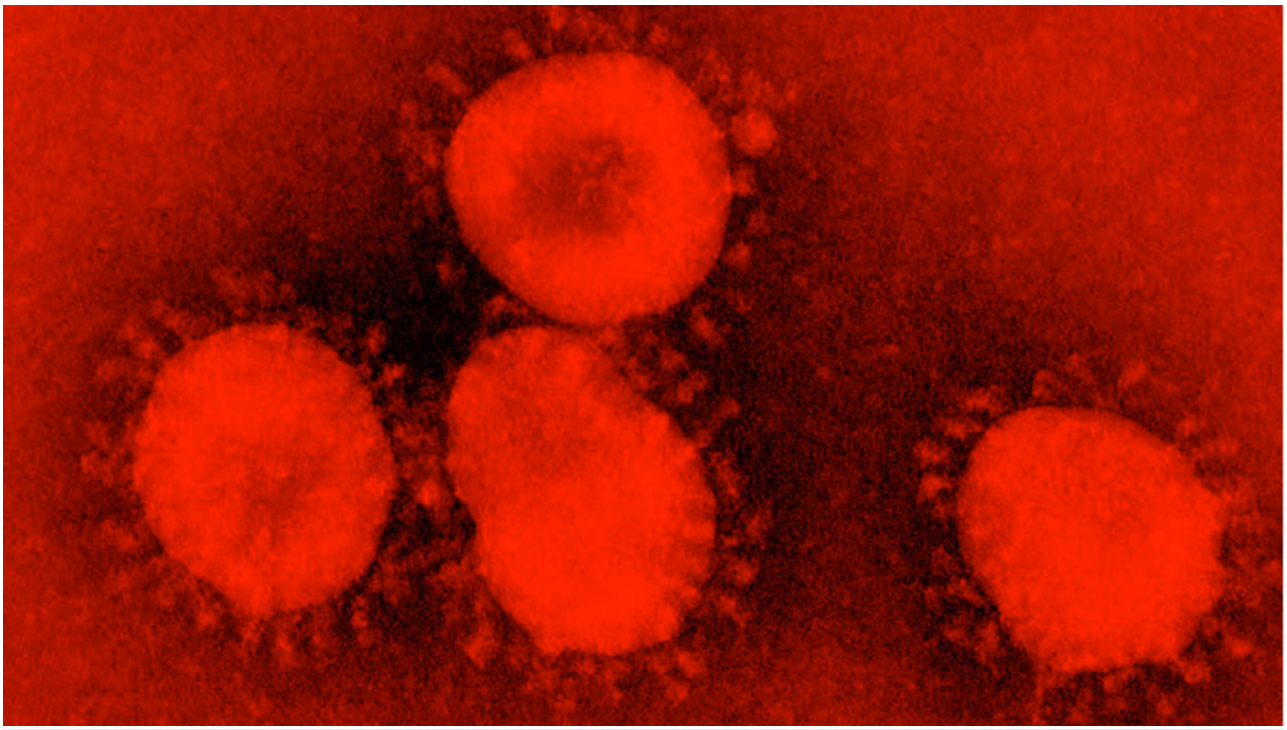
ClO2 against Covid-19

Determination of the effectiveness of oral chlorine dioxide in the treatment of COVID-19



The recent Covid-19 coronavirus pandemic demands urgent solutions with approaches unexplored. Therefore, chlorine dioxide (ClO2) in aqueous solution may be an option promising.

Case study research work:
Quasi-experimental exploratory study

Abstract

The objective of this study is to review, through prospective case research, the efficacy of oral chlorine dioxide in the treatment of patients with COVID-19 infection. The research will be carried out between April and June 2020 with a quasi-experimental design in two health care centers on a sample of twenty (20) patients, through direct intervention, who will measure the changes in the manifest symptoms of infection and negativity. a COVID-19 after administration of the study preparation, to determine the effectiveness of chlorine dioxide in the treated group.

Based on the results that are found and on the evaluation of efficacy on the basis of clinical improvement on a scale of 1 to 5, and of the negativization of COVID-19, we can conclude whether the therapeutic efficacy in this investigation is considered good by verifying whether or not there is efficacy of treatment with chlorine dioxide in COVID-19.

With this research, it is hoped to stimulate the search for new therapeutic options in the treatment of COVID-19 and contribute to the development of NEW options in medications, considering the immense number of deaths and morbidity that currently exists in the present pandemic.

Key words: COVID-19, chlorine dioxide, treatment.

Overview of test plan

Project Phase:

Phase II.

Indication:

Complementary treatment of COVID-19.

Aim of the study:

Examine the efficacy and tolerance of a preparation based on chlorine dioxide.

Research design

Quasi-experimental clinical case study.

Number of patients expected:

20 patients.

Main inclusion criteria:

COVID-19 infection.

Substance or drug under study:

Chlorine dioxide 3.000 ppm administered in water dilutions.

Dosage:

10 cc of Chlorine Dioxide 3000 ppm diluted in one litre of water to be taken in equal doses in 24 hours.

Route and duration of medication administration:

The medication will be taken orally for one month.

Main efficiency criteria:

Assessment according to "visual analogue scale" (VAS), 10-point scale (1=poor VAS; 10=optimal), evaluation by the patients.

Negativation of COVID-19 in the patient.

Tolerance criteria:

Adverse reactions.

Semiological, clinical and laboratory examinations are planned at the beginning of the treatment under study (or basal) and after 7, 15 and 30 days.

Statistical evaluation:

The equivalence between the groups of the main objective criteria will be assessed in a confirmatory way at the end of the treatment, unilaterally through the SSSP.

Introduction

The CDC (Centers for Disease Control and Prevention) is responding to an outbreak of respiratory disease caused by a new coronavirus that was first detected in China and has now been detected in nearly 90 locations internationally, including the United States. The virus has been called "SARS-CoV-2" and the disease it causes has been called "coronavirus disease 2019" (shortened to "COVID-19").

On 30 January 2020, the Emergency Committee of the International Health Regulations of the World Health Organization declared the outbreak a "public health emergency of international concern" (PHEIC). Defined as "an extraordinary event to be determined, as provided for in these Regulations":

I. "For constituting a public health risk to other States through the international spread of disease;

II. and potentially requiring a coordinated international response." This definition implies a situation that: is serious, unusual or unexpected; has public health implications beyond the national border of the affected State; and may require immediate international action.

On January 31, 2020, Secretary of Health and Human Services Alex M. Azar II declared a public health emergency (PHE) for the United States to help the nation's health care community respond to COVID-19 (taken from Colombia's national academy of medicine.)

Based on these considerations, there is an urgent need to find routes that can bring something new, hopefully fast, effective and economical that will solve or mitigate the current pandemic.

In this work we will use the bases of translational medicine to bring to conventional medicine, studies and treatment that are born from the field of therapeutic alternatives.

Problem Statement

1. Description of the problem

Covid-19 is an infectious disease caused by the SARS-CoV-2 virus. It was first detected in the Chinese city of Wuhan (Hubei Province) in December 2019. Within three months, it spread to virtually all countries in the world and was declared a pandemic by the World Health Organization.

It produces flu-like symptoms, including fever, cough, dyspnea, myalgia and fatigue. Sudden loss of smell and taste has also been observed. In severe cases it is characterized by pneumonia, acute respiratory distress syndrome, sepsis and septic shock leading to about 3% of those infected dying. There is no specific treatment; the main therapeutic measures are to relieve the symptoms and maintain vital functions.

