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Chlorine Dioxide as an Alternative Treatment for COVID-19

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Abstract

Frontline In December 2019, the first case of COVID-19 was reported in Wuhan, China and spread rapidly worldwide. This disease has caused millions of deaths, and to date, there is no fully effective drug against this disease. This study evaluated the negative and positive effects of Chlorine Dioxide (ClO_2) as an alternative therapy for the treatment of COVID-19. Information was collected from the medical records of 1,136 patients treated for COVID-19 with three different protocols of a ClO_2 aqueous solution at a mean dose of 1.41 mg/kg. The average time of the resolution of the symptoms was 4.84 days, and the complete treatment lasted 15.87 days. Furthermore, 6.78% of the patients presented mild and sporadic adverse reactions such as headache, dizziness, vomiting, diarrhea and nausea. No side effects endangered the health of the patients. Blood tests did not reveal any systemic abnormalities after ClO_2 consumption. Hepatic enzymes, glucose, total cholesterol, and triglycerides decreased to normal at the end of treatment. Without any complications, 99.03% of the patients were discharged. Our findings show that, when used at the appropriate concentration and dosage, ClO_2 as a solution effectively treats COVID-19 while also being safe for human consumption.

Keywords: Chlorine dioxide; COVID-19; Treatment, Pandemic; SARS-CoV-2

Introduction

The new disease reported at the end of 2019 (COVID-19), caused by the novel coronavirus SARS-COV-2, is mainly characterized by acute respiratory symptoms accompanied by fever, malaise, headache and, occasionally, digestive and nervous symptoms [1,2]. These symptoms are caused by excessive inflammatory responses [3,4] and coagulopathies due to endothelial damage caused by the SARS-CoV-2 Spike protein [5]. Since early 2020 when the World Health Organization declared it, the COVID-19 pandemic has severely affected most countries in terms of morbidity and mortality and in terms of the economic and social cost of the measures taken to curtail the pandemic. One of the main challenges posed by this disease has been finding effective medication to treat COVID-19 [6]. Chlorine Dioxide (ClO_2) is a soluble gas that is used in different countries to disinfect drinking water [7-9] due to its antimicrobial activity [10]. When both air and water are present, ClO_2 is distributed between the two phases in an equilibrium relationship determined by temperature and atmospheric pressure [11]. ClO_2 is known to denature tyrosine and tryptophan residues due to oxidation [10,12], and also has immune modulatory action as it inhibits the transcription of NF-kB [13,14]. In this context, it is possible to assume that ClO_2 can react with the SAR-CoV-2 spike protein (composed of 54 tyrosine residues, 12 tryptophan and 40 cysteine residues) and inactivate the virus [15]. In addition, by neutralizing reactive oxygen molecules and cytokines with ClO_2 [16,17], it is possible to control the excessive inflammation associated with severe COVID-19 [1]. Although cysteine, tyrosine, and tryptophan residues can also be found in human tissues, ClO_2 is much less toxic to humans or animals than to bacteria and viruses due to its size selectivity [16,18] and due to the content of antioxidants like glutathione in mammalian cells [19]. While ClO_2 has been categorized as a hazardous compound when used for other applications in other forms and dosages, due to a few, non-lethal, reported side effects [19], it is important to consider that most of these cases are clinical reports of intoxication with sodium chlorite ($NaClO_2$) or sodium hypochlorite (Bleach, NaClO), and not ClO_2. Regardless, health authorities have issued misleading information that lacks scientific evidence about the toxicity of this chemical compound, thus affecting the development and implementation of ClO_2 as a possible treatment for COVID-19.

To date, none of the drugs granted approval or emergency-authorization by the Food and Drug Administration (FDA) to treat COVID-19 has demonstrated high effectiveness in reducing symptoms, hospitalization, and death. That is why it is critical to evaluate new compounds that could reduce the impact of the current pandemic, such as Ivermectin [20,21]. The evidence on the safety and efficacy of ClO_2 is just beginning to be accepted in the medical community, although official regulatory institutions do not accept it yet. Here, we examined medical data from 1,136 COVID-19 patients who used ClO_2 solutions (CDS) as an alternative treatment. We assessed the side effects produced by consuming a CDS and its potential effectiveness in preventing severe disease and death.

Materials and Methods

Data collection: Baseline and clinical information

The clinical records of 1,136 positive/suspected COVID-19 patients (treated by the same physician) who voluntarily requested therapeutic management at home in Mexico were reviewed; these records ranged from May 30, 2020, to January 15, 2021. The inclusion criteria for the clinical records were as follows: 1) Patients that were diagnosed by molecular tests (Real-Time Reverse Transcriptase (RT)-PCR to SARS-CoV-2, antigen detection, specific Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibodies against SARS-CoV-2), computed assisted tomography of the lungs, chest radiographies, or a combination of clinical manifestations such as headache, fever, cough, throat pain, dyspnea, malaise, and fatigue [1,22]; 2) patients that were informed of the benefits and possible side effects of ClO_2 consumption before starting treatment and that they had signed the informed consent form.

