± 0,3	0,9018	0,6 IC ± 0,3	0,0017	0,4 IC ± 0,2	0,0043
	Exp	0,6 IC ± 0,2		0,1 IC ± 0,1		0,0 IC ± 0,0	
General pain	Ctrl	2,1 IC ± 0,4	0,8660	2,4 IC ± 0,4	0,0000	2,6 IC ± 0,4	0,0000
	Exp	2,1 IC ± 0,7		0,5 IC ± 0,2		0,0 IC±0,1	
Lumbar/affect	Ctrl	1,5 IC ± 0,3	0,7827	1,6 IC ± 0,2	0,9633	1,6 IC±0,2	0,0067
	Exp	1,6 IC ± 0,3		1,7 IC ± 0,3		2,0 IC±0,2	

Table 3: Result of the comparison of the Control Group versus the Experimental Group through a Wilcoxon – Mann – Whitney test (α 95%) for Biochemical Parameters on the Likert Scale.

Parameter	Group	Day 0 median (IC) | *P*-value		Díay 7 median(IC) | *P*-value		Day 14 median (IC) | *P*-value	
lymphocytes	Ctrl	1,5 IC ± 0,3	0,7827	1,6 IC ± 0,2	0,9633	1,6 IC ± 0,2	0,0067
	Exp	1,6 IC ± 0,3		1,7 IC ± 0,3		2,0 IC ± 0,2	
leukocytes	Ctrl	2,6 IC ± 0,4	0,2582	3,1 IC ± 0,3	0,4842	3,3 IC ± 0,2	0,0002
	Exp	2,8 IC ± 0,4		2,9 IC ± 0,3		2,5 IC ± 0,3	
Platelets	Ctrl	2,4 IC ± 0,3	0,0816	2,7 IC ± 0,2	0,0202	3,0 IC ± 0,2	0,0212
	Exp	2,7 IC ± 0,3		3,3 IC ± 0,4		2,6 IC ± 0,3	
PC Reactive	Ctrl	3,2 IC ± 0,2	0,0398	3,4 IC ± 0,2	0,0001	3,5 IC ± 0,2	0,0000
	Exp	3,0 IC ± 0,0		2,0 IC ± 0,5		1,4 IC ± 0,2	
Lactate DH	Ctrl	2,6 IC ± 0,3	0,0422	2,7 IC ± 0,3	0,0036	2,7 IC ± 0,2	0,0000
	Exp	3,2 IC ± 0,4		1,9 IC ± 0,4		1,5 IC ± 0,2	
AST	Ctrl	3,2 IC ± 0,4	0,5319	3,2 IC ± 0,3	0,0403	3,5 IC ± 0,3	0,0000
	Exp	3,2 IC ± 0,4		2,5 IC ± 0,6		1,9 IC ± 0,3	
Dimero D	Ctrl	3,1 IC ± 0,4	0,3060	3,4 IC ± 0,4	0,0194	3,5 IC ± 0,3	0,0029
	Exp	3,4 IC ± 0,5		2,6 IC ± 0,4		2,6 IC ± 0,4	
Lactate	Ctrl	1,9 IC ± 0,3	0,0145	2,2 IC ± 0,2	0,0003	2,5 IC ± 0,2	0,0000
	Exp	2,5 IC ± 0,4		1,5 IC ± 0,3		1,1 IC ± 0,1	

with a larger sample number, in particular double blind that would increase the cost significantly. On the other hand, it is the only way to carry out a study when there are ethical and feasibility problems to carry out a random assignment of the sample (Manterola et al), or when it is necessary to carry it out under natural conditions and in this case, due to manifest urgency. given the pandemic.

The disadvantages are the high susceptibility to biases, especially those of selection and confusion, so to reduce it, we used random probability sampling, numbering the patients who were diagnosed and treated, selecting odd-numbered patients for inclusion in the research; the sample of control patients were selected in the same way.

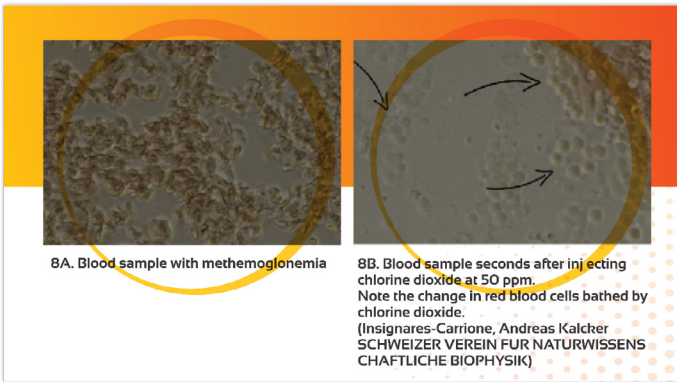

Figure 8: Blood samples with methahemoglobinemy and with ClO_2.