The most frequent form of human-to-human transmission, airborne, is due to the small droplets (known as Flügge droplets) that are emitted when talking, sneezing, coughing or breathing out.

The routes of person-to-person transmission of SARS-CoV-2 include direct transmission, such as coughing, sneezing, droplet transmission, and contact transmission, such as contact with oral, nasal, and ocular mucous membranes.

Research to find an effective treatment began in January 2020, but results are not likely to be available until 2021. In late January, the Chinese Center for Disease Control and Prevention began testing the effectiveness of some pre-existing effective treatments for pneumonia in patients with VICD-19. Experiments have also been made with Remdesivir, an RNA polymerase inhibitor, and with interferon beta.

There is no known effective treatment for the disease. WHO recommends that randomised controlled trials be conducted with volunteers to test the effectiveness and safety of some potential treatments.

Based on this, we are looking into research processes given in the past, to make a transfer (translational medicine) of those initial and promising observations in the infectious treatment to the treatment of Covid-19. (Reference: Wikipedia.)

2. Delimitation of the problem

Based on the previous description, it was considered that the research that could really contribute to the approach of the previously raised problem, should be directed to the development of a proposal of therapeutic possibilities studied in the past, based on both conventional and non-conventional research and respecting the knowledge, culture, paradigmatic and epistemological positions, as well as the experience obtained during all the years of history in the use of the different procedures used by conventional medicine and alternative medicines (WHO, 2002); Furthermore, if the therapy chosen comes from

so-called alternative medicine, it should introduce elements that will allow this methodology to be brought closer to that of official medicine through procedures that, starting from qualitative elements, may undergo some degree of quantitative transformation that will lead to a rapprochement between the different medical visions and also strengthen the traditional qualitative methods of research in medicine as a whole.

3. General and specific research objectives

3. 1. GENERAL OBJECTIVE:

To determine the effectiveness of oral chlorine dioxide in the treatment of Covid-19

3. 2. SPECIFIC OBJECTIVES:

To measure the positivity or negativity of Covid-19 in patients who received treatment with chlorine dioxide

To determine clinical improvement based on the VAS scale.

3. 3. EXPECTED RESULTS:

We hope to reduce morbidity and especially mortality from Covid-19 viral infection through chlorine dioxide management.

4. Research question

Thus, based on the delimitation of the problem, the following research question arises: **Could the use of chlorine dioxide modify the morbimortality in patients infected with Covid-19?**

Justification

In view of the avalanche of deaths caused by the coronavirus in the absence of truly effective treatment, we have developed a protocol for dealing with COVID-19 infection, particularly in hospitalized patients and in the ICU, in an attempt to reduce the morbidity and mortality presented by the viral infection.

In addition to the general and specific recommendations for hospitalized patients and ICU patients, and the conventional protocol treatment (ventilatory support, hydroxychloroquine, azithromycin, etc.), we recommend a complementary experimental and exploratory approach that seeks to reduce the destructive and fibrotic effects of the process, as well as the leukocyte storm and antiphospholipid syndrome that occur in many cases, and in other cases to prevent and reduce patient recovery times.

Finally, we consider that it is pertinent and significant to carry out this research, because by using the epistemological and conceptual bases of conventional research, research carried out for years in the field of unconventionality with much empirical and experimental research approaches, can move into the field of evidence, transferring the work and efforts of many years, the territory of conventional science, reaching new and better possibilities to help patients (translational medicine), especially with drugs or substances potentially useful in cases such as the present pandemic of COVID-19.

State of the art

State of the art at international level in treatments in research against Covid-19:

1. Vaccines

Three vaccination strategies are being investigated. First, researchers aim to build a whole virus vaccine. The use of such a virus, either inactive or killed, aims at a rapid immune response of the human body to a new infection with COVID-19. A second strategy, subunit vaccines, aims to create a vaccine that sensitizes the immune system to certain subunits of the virus. In the case of SARS-CoV-2, this research focuses on the S-spike protein that helps the virus introduce the enzyme ACE2. A third strategy is nucleic acid vaccines (DNA or RNA vaccines, a novel technique for creating a vaccine). Experimental vaccines of any of these strategies would have to be tested for safety and efficacy.

Several organizations in different countries are in the process of developing a vaccine. The U.S. National Institutes of Health hopes to conduct human trials of a vaccine by April 2020. The Chinese Center for Disease Control and Prevention (CCDC) has begun developing vaccines against the new coronavirus and is testing the effectiveness of existing drugs for pneumonia. The Chinese Military Academy of Medical Sciences said it has "successfully" developed the recombinant coronavirus vaccine, and said it is preparing for "large-scale" production, according to a statement issued by the Chinese Ministry of Defense. The Coalition for Innovations in Epidemic Preparedness (CEPI) is funding three vaccine projects and hopes to have a vaccine in trials by June 2020 and approved and ready in one year. The University of Queensland in Australia received $10.6 million in funding from CEPI to develop a "molecular clamp" vaccine platform. Moderna Inc. is developing an mRNA vaccine with funding from EIPC. Inovio Pharmaceuticals received a grant from CEPI and designed a vaccine within two hours of receiving the gene sequence. The vaccine is being manufactured so that it can first be tested on animals.

Israeli scientists hope to have an oral vaccine ready in 90 days, after going through the safety testing phase.

By early March 2020, some 30 vaccine candidates were in development, with products from Gilead Sciences and Ascletis Pharma in phase III clinical trials.

2. Antivirals

On Jan. 23, Gilead Sciences was in communication with researchers and physicians in the United States and China about the ongoing outbreak of Wuhan coronavirus and the potential use of Remdesivir as an investigational treatment.

In late January 2020, Chinese medical researchers expressed their intention to begin clinical trials with Remdesivir, chloroquine and Lopinavir/Ritonavir, which appeared to have inhibitory effects on SARS-CoV-2 at the cellular level in exploratory in vitro experiments. Nitazoxanide has been recommended for further in vivo studies after demonstrating low concentration inhibition of SARS-CoV-2. On February 2, 2020, physicians in Thailand claimed to have successfully treated a patient with a combination of Lopinavir/Ritonavir and the influenza drug Oseltamivir. On February 5, China began patenting Remdesivir for use against the disease. Phase 3 clinical trials with Remdesivir are underway in March in the US, China and Italy.

In late January, Russia's Ministry of Health identified three adult drugs that may help treat the disease. They are ribavirin, Lopinavir/Ritonavir and interferon beta-1b. These drugs are commonly used to treat hepatitis C, HIV infection and multiple sclerosis, respectively. The ministry provided Russian hospitals with descriptions and guidelines on the mechanism of action of treatment and recommended doses. In February, China began using Triazavirin, a 2014 drug developed in Russia, to test whether it is effective in controlling the disease. The drug was developed at Ural Federal University in Ekaterinburg to treat H5N1 (bird) flu. It has been used against COVID-19 because of the similarity between the two diseases. The drug also appears to be effective against Rifty Valley Fever, West Nile virus, and others.

On March 18, an article reported that treatment with Lopinavir/Ritonavir was negative in clinical trials with 199 patients in China. There are no benefits.

Chinese researchers discovered that Arbidol, an antiviral drug used to treat flu, could be combined with Darunavir, a drug used in the treatment of HIV, to treat patients with coronaviruses.

