A retrospective observational study of Chlorine Dioxide effectiveness to covid19-like symptoms prophylaxis in relatives living with COVID19 patients

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Abstract

To date, there is no effective prophylactic agent to prevent COVID-19. However, the development of symptoms similar to covid19 could be prevented with an aqueous solution of chlorine dioxide (ClO_2). This retrospective study evaluated the effectiveness of an aqueous solution of ClO_2 (CDS) as a prophylactic agent in 1,163 family members living with positive/suspected COVID19 patients. Prophylactic treatment consisted of 0.0003% chlorine dioxide solution (CDS) orally for at least fourteen days. Family members in whom no reports of the development of covid19-like symptoms were found in the medical history were considered successful cases. The efficacy of CDS in preventing covid19-like symptoms was 90.4% (1,051 of 1,163 relatives did not report any symptoms). The comorbidities, sex and severity of the illness of the sick patient did not contribute to the development of symptoms similar to covid19 ($P = 0.092$, $P = 0.351$ and $P = 0.574$, respectively). However, older relatives were more likely to develop covid19-like symptoms (ORa = 4.22, $P = 0.002$). There was no evidence of alterations in blood parameters or in the QTc interval in relatives who consumed CDS. The recent findings regarding Chlorine Dioxide justify designing clinical trials to assess its efficacy for preventing SARS-CoV-2 infection.

Introduction

The coronavirus disease of 2019 (COVID19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a pathology transmitted directly or indirectly through aerosols and whose significant symptoms include mild to severe pneumonia.[1,2]

It has been shown that a high percentage of infections (mean 16.6%) occurs mainly in family nuclei,[3,4] mostly because houses are closed environments that make it hard to maintain social distance, there is a reduced use of personal protective equipment, and it is not possible to completely isolate a sick family member.[4] Attributable to the global problems and the rapid spread of this disease, there are research groups dedicated to testing drugs that contribute to prevent and improve the prognosis of the disease (e.g. Ivermectin,[5] Vitamin D,[6] and Hydroxychloroquine[7]). However, the global crisis continues, and it is necessary to test other substances that could effectively prevent the spread of SARS-CoV-2 and develop COVID19.

Aqueous solutions of Chlorine Dioxide (ClO_2) have antimicrobial potential due to the denaturation of the viral capsids' specific proteins.[8] For example, ClO_2 was shown to have the ability to inactivate Influenza Virus caused by oxidating tryptophan 153 residue in the receptor-binding site.[9] Considering SARS-CoV-2 spike protein composition (12 tryptophan, 54 tyrosine, and 40 cysteine residues), it can be assumed that ClO_2 also has the potential to inactivate this virus.[10] There are a lot of unique properties that make ClO_2 an ideal, non-specific antimicrobial: It has been demonstrated that ClO_2 is a size-selective antimicrobial

agent that can neutralize microorganisms rapidly.[11] Furthermore, it can be used in animals and humans without adverse effects in proper concentrations because of its incapability to penetrate the tissues.[8,11]

The current COVID-19 situation has shown the importance of having antiviral compounds available to act quickly. Nowadays, there is no drug (prophylactic or therapeutic) approved by the Food and Drug Administration (FDA) against COVID-19, and that had demonstrated high effectiveness.[12–14] For this reason, it is essential to investigate new compounds that can help to reduce the impact of the current pandemic. This study analyzed clinical information from healthy people who consumed an aqueous solution of ClO_2 as a prophylactic agent when living with positive/suspected COVID19 patients. We evaluated the effectiveness of ClO_2 in preventing the development of covid19-like symptoms.

Materials And Methods

Baseline and clinical information

This retrospective study was carried out using clinical records of 1,163 healthy subjects (without covid19-like symptoms), from now on referred to as relatives, who live with positive/suspected COVID19 patients (sick patients) in different cities (mainly Queretaro) in Mexico; from May 30, 2020, to January 15, 2021. The inclusion criteria were as follows: 1) relatives living in the same house with a sick patient diagnosed by Real-Time Reverse Transcriptase (RT)-PCR Viral Nucleic Acid Test to SARS-CoV-2[15] and complementary tests like antigen detection test,[16] serology test for specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies against SARS-CoV-2,[17] computed tomography,[18] chest radiography,[19] or clinical manifestations such as fever, cough, dyspnea, malaise, and fatigue;[1] 2) relatives whose voluntarily requested prophylactic management at home and that, after were informed of the benefits and possible secondary effects of ClO_2 consumption, signed informed consent. Baseline (sex, age, and comorbidities) and clinical (date of prophylactic management request, partial oxygen saturation [SpO_2] and covid19-like symptoms) information were collected from medical records. Moreover, the sick patient's disease severity status (mild, moderate or severe) was included.