Variables that were collected from the medical records were: sex, age, comorbidities, previous medications, date of onset, date of discharge or date of death, secondary effects posterior to a CDS consumption, millilitres of ClO_2 consumed per day ("ClO_2 per day"), partial oxygen

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saturation (SpO_2), oxygen supplementation (O_2 L/min) and COVID-19-like symptoms. Additionally, six variables were calculated for each patient from the data collected: namely, duration of COVID-19-like symptoms ("days of symptoms"), treatment duration ("duration of treatment"), millilitres of ClO_2 consumed throughout the treatment ("total ClO_2"), ClO_2 dose during treatment ("ClO_2 dose"), cost of ClO2 per day ("cost per day"), and the cost of ClO_2 during the whole treatment ("total cost"). Moreover, patients' disease severity (mild, moderate or severe) was determined according to the parameters established in the Coronavirus Disease (COVID-19) Treatment Guidelines [23] and the Interim algorithms for COVID-19 care of the Mexican Social Security Institute [24].

Therapeutic management: Chlorine dioxide solution

Two groups of patients were analyzed: 1) Multidrug patients: persons consuming drugs usually used for treating COVID-19 (Azytromicine, Dexamethasone, Ivermectin and Hydroxychloroquine) plus a CDS, and 2) Exclusively ClO_2 patients: people treated only with a CDS. All patients were treated at home by their relatives or nurses following the indications of the treating physician. Two types of oral aqueous solutions made with ClO_2 at 3000 ppm (3 mg/ml) were used for treating COVID-19: Protocol C (ClO_2 in 1000 ml of water, divided in ten intakes of 100 ml that were administered orally every hour, per day) and Protocol F (ClO_2 in 500 ml of water, divided in ten intakes of 50 ml that were administered orally every 15 minutes, 1 to 5 times a day). For intravenous use, Protocol Y (ClO_2 in 500 ml of 0.9% sterile saline solution plus 5 ml of 10% calcium gluconate and 10 ml of 7.5% sodium bicarbonate, administered at a mean rate of 70 ml per hour). All patients started treatment with Protocol F and, depending on the severity of the disease, were placed on Protocols C, F or Y until the symptoms were resolved. After the disappearance of symptoms, they continued with Protocol C as maintenance until the treatment ended (14-21 days depending on the severity of the disease).

The ClO_2 used by patients for oral use was made by oxidation of 28% sodium chlorite ($NaClO_2$) and 4% Hydrochloric Acid (HCl) as an activator [19]. For intravenous use, ClO_2 was produced with the membrane electrolysis method [9]. As per the instructions given to each patient, The ClO_2 solution was kept in a closed bottle, protected from direct sunlight and maintained below 11°C [19,25].

Overall physical status of patients

Symptoms reported voluntarily by the patients were used to calculate the incidence of each COVID-19-like symptom. Patients who died during the course of the disease were considered as non-successful cases of the treatment. Patients' clinical condition was evaluated for a subset of 57 patients (mainly severe COVID-19 cases) for which there was data on complete blood count and a metabolic biomarker panel test before and after treatment. As reference values, we used those reported for the healthy Mexican adult population [26,27].

Statistical analysis

An initial analysis of the data using descriptive statistics allowed attaining an overall view of the baseline information in the patients included in this study. Before proper data analysis, the distribution of each variable was examined. Variables deviated from a normal distribution, and there was evidence of heteroscedasticity; thus, we used Kruskal-Wallis tests to compare the values of ClO_2 per day, days of symptoms, duration of treatment, total ClO_2 administered, ClO_2 dose, cost per day, and total cost among disease severity (mild, moderate, and severe). Duration of symptoms and duration of treatment between comorbidities was also analysed using Kruskal-Wallis tests. The Wilcoxon rank-sum test was used to compare the days of symptoms and the duration of treatment between multidrug patients and exclusively ClO_2 patients, also to compare outcomes between blood tests (complete blood counts and metabolic panel test) before and after treatment. The effectiveness of the treatment was assessed by dividing the non-successful cases by the total number of patients. A linear regression model with logarithmic transformation was fitted to analyze the association of duration of treatment until the end of symptoms, with SpO_2 and O_2 L/min. Logistic regression was fitted to analyze the association of age, sex, and comorbidities with the severity of the disease. A p-value <0.05 was considered statistically significant. Continuous outcomes were measured as the mean difference and 95% Confidence Intervals (CI). To reduce information bias in this study, the treating physician was not involved in digitization or statistical analysis. All analyses were conducted using Rv.3.6.1 [28].

Ethical approval

The Ethics Committee of the Centro Médico Jurica waived the need for ethical approval and the need to obtain consent for the collection, analysis, and publication of retrospectively obtained data because it is a non-interventional study in which the information was captured from old medical records, maintaining the anonymity of each person and because all patients signed informed consent before treatment.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Results

Descriptive analysis of patients

A Primary information was collected from 1,136 patients (Table 1) in 30 states of Mexico, mainly Querétaro (53.07%), Mexico City (10.22%) and Jalisco (5.11%). Of the entire sample set, 487 (42.87%) patients were diagnosed as positive for COVID-19 by molecular test or diagnostic imaging; the remaining 649 patients (57.13%) were diagnosed due to the COVID-19-like symptoms. At the end of the treatment, 213 (18.75%) patients underwent an antibody-specific test for SARS-CoV-2, and 154 (72.30%) were positive (93 for IgG and 61 for IgM). Patients were classified according to the severity of the disease into three groups: mild, moderate, and severe based on symptoms and SpO_2.

The study comprised 551 (48.50%), men 525 (46.21%) women, and 60 (5.28%) for which there was no information regarding sex. Severity was associated with sex (x^2=16.89, df=2, P=0.0002); males were 1.8 times more likely than females to developing a severe case of COVID-19 (RR=1.8, 95% CI: 1.33-2.42, P<0.001).The mean age was 46.72 (range 1-93) years, and COVID-19 was most prevalent in age groups 40-49 and 50-60 years (19.01%, 21.04%; respectively). The risk of developing a severe disease was determined by age (x^2=82, dF=7, P<0.0001), increasing by 4% for each year of life (OR=1.04, 95% CI: 1.03-1.05, P<0.001). The risk of presenting a more serious disease was higher after 30 years old (Figures S1 and S2).