Chloroquine phosphate has demonstrated apparent efficacy in the treatment of VID-19-associated pneumonia. In clinical trials with 100 patients it was found to be superior to control treatment in inhibiting exacerbation of pneumonia, improving lung imaging findings, promoting negative conversion to the virus, and shortening disease. Research results showed that the SARS-CoV-2 protein ORF8 and the surface glycoprotein could bind to porphyrin, respectively, while the SARS-CoV-2 proteins orf1ab, ORF10 and ORF3a could coordinate with heme to dissociate iron to form porphyrin. The mechanism seriously interfered with the normal anabolic pathway of heme in the human body and this results in human disease. Based on validation analysis of these findings, chloroquine may prevent orf1ab, ORF3a and ORF10 from attacking heme to form porphyrin, and inhibit ORF8 and surface glycoprotein binding to porphyrins to some extent.

Researchers at the Norwegian University of Science and Technology (NTNU) have created a database with 120 human-safe broad-spectrum antiviral agents and identified 31 drug candidates for the treatment of SARS-CoV-2.

China's National Center for Biotechnology Development said March 17 that the antiviral drug Favipiravir, an RNA polymerase inhibitor, showed positive results in a case-control study of 80 patients at Shenzhen People's Hospital No. 3. Those treated with Favipiravir were negative within a shorter period of time compared to those in the control group, and it recommends that it be included in treatment.

Recent studies have shown that initial priming of the peak protein by the transmembrane protease serine 2 (TMPRSS2) is essential for the entry of SARS-CoV-2, SARS-CoV and MERS-CoV through interaction with the ACE2 receptor. These findings suggest that the TMPRSS2 inhibitor Camostat approved for clinical use in Japan to inhibit fibrosis in liver and kidney disease, postoperative reflux esophagitis and pancreatitis may be an effective off-label treatment option.

Hydroxychloroquine, a less toxic chloroquine derivative, would be more potent in inhibiting SARS-CoV-2 infection in vitro. On 16 March 2020, a leading French authority and advisor to the French Government on COVID-19, Professor Didier Raoult of the Institut Universitaire Hospitalier des Maladies Infectifs (IHU-Méditerranée infection) in Marseille (Bouches-du-Rhône, Provence-Alpes-Côte d'Azur), announced that a trial involving 24 patients in south-eastern France had shown chloroquine to be an effective treatment for COVID-19. These patients were given 600 mg of hydroxychloroquine (brand name Plaquenil) every day for 10 days. This led to a "rapid and effective acceleration of their healing process, and a sharp decrease in the amount of time they remained contagious. Although chloroquine has a long safety record, patients were closely monitored for drug interactions and possible serious side effects. Professor Raoult said: "We included everyone

who agreed [to be treated], which was almost everyone. Two cities in the protocol, Nice and Avignon, gave us patients [infected] who had not yet received treatment We were able to determine that the patients who had not received Plaquenil [the drug containing hydroxychloroquine] were still contagious after six days, but of those who had received Plaquenil, after six days, only 25% were still contagious. In Australia, the Director of the Clinical Research Centre at the University of Queensland, Professor David Paterson, announced his intention to conduct a major clinical research trial on the efficacy of chloroquine and Remedesivir as treatments for VOC-19. The trial would compare one drug, against the other drug, against the combination of the two drugs. Professor Paterson hoped to begin enrolling patients by the end of March 2020.

A limited French study shows that hydroxychloroquine combined with azithromycin is faster than hydroxychloroquine alone in transforming patients with COVID-19 to negative.

3. Against the cytokine storm

Tocilizumab has been included in the treatment guidelines by the National Health Commission of China after a small study was completed. It is undergoing a national phase 2 non-randomized test in Italy after showing positive results in people with severe disease. In combination with a serum ferritin blood test to identify cytokine storms, it is intended to counteract such developments, which are believed to be the cause of death in some affected people. Interleukin-6 receptor antagonist was approved by the FDA for the treatment of cytokine release syndrome induced by a different cause, CAR T cell therapy, in 2017.

The Feinstein Institute at Northwell Health announced in March a study of "a human antibody that can prevent the activity" of IL-6. Called sarilumab, it was developed jointly by Regeneron Pharmaceuticals and Sanofi.

4. Passive antibody therapy

Research is underway to use blood donations from healthy people who have already recovered from COVID-19, a strategy that has also been tested for SARS, a former cousin of COVID-19. The mechanism of action is that antibodies naturally produced in the immune system of those who have already recovered are transferred to people who need them through a non-vaccine based form of immunization. Other forms of passive anti-

body therapy, such as manufactured monoclonal antibodies, may come after biopharmaceutical development, but production of convalescent serum could be increased for faster deployment.

San Francisco-based Vir Biotechnology is evaluating the effectiveness of previously identified monoclonal antibodies (mAbs) against the virus.

Researchers from Utrecht University and Erasmus MC announced that they have found a human monoclonal antibody that blocks SARS-CoV-2 infection.

A systematic search was conducted on the use of chlorine dioxide in the international literature for indexed literature including sources such as Pubmed (Medline), LILACS, Cochrane Library, Science Direct, EBSCOhost, SCIELO, and Med scape.

In Pub med we found 4 references , in LILACS 18 references , in SCIELO 61 references , in Science Direct 1168 references , in Cochrane Library 56 references and in MedScape 19 articles .

The most significant findings in the literature referenced above are focused on area disinfection, oral health use, agronomy use and a phase 1 study in rats with influenza A induced infection in two groups, one treated with chlorine dioxide and the other without.

Theoretical field

1. Chlorine dioxide and the basis of its therapeutic application

The therapeutic action of chlorine dioxide is given by its pH selectivity. 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, chlorine dioxide when dissociated 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 meets acidity, either by lactic acid or by the acidity of the pathogen. Its therapeutic effect is due -among others- to the fact that it helps in the recovery of many types of diseases by creating an alkaline environment, while at the same time eliminating small acidic pathogens, according to my criteria, through oxidation, with an electromagnetic overload impossible to dissipate by unicellular organisms. **Andreas Kalcker.*

Multicellular tissue has the capacity to dissipate this load and is not affected in the same way. Biochemistry, in turn, defines cell protection through the sulfhydric groups. Chlorine dioxide, which is the second strongest known disinfectant after ozone, is much more suitable for therapeutic use 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 bacterial resistance to ClO2. Although ozone is stronger in antiseptic terms, 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 therapeutic applications in vivo.

Chlorine dioxide is a selective oxidant and unlike other substances it does not react with most components of living tissue. Chlorine dioxide does react rapidly with phenols and thiols essential for bacterial life. In phenols the mechanism consists of attacking the benzene ring eliminating odor, flavor and other intermediate compounds (Stevens, A.; Seeger, D.; Slocum, C., Products of Chlorine Dioxide Treatment of OrganicMaterials in Water, Water Supply Research Div.) Chlorine dioxide effectively kills viruses and is up to 10 times more effective (Sanekata T, Fukuda T, Miura T, Morino H, Lee C et al. (2010) Evaluation of the antiviral activity of chlorine dioxide and sodium hypochlorite against feline calicivirus, human influenza virus, measlesvirus, canine distemper virus, human herpesvirus, human adenovirus, canine adenovirus and canine parvovirus. Biocontrol Sci 15/2: 45-49.doi:10.4265/bio.15.45. PubMed: 20616431) than the sodium hypochlorite (bleach or bleach) that was tested in a comparative (Tanner R (1989) Comparative testing and evaluation of hard-surface disinfectants. J Ind Microbiol 4: 145-154. doi:10.1007/BF01569799.) It also proved to be highly effective against small parasites, protozoa (EPA Guidance Manual, Alternative Disinfectants and Oxidants, 4.4.3.2 Protozoa Inactivation... Available: http://www.epa.gov/ogwdw/mdbp/pdf/ alter/chapt_4.pdf.)