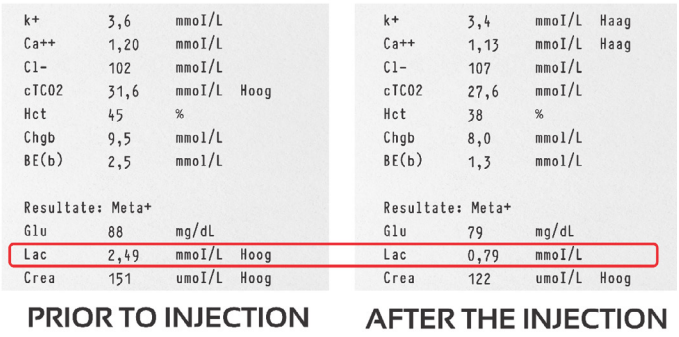

Figure 9: Variations in serum lactate before and 10 min after an IV clorine dioxide injection at 50 ppm. (A. Kalcker. SCHWEIZER VEREIN FUR NATURWISSENS CHAFTLICHE BIOPHYSIK).

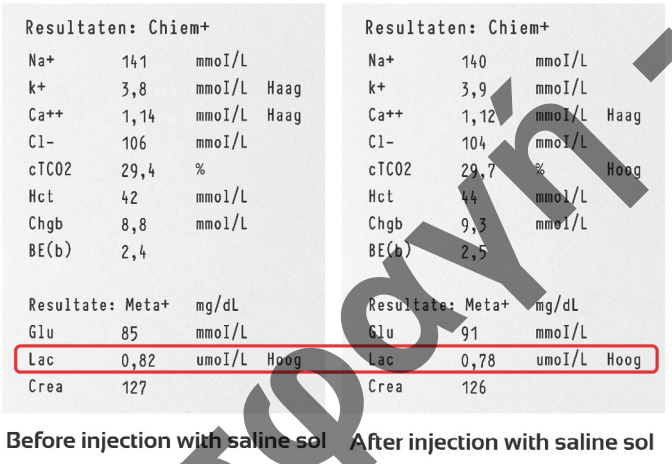

Figure 10: Lactate variations before and one hour after injection with saline sol.

On the other hand, we chose not to use existing groups so as not to compromise the external validity and applicability of the results. Another inherent difficulty in our study is the risk of presenting a placebo effect and a Hawthorne effect, which we could not minimize given that, given the humanitarian crisis of the pandemic, we did not consider it ethical for the subjects to participate in the study without being informed of the intervention that would be applied to them (Molina and Ochoa, 2014). In fact, all participants signed an informed consent for the use of a drug or substance under investigation, in particular because chlorine dioxide has not yet complied with the corresponding process to be classified as a drug.

Regarding the results and the possible explanations for them, the most important thing in the experimental group is the negativization of the RT-PCR in one hundred percent of the cases at seven days, as well as the rapid way in which the results are reduced. general symptoms in patients, in particular fever, cough, dyspnea, asthenia and general pain, which is achieved in 70% of cases seven days after treatment, a very marked reduction in VAS values in percentage similar to 7 days, in particular reduction of sore throat by 100%, reduction of low back pain by almost 80%, results that reveal a significant improvement in morbidity in patients.

In the initial stage of administration of chlorine dioxide, patients show improvement in their febrile symptoms, this could be attributed to its direct virucidal effect due to its action on the spike and on the virus RNA, through the mechanism that we explained above. Oxidation of amino acids and guanine of viral RNA. Additionally, patients begin to improve their sore throat, dry cough and dyspnea. This effect could be attributable to a direct anti-inflammatory action, possibly through an action on inflammasomes and it is even postulated that it may be possible due to action on NETosis processes, through a mechanism that has not yet been clearly elucidated and that we are in the process of developing investigate in detail.

Although we did not include the oxygen saturation measurement variable by pulse oximetry in the parameters of this investigation, we did the measurement in all patients, observing a considerable improvement in some cases in oxygen saturation; being a consistent observation, this improvement could be explained by the action of the dioxide through the oxidative mechanism of amino acids of the virus "anchored" to the unitβ1 of hemoglobin, improving oxygenation. We verified this mechanism as a possibility, in the research that we did in molecular biology through in silico simulation, in Japan, and it will be the subject of a future paper. In the same way, Pichert (2019) in his research suggests that chlorite interacts with the forms of hemoglobin and oxidized hemoglobin. Chlorite inactivates iron hemoglobin and methemoglobin. By these mechanisms, chlorite effectively decreases the yield of cytotoxic hemoglobin species that may appear later of excessive hemolysis of red blood cells in pathological situations.