A total of 25 different symptoms were reported by patients, with the most frequent symptoms (Table S1) being headache (49.65%), malaise (44.45%), throat pain (37.41%), fever (22.89%), dry cough (17.34%), weakness (14.70%), thoracic pain (12.32%), dyspnea (9.5%), anosmia (9.15%) and ageusia (8.71%). The average duration of symptoms was 4.84 days (95% CI: 4.32-5.36 days) and was different depending on the severity of the disease (mild: 2.52 to 3.33 days, moderate: 7.89 to 12.21 days, and severe: 6.73 to 9.95 days; Kruskal-Wallis, x^2=234.89, df=2, P<0.001 (Table 2).

Figure 1: Descriptive information of the 1,136 patients in this study according COVID-19 severity.

	COVID-19 Severity					
	Mild		**Moderate**		**Severe**	
SpO_2 (%)	≥ 95		90-94		<90	
	n	%	n	%	n	%
Patients	776	68.31	109	9.59	251	22.09%
Sex	16	16	16	16	16	16
Male	351	45.23	49	44.95	151	60.16
Female	375	48.32	60	55.05	90	35.86
Other	50	6.44	0	0.00	10	3.98
Age	16	16	16	16	16	16
0-9	29	3.74	0	0.00	1	0.40
10-19	48	6.18	5	4.59	0	0.00
20-29	38	4.90	6	5.50	6	2.39
30-39	49	6.31	7	6.42	9	3.58
40-49	80	10.31	18	16.51	13	5.18
50-59	64	8.25	19	17.43	42	16.73
60-69	41	5.28	10	9.17	23	9.16
>70	31	3.99	12	11.01	33	13.15
No info	396	51.03	32	29.36	124	42.63

Figure 2: Variables calculated from the data collected of patients treated with a Chlorine Dioxide aqueous Solution against COVID-19.

	Disease Severity		
	Mild	**Moderate**	**Severe**
Days of symptoms	2.52-3.33[a]	7.89-12.21[bc]	6.73-9.95[bc]
Duration of treatment	14.86-15.69[a]	17.19-21.95[b]	14.41-17.73[c]
ClO_2 dose (mg/kg)	0.87-0.94[a]	1.16-1.33[b]	1.98-2.18[c]
ClO_2 per day (ml)	20.43-21.93[a]	27.17-30.97[b]	46.33-50.89[c]
Total ClO_2 (ml)	309.83-337.38[a]	518.77-619.19[b]	733.67-828.79[b]
Cost per day (USD)	1.02-1.10[a]	1.36-1.55[b]	2.32-2.54[c]
Total cost (USD)	15.49-16.87[a]	25.93-30.96[b]	36.68-41.44[b]

[a,b,c]Significance statistical by columns (disease severity); Values in the table for each variable are presented in 95% Confidence Interval.

Chlorine dioxide treatment

A total of 1,067 (93.96%) patients were discharged after 15.87 days (95% CI: 15.35-16.39 days) of treatment, 59 (5.19%) abandoned the treatment after 11.43 days (95% CI: 7.98-14.88 days), and 10 (0.93%) were hospitalized after 8.6 days (95% CI: 2.08-15.11 days) of treatment, where they died. The calculated effectiveness of the ClO_2 treatment was 99.07% (1,057 of 1,067 patients survive). Of the total of patients, 77 (6.78%) reported mild-sporadic secondary effects posterior to ClO_2 intake: headache (2.20%), diarrhea (1.58%), gastritis (1.32%), dizziness (1.14%), nausea (1.05%), vomit (0.44%), rash (0.44%), throat pain (0.26%), myalgia (0.18%), colitis (0.18%), tachycardia (0.09%), and chills (0.09%). Six hundred sixty-six patients (58.63%) were treated exclusively with a CDS, and 470 patients (41.37%) were treated against COVID-19 with five or more drugs in addition to the CDS (Table S2). The duration of symptoms in those patients treated solely with a CDS was less compared with those treated with various drugs (95% CI: 2.77-3.75 days vs. 7.33-8.97 days, respectively; Wilcoxon Rank Sum Test, $P<0.001$).

Depending on the severity of the disease and the evolution of the patients, different protocols were used during treatment. Nine hundred and sixty-one (84.59%) patients used Protocol C, 474 (41.72%) used Protocol F, and 42 (3.70%) used Protocol Y. Protocol C was used extensively in mild and moderate patients, Protocol F in severe patients, and Protocol Y was mostly used as a complementary treatment in severe cases (Figure 1). The mean daily dose used to treat COVID-19 patients was 1.41 mg/kg (95% CI: 0.97-1.85 mg/kg), corresponding to 32.95 ml per day (95% CI: 22.72-43.18 ml/day) for 15.87 days (95% CI: 15.35-16.39 days). However, for each protocol (C, F and Y), the dose and days of consumption varied according to the severity of the disease (Table 3). Overall, patients were treated with the following doses and duration: Protocol C (mean: 20.16 ml per day [95% CI: 18.94-21.37 ml/day] for 8.99 days [95% CI: 8.46-9.52 days]), Protocol F (mean: 39.13 ml per day [95% CI: 35.34-42.92 ml/day], 2.75 times per day [95% CI: 2.53-2.97 intakes/day] for 5.36 days [95% CI: 4.74-5.98 days]); and Protocol Y (mean: 89.92 ml per day [95% CI: 46.65-133.19 ml/day] for 1.77 days [95% CI: 1.39-2.14 days] in 2.12 infusions per day [95% CI: 1.64-2.60 infusions/day]). Nine patients gargled with a 0.015% aqueous solution made from 5 ml of ClO_2 in 100 ml of water in case of throat pain or nasal congestion.