One issue of great concern to medical professionals in medical scientific terms is the reactivity of chlorine dioxide with essential amino acids. In tests on the reactivity of chlorine dioxide with 21 essential amino acids, only cysteine (Ison A, Odeh IN, Margerum DW (2006) Kinetics and mechanisms of chlorine dioxide and chlorite oxidations of cysteine and glutathione.Inorg Chem 45: 8768-8775. doi:10.1021/ic0609554. PubMed:17029389.), tryptophan (Stewart DJ, Napolitano MJ, Bakhmutova-Albert EV, Margerum DW (2008) Kinetics and mechanisms of chlorine dioxide oxidation of tryptophan. Inorg Chem 47: 1639-1647. doi:10.1021/ic701761p.PubMed: 18254588.) and tyrosine (Napolitano MJ, Green BJ, Nicoson JS, Margerum DW (2005) Chlorine dioxide oxidations of tyrosine, N-acetyltyrosine, and Dopa. Chem Res Toxicol 18: 501-508. doi:10.1021/tx049697i. PubMed: 15777090) proline and hydroxyproline were reactive at a pH around 6. (Tan, H.K., Whee-

ler, W.B., Wei, C.I., Reaction of chlorine dioxide with amino acids and peptides, Mutation Research, 188: 259-266, 1987) . These amino acids are relatively easy to replace.

Cysteine and Methionine (Loginova IV, Rubtsova SA, Kuchin AV (2008) Oxidation by chlorine dioxide of methionine and cysteine derivatives to sulfoxide. Chem Nat Compd 44: 752-754. doi:10.1007/s10600-009-9182-8.) are two aromatic amino acids containing sulfur, tryptophan and tyrosine and the 2 inorganic ions FE2+ and Mn2+. Cysteine, due to its belonging to the thiol group, is an amino acid up to 50 times more reactive with all microbial systems than the other four essential amino acids, and therefore it is impossible for it to build up resistance against chlorine dioxide. Although not scientifically proven to date, pharmacodynamics usually assumes that the cause of its antimicrobial effect is due to its reactions to the four amino acids listed above or to protein and peptide residues.

2. Chlorine dioxide and the basis of its therapeutic application in COVID-19

Chlorine dioxide (ClO2) has been used since 1944 in the treatment of drinking water because of its biocidal power as well as in most bottled water suitable for consumption because of its almost zero toxicity in aqueous solution (9#Toxicity of clo2 and chlorite ions). It is used systematically in the disinfection and preservation of blood transfusion bags. [2# Alcide studies on blood disinfection] Being a selective oxidant [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3818415/] its mode of action is very similar to phagocytosis, where a mild oxidation process is used in the elimination of all types of pathogens. Chlorine dioxide (ClO2) is a yellowish gas that, to date, is not part of the conventional pharmacopoeia despite its proven effectiveness in the denaturation of viruses. There are up to 6 different patents for its use in treatments such as the disinfection or sterilization of blood components (blood cells, blood proteins, etc). US Patent 5019402 Direct link to Google Patents: http://goo.gl/LzpqdX parenteral (intravenous) treatment of HIV infections. US Patent 6086922 A Date: 19/3/1993 Inventor: Friedrich W. Kuhne Direct link to Google Patents: http://goo.gl/LJTbo8y or for the treatment of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) or multiple sclerosis (MS) U.S. Patent 8029826 B2 Date: 04/10/2011 Inventor: Michael S. McGrath U.S. government supported patent where the government itself may have rights. Direct link to Google Patents: http://goo.gl/HCPxC7. Among other ailments and uses. **(SEE ANNEX.)**

The recent Covid-19 coronavirus pandemic demands urgent solutions with unexplored approaches. Therefore, chlorine dioxide (ClO2) in aqueous solution may be a promising option.

Premises:

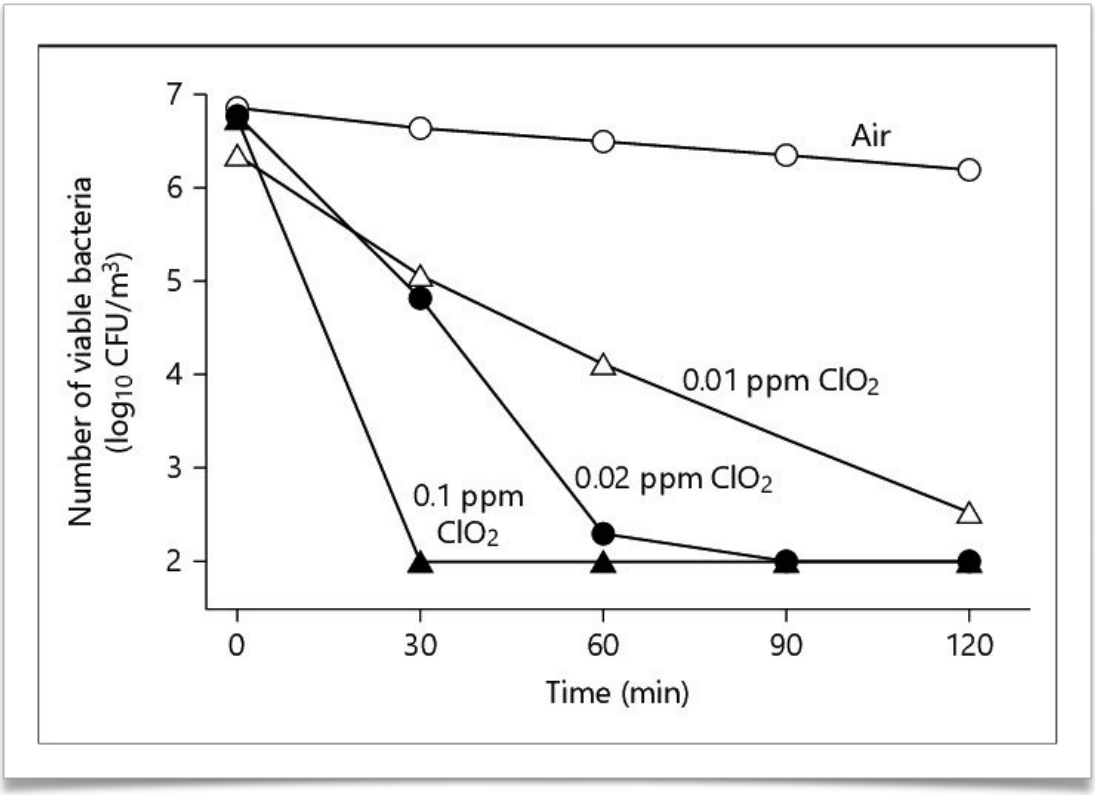
1. Chlorine dioxide can fight viruses by the process of selective oxidation through denaturation of capsid proteins and subsequent oxidation of the genetic material of the virus, leaving it disabled. As there is no possible adaptation to the oxidation process, it prevents the development of resistance by the virus, making chlorine dioxide (ClO2) a promising treatment for any viral subspecies.

2. There is scientific evidence that chlorine dioxide is effective against the coronavirus SARS-CoV-2, a base virus of COVID-19.