Likewise, in the laboratory of the Liechtensteiner Verein für Wissenschaft und Gesundheit in Switzerland we were able to verify the immediate oxygenation of erythrocytes, by injecting chlorine dioxide at a concentration of 50 ppm to a sample of red blood cells with methemoglobinemia, using contrast microscopies. Phase and direct (Figure 8).

An interesting characteristic when we observe the behavior of the reduction of thrombocytosis in the 21 days of treatment, is that there could be an action of dioxide on the rheological behavior of the blood, an idea that is reinforced with the evident decrease of D-dimer in treated patients with the dioxide.

The lymphopenia observed in most patients could be due to a process that begins with disorganization of the cytoskeleton, condensation of chromatin and cytoplasm, loss of mitochondrial function, DNA fragmentation and terminal formation of ruptured membranes or apoptotic bodies, finally eliminated by macrophages. This phenomenon is mediated by the synthesis of the caspase-8 complex, which we consider could be activated by non-canonical means. The complex is favored by protein kinase-R, also accelerated by interferon generated in the presence of the virus. The signaling pathways that are activated by these receptors initiate an inflammatory response, with antiviral effects,

The virus also activates the transforming growth factor-b through neuraminidase, thus generating another cascade that ends with c-Jun-N-kinase and triggers transcription followed by the expression of pro apoptosis genes. The virus could synthesize the virulence peptide PB1-F2, a small fragment responsible for destroying lymphocytes, a circumstance that could explain the lymphopenia observed in COVID19. The action could also be mediated by action on inflammasomes, where the signaling (redox) by ATP can induce the desubiquitination of NLRP3, possibly induced by chlorine dioxide.

Regarding the increase in lactate, it is clear that it can be caused by dysfunction of the enzyme pyruvate dehydrogenase (PDH), as has been demonstrated in patients with sepsis, by mitochondrial dysfunction, or by hyperlactacidemia. The observed improvement could be explained through a mechanism in which chlorine dioxide has a cellular oxygenating effect directly through the release of oxygen or by redox signaling mechanisms with enzyme activation / inhibition that activate the pyruvate pathway with efficient ATP production.

When we inject direct chlorine dioxide into the vein, the amount of lactate in the blood is reduced, as can be seen in the following graph which shows in a comparative way the level of lactate in the blood and after intravenous chlorine dioxide application at 50 ppm at ten minutes post injection (Figure 9).

In comparison, when administering normal saline solution via direct intravenous, and measuring the lactate levels, we observe that there is no variation in the lactate level (Figure 10).

The data obtained in this research validates the effectiveness of chlorine dioxide in COVID19. This is the first phase IIa clinical trial in the world. In this study there were no inconclusive results. The phase IIa study design is appropriate for the research phase of a new molecule - such as chlorine dioxide - in its development as a potential drug.

There is much to explore about chlorine dioxide and its therapeutic possibilities, about which there is enough reasonable information to continue to study further.

The findings of this research open a complete world of possibilities for medical therapists in the world, as these initial results will motivate more formal research, will support the search for new therapeutic options, particularly in COVID19, and will allow the generation of research spaces at the molecular level and genomics on the processes of cellular respiration, redox signaling and the implantation of oxidative therapies as a new possibility for the approach of multiple pathologies with altered common intracellular bioenergetic mechanisms.

The results can be extended to the control of infectious diseases in agronomy, the development of new nanotechnologies in pharmaceuticals and humans in general by alleviating and controlling COVID19 and other pandemics or epidemics that may occur in the short future.

The results found here, rather than expanding previous studies, as it is a pilot study and the first of its kind in the world, enable the initiation of many studies on dioxide and the related issues noted.

Conclusion

In conclusion, we can affirm without a doubt, based on test of comparison of proportions and its confidence interval, as well as the paired tests where we used the Wilcoxon – Mann – Whitney test (α: 95%), that the data in most of the variables ($P < 0.05$) obtained indicate that chlorine dioxide is effective in the treatment of COVID19, making RT-PCR negative in one hundred percent of cases at 7 days, significantly and rapidly modifying the symptoms of the disease, significantly reducing laboratory parameters to normality within 14 to 21 days. We recommend conducting randomized double-blind studies and delving into studies of toxicological safety and therapeutic efficacy of chlorine dioxide in pathologies of epidemiological impact in the near future.

Recognition

We want to express our gratitude for your collaboration and contributions to the doctor

Mitchell B. Liester, Doctor of Medicine, University of Colorado School of Medicine, Colorado Springs Branch for their conceptual contributions and selfless support in the search for new options for patients.

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