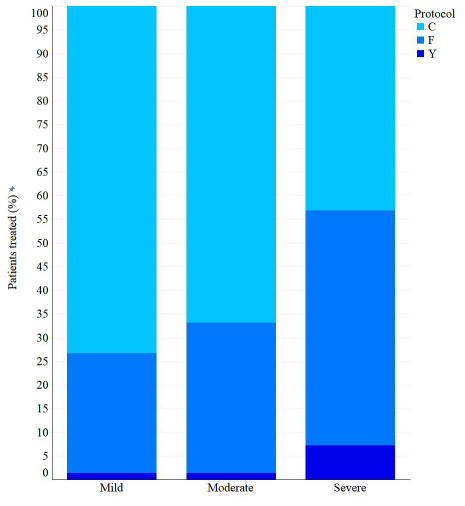

Figure 1: Use of ClO_2 protocols depending on the COVID-19 severity.

Figure 3: Dosage and days of consumption according disease severity and protocol (C, F and Y) in patients treated with a Chlorine Dioxide aqueous Solution against COVID-19.

Protocol	Disease Severity	n	%	Dose (mg/kg)	Dose (ml)	Days of consumption
C	Mild	701	72.94	0.65-0.76	15.22-17.67	9.63-10.81
	Moderate	99	10.30	1.11-1.50	26.00-34.90	6.51-10.21
	Severe	161	16.75	1.16-1.52	27.01-35.46	4.93-7.49
F	Mild	242	51.05	0.80-1.14	18.72-26.50	6.58-8.46
	Moderate	47	9.92	1.39-2.31	32.45-53.91	2.80-6.42
	Severe	185	39.03	2.28-2.97	53.15-69.37	3.39-5.21
Y	Mild	13	30.95	1.10-4.12	25.79-96.10	1.20-2.45
	Moderate	2	4.76	1.40-5.05	32.70-117.90	0.10-3.25
	Severe	27	64.28	3.58-5.40	83.45-126.35	1.27-2.24

There were differences in the duration of treatment (Kruskal-Wallis, x^2=30.42, df=2, P<0.001), ClO_2 dose (Kruskal-Wallis, x^2=116.62, df=2, P<0.001), and ClO_2 per day (Kruskal-Wallis, x^2=72.20, df=2, P<0.001) among patients with mild, moderate or severe COVID-19 (Table 3). The average ClO_2 consumed by patients throughout the treatment was 557.94 ml (95% CI: 390.19-725.66), and it was different in each severity (mild: 309.83-337.38 ml, moderate: 518.77-619.19 ml, and severe: 733.67-828.79 ml; Kruskal-Wallis, x^2=52.05, df=2, P<0.001). The estimated mean duration of symptoms is 2.82 (95% CI: 1.16, 4.47, p<0.001) days less for each mg/kg of ClO_2, adjusting for severity.

Overall physical well-being

Patients began the treatment with a mean SpO_2 of 86.05% (95% CI: 85.12-87.17%), increasing the blood oxygen each day of treatment. In total, 126 patients (101/251 [40.24%] with severe symptoms, 21/109 [19.27%] with moderate symptoms and 4/776 [0.51%] with mild symptoms) used supplementary oxygen (mean: 5.77 Liters per minute [95% CI: 5.18-6.36 L/min] for 4.32 days [95% CI: 3.37-5.27 days]). Between days 7-8 after the start of treatment, 90% of the patients reported an increase in SpO_2 above 90% and a week later above 95%, at a rate of SpO_2=3.58*ln(duration of treatment) (Figure 2a). The days to reach 90% SpO_2 did not differ between patients that received supplemental oxygen and those that did not (95% CI: 7.53-9.47 days, P=1.00); however, it took almost five days less for patients with supplementary oxygen to have a SpO_2 of 95% compared to those who did not use it (95% CI: 12.53-14.47 days vs. 18.52-20.48 days, P=0.004). Oxygen supplementation decreased at a rate of -2.45*ln (duration of treatment) (Figure 2b). Furthermore, the duration and amount of oxygen administered differed according to severity (Kruskal-Wallis, x^2=9.6382, df=2, P=0.008; x^2=16.89, df=2, P=0.002; respectively).

All complete blood count parameters were within normal ranges before and after treatment with ClO_2. All patients, for which blood metabolites were available, started treatment with elevated levels of ferritin, C-Reactive protein, lactic dehydrogenase, alaline aminotransferase, gamma-glutamyl transferase, glucose, total cholesterol, and triglycerides. After the ClO_2 consumption, most of these parameters decreased to normal physiological values. The exceptions were serum concentration of ferritin, C-reactive protein, and lactic dehydrogenase, which decreased but did not attain normal levels during the duration of the study (Table 4).