Below is a list of different studies:

- Study on the resistance of coronavirus associated with severe acute respiratory syndrome https://www.ncbi.nlm.nih.gov/pubmed/15847934
- American Society for Microbiology study on the deactivation of Human and Ape Rotavirus with Chlorine Dioxide https://www.ncbi.nlm.nih.gov/pmc/articles/PMC238879/
- Comparative study of the Japanese Institute of Infectious Diseases on the antiviral activity of Chlorine Dioxide and Sodium Hypochlorite against different human viruses such as influenza virus, measles, adenovirus or Herpes as well as other animal viruses mainly feline and canine, resulting in a 10x more effective antiviral activity by Chlorine Dioxide with respect to Sodium Hypochlorite. https://www.researchgate.net/publication/45113969_Evaluation_of_the_Antiviral_Activity_of_Chlorine_Dioxide_and_Sodium_Hypochlorite_against_Feline_Calicivirus_Human_Influenza_Virus_Measles_Virus_Canine_Distemper_Virus_Human_Herpesvirus_Human_Adenoviru
- Study of the department of microbiology and medicine of the University of New England on the deactivation of the human Retovirus with Chlorine Dioxide https://aem.asm.org/content/56/5/1363
- Japanese study of the Tottori University on the deactivation of the feline Calcivirus after being exposed to the Chlorine Dioxide. https://www.ncbi.nlm.nih.gov/pubmed/20616431
- Italian study by the University of Palma on the deactivation of viruses resistant to oxidizing agents, such as Coxsackie virus, HAV and feline Calcivirus https://www.ncbi.nlm.nih.gov/pubmed/18274345
- Study by the Institute of Public Health and Environmental Medicine in Tainjin, China, on the deactivation by Chlorine Dioxide of the Hepatitis A virus https://www.ncbi.nlm.nih.gov/pubmed/15016528

- Study by the Biology Department of New Mexico State University, USA on the deactivation of Polyvirus with Chlorine Dioxide and Iodine https://www.ncbi.nlm.nih.gov/pmc/articles/PMC242149/pdf/aem00180-0060.pdf
- Pharmacology. 2016;97(5-6):301-6. doi: 10.1159/000444503. Epub 2016 Mar 1. Inactivation of Airborne. Bacteria and Viruses Using Extremely Low Concentrations of Chlorine Dioxide Gas. https://www.ncbi.nlm.nih.gov/pubmed/26926704



3. Toxicity: The biggest problems with drugs in general are due to their toxicity and side effects. There is toxicity with chlorine dioxide in case of massive inhalation, but there is no clinically proven death even in high doses by oral ingestion. The lethal dose (LD50, acute toxicity ratio) is considered to be 292 mg per kilogram for 14 days, where the equivalent in a 50 kg adult would be 15,000 mg administered for two weeks. The sub toxic oral doses that can be used are about 50 ppm dissolved in 100 ml of water 10 times a day, which is equivalent to 500 mg. In addition, chlorine dioxide, when dissociated, breaks down into common salt - NaCl - and oxygen - O2 - within the human body.

Possible operation of chlorine dioxide in viruses

As a general rule, most viruses behave in a similar way and once they bind to the appropriate host type - bacteria or cell, depending on the case - the nucleic acid component of the virus being injected takes over after the protein synthesis processes of the infected cell. Certain segments of the viral nucleic acid are responsible for the replication of the genetic material in the capsid. In the presence of these nucleic acids, the CLO2 molecule becomes unstable and dissociates, releasing the resulting oxygen into the environment, which in turn helps to oxygenate the surrounding tissue by increasing mitochondrial activity and thus the immune system response.

The nucleic acids, DNA-RNA, consist of a chain of puric and pyrimidine bases, see: guanine (G), cytosine (C), adenine (A) and thymine (T). It is the sequence of these four units along the chain that makes one segment different from another. The guanine base, which is found in both RNA and DNA, is very sensitive to oxidation, forming 8-oxoguanine as a byproduct of it. Therefore, when the CLO2 molecule comes into contact with guanine and oxidizes it, it leads to the formation of 8-oxoguanine, thus blocking the replication of the viral nucleic acid by base pairing. Although replication of the protein capsid can continue; the formation of the fully functional virus is blocked by oxidation.

Possible precautions and contraindications

Chlorine dioxide reacts with antioxidants and various acids, so the use of vitamin C or ascorbic acid during treatment would not be recommended, as it would cancel out the effectiveness of chlorine dioxide in eliminating pathogens (the antioxidant effect of one prevents the selective oxidation of the other).

It has been shown that stomach acid does not affect its effectiveness. Although chlorine dioxide is very soluble in water, it does not hydrolyze, so it does not generate toxic carcinogenic THMs (trihalomethanes) like chlorine. It also does not cause genetic mutations or malformations.

Listing of efficacy in pathogens_ Referenced:

Virus

Adenovirus Type 40 6
Calicivirus 42
Canine Parvovirus 8
Coronavirus 3
Feline Calici Virus 3

Foot and Mouth disease 8
Hantavirus 8
Hepatitis A, B & C Virus 3,8
Human coronavirus 8
Human Immunodeficiency Virus 3
Human Rotavirus type 2 (HRV)15
Influenza A22
Minute Virus of Mouse (MVM-I)8
Mouse Hepatitis Virus spp.8
Mouse Parvovirus type 1 (MPV-1)8
Murine Parainfluenza Virus Type 1 (Sendai)8 Newcastle Disease Virus 8
Norwalk Virus 8
Poliovirus 20
Rotavirus 3
Severe Acute Respiratory Syndrome (SARS) coronavirus 43 Sialodscryoadenitis Virus 8
Simian rotavirus SA-1115
Theiler's Mouse Encephalomyelitis Virus 8
Vaccinia Virus 10

Bacteria

Blakeslea trispora 28
Bordetella bronchiseptica 8
Brucella suis 30
Burkholderia spp.36
Campylobacter jejuni 39
Clostridium botulinum 32
Clostridium dificile 44
Corynebacterium bovis 8
Coxiella burneti (Q-fever) 35
E. coli spp .1,3,13
Erwinia carotovora (soft rot) 21
Franscicella tularensis 30
Fusarium sambucinum (dry rot) 21
Helicobacter pylori 8
Helminthosporium solani (silver scurf) 21

Klebsiella pneumonia 3
Lactobacillus spp .1,5
Legionella spp. 38,42
Leuconostoc spp.1,5
Listeria spp. 1,19
Methicillin-resistant Staphylococcus aureus 3 Mycobacterium spp.8,42
Pediococcus acidilactici PH31
Pseudomonas aeruginosa 3,8
Salmonella spp.1,2,4,8,13
Shigella 38
Staphylococcus spp.1,23
Tuberculosis 3
Vancomycin-resistant Enterococcus faecalis3 Vibrio spp.37
Multi-Drug Resistant Salmonella typhimurium3 Yersinia spp.30,31,40

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Bacillus spp.10,11,12,14,30,31
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Bacillus thuringiensis 18

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Beta Lactams 29
Amplicons 46
Volatile organic compounds (VOCs)47

Fungus and protozoa

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Cryptosporidium 34
Cryptosporidium parvum Oocysts 9
Cyclospora cayetanensis Oocysts 41
Giardia 34
Alternaria alternata 26
Aspergillus spp.12,28
Botrytis species 3

Candida spp.5, 28
Chaetomium globosum 7
Cladosporium cladosporioides 7
Debaryomyces etchellsii 28
Eurotium spp.5
Fusarium solani 3
Lodderomyces elongisporus28
Mucor spp.28
Penicillium spp.3,5,7,28
Phormidium boneri3
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Saccharomyces cerevisiae 3
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ANEXX I

Patents filed for Chlorine Dioxide and Sodium Chlorite:

*Patent on a stabilized solution of CHLORINE DIOXIDE for use as a universal biocide: chemical substances intended to destroy, counteract, neutralize, prevent the action of any organism considered harmful to man. U.S. Patent 20120225135 A1 Date: 6/9/2012 Inventor: Tadeusz Krogulec. Direct Link Google Patents: http://goo.gl/RAUFWe

*Patent on the use of several substances including SODIUM CHLORITE for the treatment of allergic asthma, allergic rhinitis and atopic dermatitis. US Patent 8435568 B2 Date: 7/5/2013 Inventors: Mathias Brosz, Friedrich-Wilhelm Kuhne, Klaus Blaszkiewitz , Thomas Isensee. Direct Link Google Patents: http://goo.gl/AEBndF

*Patent on the use of CHLORINE DIOXIDE for the parenteral (intravenous) treatment of HIV infections The object of the present invention is to provide an agent which inactivates the HIV viruses in the blood without having a detrimental influence on the body of the patient. U.S. Patent 6086922 A Date: 3/19/1993 Inventor: Friedrich W. Kuhne Direct Link Google Patents: http://goo.gl/LJTbo8

*Patent on the use of CHLORINE DIOXIDE for the prevention and treatment of bacterial infections, including mastitis, in the udder of mammals Compositions include chlorine dioxide in an amount varying from 5 ppm to 1000 ppm. U.S. Patent 5252343 A Date: 12/10/1992 Inventor: Robert D. Kross. Direct Link Google Patents: http://goo.gl/emKbrx

*Patent on the use of CHLORINE DIOXIDE for the disinfection or sterilization of essentially blood components (blood cells, blood proteins, etc.) The composition is formed by adding a compound that releases chlorine dioxide with a weak organic acid. U.S. Pa-

tent 5019402 A Date: 5/28/1991 Inventors: Robert D. Kross, David I. Scheer. Direct Link Google Patents: http://goo.gl/LZpqdX

*Patent covering the use of CHLORINE DIOXIDE for the control of a wide range of infectious diseases in aquaculture including the treatment of aquatic animals infected with pathogens associated with infectious diseases. Aquatic animals infected with a pathogen are treated by contact with a therapeutically effective amount of chlorine dioxide. Patent WO 1995018534 A1 Date: 05/1/1995 Inventor: Robert D Kross Direct link Google Patents: http://goo.gl/RyszsQ

*Patent dealing with the use of SODIUM CHLORITE for the treatment of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) or multiple sclerosis (MS) US Patent 8029826 B2 Date: 04/10/2011 Inventor: Michael S. McGrath (http://goo.gl/76oy3F) Patent supported by the US government where the government itself may have rights over the patent. Direct Link Google Patents: http://goo.gl/HCPxC7

SOLUMIUM: Solumium Ltd., a company co-founded by Prof. Noszticzius, manufactures products based on chlorine dioxide. It kills all pathogens, including bacteria, fungi, protozoa and viruses. And with no known side effects. Solumium is based on a new Hungarian invention: Prof. Zoltán Noszticzius and his colleagues succeeded in producing hyper-pure chlorine dioxide, one of the strongest and most friendly antimicrobial agents in the world. He won the Interdisciplinary Innovation Award in Sweden in 2015.

International patents: The Solumium production process is protected by Hungarian, European, American and Chinese patents. Solumium is opening up new perspectives in medical use.

Practical field

HYPOTHESIS

Orally administered chlorine dioxide eliminates VIDOC infection-19.

METHODOLOGY

1. Type of study:

Observational, prospective, quasi-experimental study of a group of cases Characteristics of our study: Like quasi-experimental studies, it is used, in particular, to determine

the effect of treatments or interventions. It has two basic characteristics: first, it does not require the randomization procedure for the formation of study and control groups; second, it may or may not have control groups. This quasi-experimental study offers an adequate level of internal and external validity

In addition, we will use time series without a control group, based on a single group that serves as a study and control. Once formed, periodic measurements of the dependent variable are made, then the treatment is applied and subsequently the dependent variable continues to be measured periodically.

2. Population:

The population to which the study was directed consisted of a group of patients in the medical profession with active infection with COVID-19.

3. Patients:

Patients from various health care centers, hospitals, (multi-center.)

The selection of patients was made based on the self-proposal of physicians/patients as candidates for research, which refers to their proposing themselves as cases. Similarly, simultaneity was applied, which means that the patients were obtained in the same period of time in which the cases arose.

Number of patients: 20 patients (n=20) will be included in the study. A one-to-one relationship per centre is not maintained and they were presented randomly.

4. Acceptance criteria in the study:

Inclusion criteria:

Criteria	Complies	Doesn't comply
a. Covid-19 positive		
b. Some of the characteristic symptoms of Covid-19: fever, odynophagia, breathing difficulty		
c. Age: between 18 and 80 years old		

Exclusion criteria:

Criteria	Complies	Doesn´t comply
a. Covid-19 negatives		
b. Kidney failure IV/ VI		
c. Congestive heart failure		
d. Patients on anticoagulants, particularly warfarin sodium		

5. Duration of treatment per patient

The observation period per patient is (21) twenty-one days. Reviews were performed at the beginning, at one week, at two and three weeks.

6. Total duration of the study

The study will begin in April 2020 and will be completed in June 2020.

7. Allocation of study medication

Each patient will receive, in order of admission to the study, a consecutive patient number and the corresponding study medication. The assignment of this medication was made before the start of the study, by means of a computer-generated list. Patients will receive the chlorine dioxide base preparation at 3000 ppm with written and precise instructions on how to prepare and take the dilutions.

7.1. Dosage and routes of administration:

Medication: chlorine dioxide 3000 ppm. Fco x 150 cc.

Add 10 ml of chlorine dioxide 3000 ppm to 1 litre of water, per day. One part is taken every hour, until the content of the bottle is finished (from 8 to 12 takes).

Both the original dioxide bottle and the preparation for the day should be kept refrigerated.

In case of severe or life-threatening COVID-19, the dose should be increased, slowly and progressively, in separate doses, taken throughout the day and according to how you feel, up to 30 ml per litre of water. If it is necessary to take more, another bottle of water

should be prepared. The dose should be reduced if you feel unwell or nauseous. You should not exceed 80 ml in 12 daily doses (6 ml/h for 100 kg). The duration of treatment would be the time necessary, until you feel recovered.

The medication is taken orally dissolved in the mouth, at least 30 minutes before or after a meal.

8. Recommendations regarding medication

WHAT NOT TO EAT OR DRINK:

1. Antioxidant fruit juice wait at least 4 hours after drinking chlorine dioxide, better to avoid.

2. Preferably, do not mix chlorine dioxide with: coffee, alcohol, bicarbonate, vitamin C, ascorbic acid, orange juice, preservatives or supplements (antioxidants), although they do not usually interact, they can neutralize the effectiveness of chlorine dioxide.

9. Warnings and contraindications

- The sicker the person, the slower the dose increase should be.
- It is toxic by massive inhalation, direct prolonged breathing should be avoided.
- As an interaction we have to take into account, the use of anti-coagulants (Warfarin-Coumadin.)
- DO NOT CONSUME PURE AT 3,000 ppm. MAY CAUSE SEVERE IRRITATION, VOMITING OR DIARRHEA. MAY ONLY BE CONSUMED DILUTED AS DIRECTED.