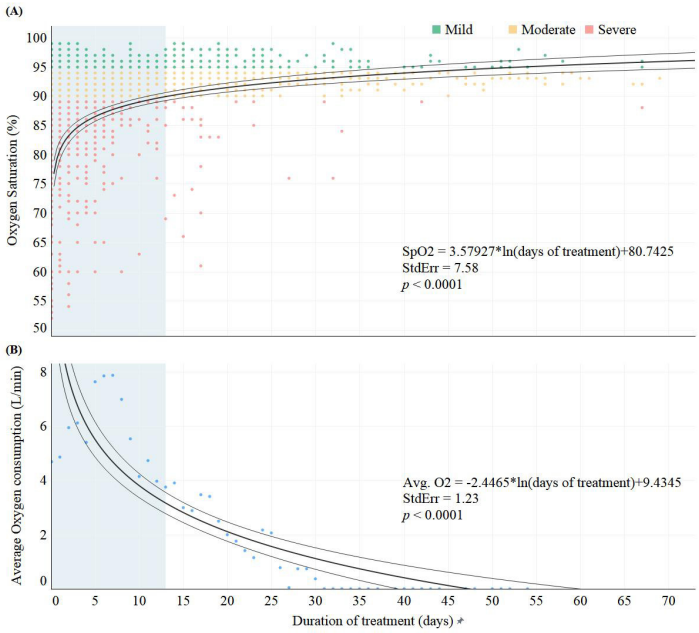

Figure 2: Linear regression model. Association of duration of treatment with a) Oxygen saturation and b) Average oxygen consumption; in patients treated with a Chlorine Dioxide aqueous Solution against COVID-19.

Figure 4: Blood parameters analyzed before and after the treatment against COVID-19 with a chlorine dioxide aqueous solution (CDS).

Blood parameter	Before				After				p-value	Reference values
		Mean ± SD				Mean ± SD			α=0.05	
RBC (10^6/μL)		4.70	±	0.76		4.73	±	0.59	0.880	4.39-6.10
Hemoglobine (gr/dL)		13.97	±	2.29		14.24	±	1.56	0.950	13.80-18.50
Hematocrit (%)		42.49	±	5.81		42.92	±	4.44	0.950	35.40-49.40
MCV (fL)		90.83	±	5.66		90.93	±	5.68	0.680	84.40-100
MCH (pg)		30.37	±	2.36		30.48	±	2.56	0.630	27.10-33.5
MCHC (gr/dL)		33.37	±	1.36		33.12	±	1.56	0.500	31.60-34.80
Platelets (10^3)		266.91	±	107.73		328.11	±	336.99	0.950	147-384
MPV (fL)		9.72	±	2.05		9.88	±	1.53	0.870	9.60-13.40
WBC (10^3)		8.08	±	3.89		6.93	±	2.50	0.350	3.84-9.79
Neutrophils (%)		66.84	±	14.79		62.54	±	15.37	0.250	39.60-76.10
Lymphocytes (%)		24.67	±	13.38		26.99	±	12.42	0.460	15.50-48.60
Monocytes (%)		5.80	±	3.08		6.91	±	3.57	0.360	3.40-10.10
Eosinophils (%)		1.39	±	1.75		1.39	±	1.54	0.740	0.30-4.50
Basophils (%)		0.28	±	0.34		0.60	±	1.71	0.500	0.00-1.60
Ferritin (ng/mL)	↑	554.65	±	907.49	↑	398.54	±	298.94	0.481	15-300
C Reactive Protein (mg/L)	↑	30.13	±	72.11	↑	16.05	±	29.96	0.561	<1
Lactic Dehydrogenase (UI/L)	↑	273.79	±	125.12	↑	242.62	±	105.24	0.400	139-205
Aspartate aminotransferase (UI/L)		30.61	±	19.93		19.16	±	7.39	0.185	12-35
Alaline aminotransferase (UI/L)	↑	75.41	±	117.01		25.88	±	14.29	0.571	9-47
Gamma-glutamyl Transferase (UI/L)	↑	135.19	±	124.10		35.22	±	29.97	0.007*	13-82
Sodium (mmol/L)		136.89	±	5.25		136.94	±	7.37	0.865	136-145
Chloride (mmol/L)		101.00	±	4.60		103.11	±	8.25	0.128	102-112
Potassium (mmol/L)		4.44	±	0.42		4.37	±	0.64	0.955	3.70-5.20
Glucose (mg/dL)	↑	152.51	±	113.20		98.53	±	27.26	0.099	<100
Urea (mg/dL)		37.57	±	22.47		32.00	±	14.00	0.324	19-58
Blood Urea Nitrogen (mg/dL)		19.20	±	10.45		14.76	±	3.77	0.122	9-27
Creatinine (mg/dL)		1.11	±	0.47		0.95	±	0.24	0.452	0.77-1.32
Cholesterol total (mg/dL)	↑	213.14	±	141.12		168.11	±	38.30	0.460	<200
Triglycerids (mg/dL)	↑	388.08	±	690.06		133.40	±	66.02	0.224	<150
Total Bilirubin (mg/dL)		0.61	±	0.25		0.76	±	0.28	0.272	0.22-1.04
Direct Bilirubin (mg/dL)		0.25	±	0.09		0.37	±	0.26	0.646	0.12-0.42
Indirect Bilirubin (mg/dL)		0.35	±	0.20		0.39	±	0.24	0.672	0.09-0.65
Alkaline phosphatase (UI/L)		73.12	±	26.56		72.37	±	20.23	0.941	40-130
Total Protein (g/dL)		6.74	±	0.49		7.43	±	0.50	0.028*	6.50-8.10
Seric Albumin (g/dL)		4.15	±	0.48		4.49	±	0.59	0.253	3.50-5.20