10. Compliance

Patient compliance will be determined by self-assessment recorded on an instrument designed for this purpose. Patients shall be instructed to record their intake and in particular the times of intake on a daily basis, and if an intake is not consumed, it shall be recorded on the instrument.

11. Return of study medication

After completion of the study, unused test samples that are returned should be counted as controls.

12. Packaging/Labeling of Study Medication

250 cc bottles containing 150 cc of chlorine dioxide will be delivered at 3,000 p.p.m. SHOULD BE KEPT AWAY FROM LIGHT AND KEPT REFRIGERATED.

The bottles are labelled as follows:

- 150 cc of chlorine dioxide 3,000 ppm.
- They are intended for clinical trials.
- No. Of study:....
- No. Of patient:....
- Batch number:.....
- Ingestion according to protocol .
- Valid until: Month 2.

13. Concomitant treatment

13. 1. **Concomitant treatment not permitted:**

Treatment with ACE2 inhibitors and NSAIDs

13. 2. **Concomitant treatment allowed:**

The simultaneous administration of another specific drug and the administration of drugs not related to the treatment of COVID-19 shall be recorded on the data record form, stating the indication, name, frequency, route of application, dosage and duration of treatment.

14. Efficacy and tolerance criteria

- Three point improvement on the clinical VAS scale.
- Negativization of COVID-19 in 7 days.

15. Overall assessment of treatment by doctor and patient

At the end of the treatment, the doctor/patient will evaluate the overall effectiveness and tolerance.

The evaluation of efficacy will be based on a scale of 1 to 5, where 1= very good, 2= good, 3= moderate, 4= unsatisfactory and 5= poor, evaluation determined by improvement in the visual analogue scale VAS.

16. Course of study

At the beginning of the study, the anamnesis will be made, the inclusion and exclusion criteria will be made and an exploration of the general physical state of the patient will be carried out. Samples will be taken to determine COVID-19. The doctor/patient will receive explanations about the study and will give his or her consent to participate in it.

The physician/patient will receive an explanation of the study and consent to participate in the study:

- Start of the study.
- After 1 week.
- After 2 weeks.
- After 3 weeks.

16. 1. Planning and statistical evaluation

The quantitative data corresponding to the analytical measurements of the sample will be analyzed by means of frequency distributions and/or central tendency measurements (mean, median.)

16. 2. Aspects of the methodology

Chlorine dioxide will be produced by a reaction based on two raw materials :

- 25 % sodium chlorite, imported _____
- Hydrochloric acid 4%, imported _____

The pharmacopoeia USP will be used for the preparation of chlorine dioxide in a laboratory with GMP INVIMA for medicines, food or homeopathic, registered in batch -records and with batch numbered from 2020001.

There will be no blinding of the experiment: marking of the prepared vials, with consecutive cardinal numbers. For each patient, two (2) series of repetitions of the base medication will be made.

Store the vials in a cool, dry environment, hopefully refrigerated for use within 48 hours.

Samples will be taken for COVID 19 at the beginning, at 7 and 15 days after starting treatment.

The measurement technique for clinical qualification is based on the visual analogue scale VAS detailed in annex 1 of this document.

17. Stages of the investigation

The investigation will be carried out in three stages:

17. 1. <u>Collecting the information:</u> (ANEXX 2)

17. 2. <u>Analysis of the information:</u>

The quantitative data corresponding to the characteristics of the population under study will be analyzed using frequency distributions, measures of central tendency (mean, median), measures of dispersion (standard deviation and variance.)

17. 3. <u>Design:</u>

The design will be carried out according to the guidelines of the conceptual paradigm previously established in the theoretical framework. Two main aspects will be taken into account: Firstly, the quality of the selected population's doctors will be taken into account, who will be both executors and participants in the research. Secondly, the characteristics of the chlorine dioxide to be supplied will be taken into account, in a concentration of 3.000 ppm.

18. Statistical processing

The statistical analysis will be performed according to the indications of the SPSS statistical package.

CHRONOGRAM

No	ACTIVITIES	2020							
		APRIL	APRIL	APRIL	APRIL	MAY	MAY	MAY	MAY
1	Elaboration of the Project								
2	Presentation of the Project								
3	Information Collection								
4	Information Processing								
5	Information Analysis								
6	Consolidation and report writing								
7	Presentation - socialization								

IMPACTS

The following short and long-term impacts are expected to be generated by this study:

Short term:

- To favour treatment with reduction of morbimortality by COVID-19. To reduce the economic impact that COVID-19 is producing on the health system.
- Increased patient recovery.

Long term:

- Control and reduce morbidity and mortality from COVID-19
- Reduce the economic impact that the COVID-19 is having on countries.

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Project Summary

Name:	**Effectiveness of oral chlorine dioxide in the treatment of COVID-19**
Aim:	To determine the effectiveness of chlorine dioxide in patients with COVID-19
Justification:	In view of the avalanche of deaths produced by the coronavirus in the absence of truly effective treatment, we have drawn up a protocol for dealing with COVID-19 pneumonia, particularly in hospitalized patients and in the ICU, in an attempt to reduce the morbidity and mortality caused by the viral infection. In addition to the general and particular recommendations in hospitalized patients and in ICU and the conventional protocol treatment (ventilatory supports, hydroxychloroquine, azithromycin, etc.) we recommend a complementary approach that seeks to reduce the destructive and fibrotic effects of the process as well as the leukocyte storm and antiphospholipid syndrome and in some cases prevent, as well as reduce, patient recovery times.
Procedures:	A therapeutic intervention will be carried out where a protocol of chlorine dioxide administration by oral route will be applied, until the improvement of the picture and the negativization of the virus is achieved. In addition, the effectiveness of the therapy will be evaluated based on a survey format and an interview that will be conducted with the patient weekly for 4 weeks.
Expected risks:	Although the possible risks of applying the protocol are minimal, an allergic reaction could occur.
Benefits:	Decrease in symptoms, resolution of pneumonia and improvement in functional capacity, as well as denial of coronavirus.
Ethical concept:	**Unproven interventions in clinical practice (Declaration of Helsinki):** **37 Art.** In the treatment of an individual patient, where no intervention is proven or other known interventions have been ineffective, the physician, after seeking expert advice, with the informed consent of the patient or an authorized representative, may use an unproven intervention if in the physician's judgment it offers the hope of saving life, restoring health or alleviating suffering. This intervention must then be the subject of research designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made available to the public. 2013.10.19 **Resolution 8430 of 1993 .**

Anexx 2

Research protocol for case study

EXPLORATORY STUDY

EFFECTIVENESS OF ORAL CHLORINE DIOXIDE IN THE TREATMENT OF COVID-19

PATIENT SCREENING INSTRUMENT (PHYSICIANS WHO TREAT CORONAVIRUS AND COVID-19 POSITIVE CASES)

This instrument will be used to select patients who meet the criteria for pilot research on **the effectiveness of oral chlorine dioxide in the treatment of COVID-19.**

Please fill in each of the fields and mark with an X in the corresponding box. If the patient meets all the inclusion criteria and has no exclusion criteria, he/she is a suitable candidate to continue with the process.

Patients who are candidates will be called via video call in order to place appointments within the clinical intervention schedule.

DATE:_____
NAME AND SURNAME :_____
DNI/ID CARD: _____
DATE AND PLACE OF BIRTH:_____
AGE:_____
ADDRESS:_____
TELEPHONE:_____
JOB:_____

INITIAL MEDICAL RECORD FORM

Current symptoms:

_____
_____
_____
_____
_____
_____

BACKGROUND:

Contagiousness: where you have been in the last 48 hours, type of contacts, if there are infected people in the environment, etc.

_____
_____
_____

Medical:

_____
_____
_____

Surgical:

_____
_____
_____

Traumatics:

_____
_____
_____

Gynecological-obstetrics:

_____
_____
_____

Toxicallergics:

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Review by systems:

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Physical Exam:

C.F.: _____ R.F.: _____ A.P.: _____ Weight: _____ Height: _____

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Diagnosis:

_____
_____
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Treatment:

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_____

INFORMED CONSENT

INFORMED CONSENT FORM AND CONFIDENTIALITY FOR PARTICIPATION IN RESEARCH:

Effectiveness of oral chlorine dioxide in the treatment of COVID-19
Pilot Study

CITY AND DATE: _____

I,_____ having been informed of the purposes, objectives, intervention and evaluation procedures to be carried out in this investi-

gation and the possible risks that may arise from it, authorize _____, for the performance of the following procedures:

1. Interview and Physical Examination
2. Application of the oral chlorine dioxide protocol

Additionally, I was informed that:

- My participation in this research is completely free and voluntary, I am free to withdraw from it at any time.
- I will not receive personal benefit of any kind from participation in this research project. However, it is hoped that the results obtained will allow for improved evaluation processes of patients with clinical conditions similar to mine.
- All information obtained and the results of the research will be treated confidentially by the investigators as well as by me. This information will be archived in paper and electronic form. The study file will be kept under the responsibility of the investigators.
- Since all information in this research project is kept anonymous, personal results cannot be made available to third parties such as employers, government organizations, or insurance companies. I acknowledge that this document has been read and understood by me in its entirety freely and spontaneously.

Signature _____

Identity card _____

CLINICAL HISTORY FOLLOW-UP FORMAT

FIRST CONTROL

Date:_____

Subjective symptoms:

_____

_____

_____

_____

Objective findings:

_____

_____

_____

_____

Conduct:

_____

_____

_____

_____

SECOND CONTROL

Date:_____

Subjective symptoms:

_____

_____

_____

_____

Objective findings:

_____

_____

_____

_____

_____

Conduct:

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THIRD CONTROL

Date:_____

Subjective symptoms:

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_____
_____
_____

Objective findings:

_____
_____
_____
_____

Conduct:

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FOURTH CONTROL

Date:_____

Subjective symptoms:

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_____
_____

Objective findings:

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Conduct:

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SCALES

Name and surname:_____

Date: _____

Please read the instructions carefully:

This questionnaire is designed to give your doctor information about how the presence of the listed symptoms affects your daily life. Please fill in as many of the questions as possible and mark ONLY THE ANSWER THAT IS APPROXIMATE FOR YOU. Although more than one answer may apply to you, please check only the one that best represents your problem.

QUESTIONS, IN THIS CASE RELATING TO COVID-19.

Question I: Intensity of the sore throat (numerical scale from 0 to 10)

- I'm not in pain right now.
- The pain is very mild at this time
- The pain is moderate at this time
- The pain is strong right now
- The pain is very strong right now
- Right now the pain is the worst imaginable

Question II: Intensity of headache (numerical scale from 0 to 10)

- I'm not in pain right now.
- The pain is very mild at this time
- The pain is moderate at this time without prodromal

- The pain is strong right now
- The pain is very strong right now
- Right now the pain is the worst imaginable

Question III: Self-care (associated with headache, chest pain and odynophagia)

- I can take care of myself normally without increasing my pain
- I can take care of myself normally, but this increases my pain
- Taking care of me hurts so I have to do it slowly and carefully
- Although I need some help, I manage to get most of my care
- Every day I need help with most of my care
- I can't get dressed, I wash with difficulty and stay in bed

Question IV: Asthenia and adinamia

- I don't have asthenia or adinamia
- I can be active, but it makes me feel more tired
- Tiredness and lack of activity prevent me from living my daily life
- I get up strictly for what's necessary.
- I can't get up, I'm too tired

Question V: Fever

- I don't have a fever
- Non-quantified heat sensation
- Presence of fever
- Quantified fever of 38 ºC
- I can barely keep the improvement feeling with antipyretics.

Question VI: Cough

- I don't have a cough.
- Sometimes I have a cough
- Sometimes I have a dry cough
- I often have a dry cough
- I have a cough that limits my ability to maintain proper breathing

Question VII: Shortness of breath

- I don't have any trouble breathing
- It's a little hard for me to take a deep breath

- I can't take a deep breath and my chest hurts
- I'm having trouble breathing and I have severe pain in my chest

GUIDE FOR THE HEALTH PROFESSIONAL WHO WILL PERFORM THE INTERVENTION ABOUT THE INTERVENTION INSTRUMENTS

(Document only for the health professional performing the intervention)

1. The patient entering the intervention protocol has already been chosen as a possible candidate for the study, once he or she has already been selected by meeting the inclusion criteria and having none of the exclusion criteria.
2. The physician will proceed to explain very broadly the questions and concerns, the benefits and possible side effects that you will have with the use of chlorine dioxide, as well as the study and the type of protocol to be used. If the patient agrees to continue in the process, he or she will be given to read the project summary and be asked to sign the informed consent and confidentiality agreement.
3. The health professional must then take a medical history upon entry into the study by completing the Initial Medical History form.

a. Fill in each blank in the format with the required data.
b. Current symptoms: ask specifically about discomfort presented at the upper and lower airway level. If the patient refers to other symptoms, they should be written in the systems review segment. Ask about the time of evolution of the disease.
c. Background.
d. Review by systems: Describe if there are significant symptoms spontaneously reported by the patient that do not correspond to the airway region.
e. Physical Exam: Focus the physical exam on the cervical region, sites of both cervical and dorsal pain, explore neck angles of movement, flexibility and related pain. Explain what the Visual Analogical Scale (VAS) of pain is and ask the patient to fill in.
f. Diagnosis: Confirm diagnosis.
g. Conduct: At this stage the physician may verify whether or not the patient is eligible to be included in the study and describe whether the patient "enters the intervention protocol" or "the patient is not eligible to continue in the research protocol".

4. Once the initial protocol has been completed, the patient should be reminded to respond to the appointment each week (home or telemedicine in mild or moderate chaos) to verify compliance with the treatment and fill out some forms.

a. Fill in the patient's clinical progress by filling in the blanks.

b. In the assessment of subjective symptoms, explore the evolution of pain and functional limitation by allowing the patient to openly express what he or she is feeling without directing the question in order to obtain a certain response.
c. Explore also the compliance with the treatment on a daily basis, as well as those difficulties you have encountered to be able to fully comply with the protocol, unexpected reactions.
d. If the patient has fully complied with the protocol specifications, the conduct to be followed will describe "continuing with the protocol", but if not, the protocol will be terminated and the reasons for terminating the clinical trial will be explained.
e. Follow the same protocol every week for 4 weeks (depending on the complication picture, if the picture worsens you should consider adjusting or changing the protocol since you are not sure to what degree the patient is admitted.)

5. Diligence of the disability scale.

a. The patient will be given the disability scale so that he or she can fill it out (pending definition of which of the two scales is the simplest for the patient).
b. Hand in a questionnaire at the initial consultation, at the second check and at the fourth (last) check.

6. Data collection.

a. Once the intervention process has been completed, the health professional commits to handing over all the objective and subjective information to the research leader so that he or she can carry out the process of analyzing and discussing the results.