Discussion

This retrospective study collected information from 1,136 people who used a CDS as treatment against COVID-19. We found that ClO_2 is a safe and effective treatment for COVID-19 patients, which, regardless of severity, reduced symptoms in 99.03% of the cases. Comorbidities, age and sex were associated with the severity of COVID-19 presented by the patients (Appendix 1). Because the effect of ClO_2 depends not only on its concentration but also on the contact time [19], patients were treated with a CDS using different protocols (varies in dosage and consumption intervals) depending on the severity of the illness, at a mean dose of 1.41 mg/kg per day (range 0.67 to 5.40 mg/kg/day). Furthermore, nine patients reported gargling with a 0.015% CDS. It has been proposed that the mouth and oropharynx can be disinfected by regularly rinsing with a microbial solution such as povidone-iodine [29] or a CDS [17,19,30] to significantly reduce the viral load in the mouth and upper respiratory tract. The treatment doses used in this retrospective study were within the safety limits reported for human use [7,31,32]. In addition, the dosages used were below the "Lowest Observed Adverse Effect Level" (LOAEL); being eight times lower than the doses at which adverse effects occur and at least 30 times below lethal dose 50 (LD50=94 mg/kg; World Health Organization, 2002).

Oral consumption of ClO_2 in concentrations of 5 mg/L for 12 weeks has been shown to have no harmful effects in humans [7,31]. It was recently shown that at a dose of 0.6 mg/kg, ClO_2 has prophylactic potential against COVID-19 without causing moderate or severe negative effects in the majority of the patients; in those who reported side effects (1.12%) the symptoms were mild and sporadic [33,34]. Moreover, it has been demonstrated that ClO_2 is a size-selective antimicrobial, and in proper concentrations, it can be used in animals and humans because of its inability to penetrate the tissues [16,18,19]. Compared to other medication, COVID-19 patients that consumed ClO_2 had shorter recovery time than that reported for other treatments. It is important to note that the duration of symptoms in patients treated exclusively with ClO_2 was less than half compared to multidrug patients (3.26 days Vs. 8.15 days, respectively). Simultaneous use of various medications has been linked to increased mortality among male COVID-19 patients and increased the rate of acute kidney injury and adverse drug reactions [35]. The design of clinical trials in which a detailed follow-up is carried out is recommended to evaluate the effect of Chlorine Dioxide on recovery time and its interactions with other medications.

In this study, 6.78% reported mild transitory secondary effects posterior to the CDS intake, including headache, diarrhea, gastritis, and dizziness; similar side effects to what was reported in a previous study [34]. In those 77 patients, the dose was reduced by half immediately after the onset of symptoms. Subsequently, a gradual increase was made until reaching the treatment dose. After this adjustment, no patient reported adverse reactions again. The patients treated with intravenous CDS did not report any side effects. Our results show that ClO_2 in the used dosage is safe and does not have severe side effects, even if used in higher doses. Blood tests also corroborate the absence of adverse effects since most measured parameters were found in normal ranges after treatment. Ferritin, C-reactive protein, and lactic dehydrogenase were above standard limits. However, these analytes were lower compared to the onset of the disease. Also, hepatic enzymes, glucose, total cholesterol, and triglycerides were lower at the end of treatment.

The percentage of patients treated with a CDS who were discharged (99.03%) was higher than that reported in other studies (Ranged from 85% to 92.3%; Beigel 2020; Heras 2021; Rajter 2021). In that sense, our retrospective study warrants conducting prospective cohort or controlled randomized double-blind trials to properly compare the effect of ClO_2 with that of other drugs. Due to limited published evidence on ClO_2 as an alternative treatment in humans, conducting such studies in a controlled setup is urgent, relevant and necessary, particularly given that in our study the mean duration of symptoms in ClO_2-treated patients was 4.84 days; nearly 9 days less than the national average [36-38], and more than 20 days less than the mean recovery time of patients in India, a country with similar socio-economic conditions and demographic age-structure to Mexico [39]. Furthermore, 92.01% of the patients in our study were cured before day 10 of treatment, while in the study mentioned above only 4% were cured in the same time. Recovery time was also shorter than patients in Belgium, Hong Kong, and the United Kingdom, where they remained hospitalized for 5.9 days, 4.41 days and 5.14 days, respectively [40,41]; In Canada and Brazil, recovery time is close to 14 days, while in Japan the average period is less than 14 days [38]. A large meta-analysis (which included 25 countries) revealed that the recovery time in COVID-19 patients ranged from 5 to 29 days [6], implying that the use of ClO_2 could greatly reduce the duration of symptoms in COIVD-19 patients, even in those with severe symptoms.

Patients began the treatment with an average SpO_2 of 86.05%, a condition known as severe hypoxia [23]; 129 patients were supplemented with a mean of 5.77 Liters per minute of oxygen for 4.32 days. After one week of ClO_2 consumption, 90% of the patients had moderate hypoxia (SpO_2 between 90% and 94%), and two weeks later, patients did not have hypoxia. Interestingly, the 90% SpO_2 threshold was reached by patients with and without oxygen supplementation in the first seven days of treatment. However, severe patients without oxygen supplementation took almost five days longer to have a SpO_2 above 95% than those who did not use it. From the first intake of the CDS there was an increase in blood oxygen levels in patients which improves the physiological response and reduces the patient's anxiety to hypoxia [42]; nevertheless, oxygen supplementation was essential, mainly in patients with severe disease, as it helped speed up the recovery of sick people. Additional studies must be performed to understand the mechanism by which ClO_2 improves blood oxygen concentration.

A major benefit of ClO_2 treatment is that patients can be treated at home without being hospitalized. This prevents the occurrence of bacterial or fungal infections common in the ICU (average 40.7%), which have been significantly associated with death (OR 2.7, 95% CI: 1.2-5.9, P=0.015) [43-58]. Treatment at home increases the survival probabilities of patients, and additionally, avoiding the collapse of health systems, particularly in low and middle-income countries [6], such as Mexico. The treatment of COVID-19 generates significant expenses in public hospitals and is very expensive in private hospitals, so a large proportion of the population cannot access private care.

Limitations

While exciting, we are aware that our study has some limitations. The first is that it is a retrospective observational study, which means that conclusive evidence of the effectiveness of ClO_2 cannot be established because we could only use information from the patients' medical records and had no control over the study variables. Second, there is potential misinformation bias because relatives or patients provide the initial and clinical information. Third, it was impossible to establish with certainty that all patients had COVID-19 because diagnostic tests had not been conducted for all patients. However, 72.30% of the patients who underwent antibody testing had developed IgG or IgM against SAR-CoV-2. Fourth, because the studies used here to compare our results were obtained from populations with different ethnic, age, health, and socio-economic status, and were collected under different conditions, discussions should be interpreted carefully. Fifth, due to a lack of extra information, the interpretation of our findings could be at least partly confounded (e.g., differences in eating habits, correctly following the treatment and quality of ClO_2). These and other variables must be considered in future studies.

Conclusion

This is the first study to examine the adverse effects and the benefits of a Chlorine Dioxide solution as an alternative treatment for COVID-19. Side effects from consuming Chlorine Dioxide are rare, 6.78% of the patients reported secondary effects, and these were mild, transitory and did not endanger the patient's life. The blood tests revealed no systemic changes following Chlorine Dioxide consumption; furthermore, several initially elevated blood parameters decreased and went normal after Chlorine Dioxide treatment. From the first intake, Chlorine Dioxide improves the concentration of oxygen in the blood, which improves the physiological response. Patients treated only with Chlorine Dioxide had fewer days with symptoms compared to those treated with several drugs. 99.07% of the treated patients were discharged without any health problems. Our findings indicate that when used correctly, Chlorine Dioxide as a solution is safe for human consumption at the appropriate concentration and dosage. This study demonstrates a high level of safety and efficacy of Chlorine Dioxide in the treatment of COVID-19. These findings justify conducting RCTs to assess its efficacy against SARS-CoV-2. Such trial could pave the way for new research into the potential use of new compounds to solve current and future public health issues, which is after all, the goal of the World Health Organization and other health authorities.

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Supplementary

Appendix

Short discussion about the characteristics of patients in this study

Frontline Of all patients, 396 (34.86%) reported comorbidities, predominantly hypertension (20.95%), diabetes (16.41%), obesity (13.67%) and several diseases that cause respiratory insufficiency (bronchitis, asthma and chronic pneumonia; 9.84%). Other diseases like hypothyroidism, renal failure, chronic gastritis, heart diseases and cancer were reported in less than 3%. Comorbidities were not related to sex (x2=0.0076, df=2, P=0.9307) but were associated with severity, particularly hypertensive patients were 2.4 [95% CI-1.09, 5.31], p=0.029] more likely to be moderate, and 3.8 [95% CI-2.20, 6.74], p<0.001] more likely to be severe. Also, patients with diabetes and those with respiratory insufficiency were more likely to have a severe case of COVID19 (2.07 [95% CI-1.11, 3.85, p=0.021] and 3.31 [95% CI- 1.62, 6.76, p=0.001], respectively). It has been systematically reported that COVID19 patients with comorbidities are more prone to developing a severe disease [44,45]. Hypertensive patients were 2.4 and 3.8 more likely to develop a moderate or severe condition, respectively. The number of comorbid conditions is constantly increasing with age [46,47], explaining the observed increase in disease severity in older patients.

This study reveals that men were 1.8 times more likely to develop be a severe case of COVID19 and almost twice time more risk of dying than females, similar to that reported in other studies [48-51]. It is well known that gender is not a risk factor for developing COVID19 [50,52,53]; however, the differences in the expression of the Angiotensin-Converting Enzyme 2 (ACE2) receptor and Trans Membrane Serine Protease 2 (TMPRSS2) between males and females may explain the disparities in COVID19 severity and fatality [44,54,55]. The SARS-CoV-2 virus infects people of all ages [56,57]. We identify that two groups of people are at higher risk for developing COVID19: 40-49 years followed by 50-59 years, while the lowest incidence was in the 0-9-year-old group (Figures S1 and S2). Compared with 0 to 9-year-old, the probability of developing a severe disease is 8.71 times higher after the age of 30 and 42.84 times after 70 year old. The risk of presenting a severe COVID19 is higher in the elderly due to other conditions such as cardiovascular disease [49]. In addition, the effects of ageing on the immune system of older people make the immune response not as effective as in young people [58].

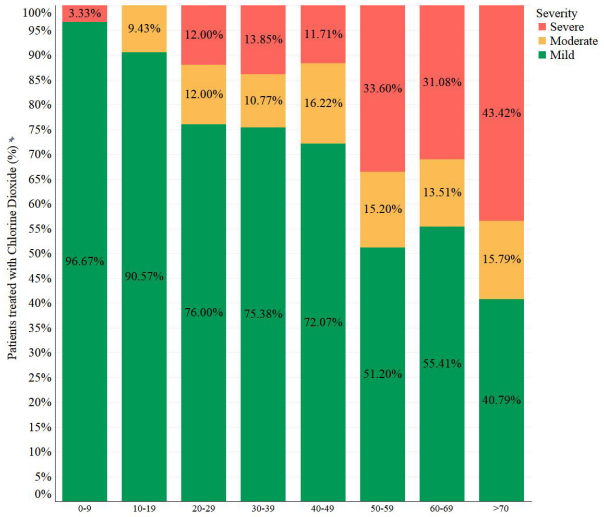
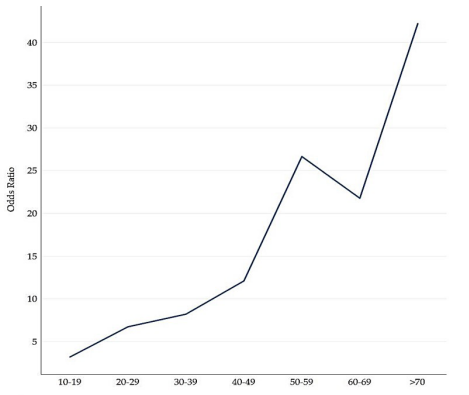


Figure S1: Percentage of the different types of severity (mild, moderate and severe) according to the age of the patients.



Age	Odds Ratio	Std. Err.	z	P > |z|	95% CI
10-19	3.198821	3.585866	1.04	0.3	0.36-28.79
20-29	6.731386	7.240875	1.77	0.076	0.82-55.43
30-39	8.207699	8.70729	1.98	0.047	1.03-65.65
40-49	12.09652	12.55278	2.4	0.016	1.58-92.46
50-59	26.65171	27.48383	3.18	0.001	3.53-201.14
60-69	21.77339	22.75088	2.95	0.003	2.81-168.79
>70	42.20759	43.84209	3.6	0	5.51-323.26

Figure S2: Percentage of the different types of severity (mild, moderate and severe) according to the age of the patients.

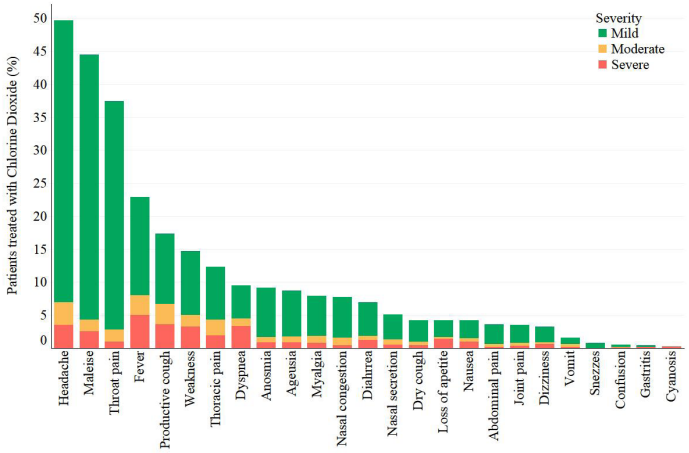


Figure S3: Principal covid19-like symptoms presented by the patients in this study.

	COVID19 Severity					
	Mild		Severe		Moderate	
Symptoms	**n**	**%**	**n**	**%**	**n**	**%**
Headache	485	62.50	39	35.78	40	15.94
Malaise	456	58.76	20	18.35	29	11.55
Throat pain	393	50.64	21	19.27	11	4.38
Fever	169	21.78	34	31.19	57	22.71
Productive cough	121	15.59	35	32.11	41	16.33
Weakness	110	14.18	20	18.35	37	14.74
Thoracic pain	91	11.73	27	24.77	22	8.76
Anosmia	85	10.95	9	8.26	10	3.98
Ageusia	79	10.18	10	9.17	10	3.98
Nasal congestion	70	9.02	13	11.93	5	1.99
Myalgia	69	8.89	12	11.01	9	3.59
Diarrhea	58	7.47	7	6.42	14	5.58
Dyspnea	57	7.35	13	11.93	38	15.14
Nasal secretion	43	5.54	9	8.26	6	2.39
Dry cough	37	4.77	6	5.50	5	1.99
Abdominal pain	34	4.38	5	4.59	2	0.80
Joint pain	31	3.99	5	4.59	4	1.59
Nausea	31	3.99	6	5.50	11	4.38
Loss of apetite	29	3.74	3	2.75	16	6.37
Dizziness	27	3.48	3	2.75	7	2.79
Vomit	11	1.42	5	4.59	2	0.80
Sneezzes	9	1.16	0	0.00	0	0.00
Confusion	4	0.52	1	0.92	1	0.40
Gastritis	3	0.39	0	0.00	2	0.80
Cyanosis	0	0.00	0	0.00	3	1.20

Table S1: Symptoms reported by patients with COVID19 according severity of the illness.

Medication	**n**	**%**
Exclusively ClO_2	666	58.63
Multidrug	470	41.37
Antibiotic	241	51.06
Azithromycin	119	25.32
Analgesic	202	42.98
Paracetamol	169	35.96
Corticosteroid	181	38.51
Dexamethasone	116	24.68
NSAID	115	24.47
Ibuprofen	76	16.17
Antiparasitic	104	22.13
Ivermectin	102	21.70
Anticoagulant	82	17.45
Enoxaparin sodium	30	6.38
Antiplalets	80	17.02
Acetylsalicylic acid	53	11.28
Antimalaric	9	1.91
Hydroxychloroquine	7	1.49

Table S2: Descriptive information about main drugs consumed in the two groups of patients analyzed.