Prophylactic Management: Chlorine Dioxide Solution

The production of ClO_2 is not governed by any regulations in Mexico yet. Chemist-pharmacists or professional Chemical-Engineers made the ClO_2 by oxidation of sodium chlorite ($NaClO_2$) using hydrochloric acid (HCl) as an activator, ensuring the product's concentration and safety. Being a chemical compound, exposure to light and temperature above 11 °C changes its composition.[8] Relatives were informed to keep the CDS in the refrigerator (between 4-10 °C) and stored in closed amber jars. Relatives began the oral prophylactic management in daily doses (0.3 mg/kg) of 0.0003% Chlorine Dioxide

aqueous Solution (CDS, 10 ml of ClO_2 at 3000 ppm in 1000 ml of water), divided into ten intakes of 100 ml/hour. This dose had been reported as adequate for human use;[20–22] additionally, is ten times below the “No Observed Adverse Effect Level” (NOAEL), almost 20 times below the “Lowest Observed Adverse Effect Level” (LOAEL), and nearly 300 times below the lethal dose 50 (LD_{50}).[10,23] Due to Mexico’s regulations during the pandemic, relatives stayed at home for at least 14 days or offset symptoms of the sick patient. Medical records show a daily follow-up for a minimum of 20 days of each relative.

Covid19-like symptoms Incidence and tracking overall physical well-being

Reported symptoms by relatives were used to calculated de incidence of covid19-like symptoms during the clinical follow-up. Relatives who reported any symptom were considered as a non-successful case of prophylactic management. To evaluate general physical well-being during prophylactic administration, 27 relatives that had a complete blood count (red blood cells, white blood cells, and platelets) and a metabolic panel test (blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, glucose, total protein, albumin, sodium, potassium, chloride, bilirubin, cholesterol, and triglycerides) before (at least three months) and after CDS consumption, were included. Typical values from the general Mexican adult population were used as reference values.[24,25] Additionally, data of 50 electrocardiograms (ECG) performed to the relatives after CDS consumption were collected to assess the QTc interval (manually measured), using the Bazzet QT correction formula.[26]

Statistical analysis

Descriptive statistics were used to have an overall view of the basic features of the baseline information. Age was categorized in five groups: 1-12, 13-19, 20-34, 35-64, >64 years. The incidence of covid19-like symptoms was calculated by dividing the number of relatives with any symptom by the total number of relatives in prophylactic management. We fitted a logistic regression model to analyze the association of age, sex, family size, comorbidities, and the sick patient’s disease severity with the symptoms reported. Multicollinearity was analyzed and discarded. Adjusted odds ratio (aOR) and its 95% confidence intervals are presented. Risk Ratio (RR) was calculated to compare the prophylactic effectiveness of CDS with current prophylactic drugs, and we use an Ivermectin meta-analysis data [5], which has presented the highest effectiveness so far. Wilcoxon rank-sum tests were performed to compare outcomes between blood tests (complete blood counts and metabolic panel test) before and after CDS consumption. To compare the QTc interval of relatives that consume CDS against COVID19 patients treated with Hydroxychloroquine, we performed an Analysis of Variance (ANOVA). A *p-value* <0.05 was considered statistically significant. To reduce information bias in this study, the treating physician was not involved in digitization or statistical analysis. All analyses were conducted using STATA v.15.1.[27]

Ethical approval

For this type of study (retrospective), formal consent is not required[28]. Each subject included in this study signed informed consent before starting the prophylactic management.

Data availability

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

Results

Background of study participants

Information was collected from 1,163 relatives belonging to 554 family nuclei, in 13 Mexico's states, mainly from Queretaro (52.25%) and Mexico City (12.61%). The sample comprised 567 women (48.75%), 442 men (38.00%) and 154 without information (13.24%), with a mean at the onset of 40.37 (range 2-89) years. One hundred eighty-one relatives reported concomitant diseases, predominantly hypertension (17.39%), diabetes (15.76%) and respiratory diseases (bronchitis, asthma and chronic pneumonia; 7.06%). Other conditions like cancer, renal failure, hypothyroidism, heart diseases and arthritis were reported in less than 1%.

The calculated incidence of covid19-like symptoms was 9.63%. In total, 112 relatives (67 women [59.82%], 41 men [36.61%], and four without information [3.57%]) reported at least one sporadic-mild covid19-like symptom between 4-5 days after the request for prophylactic management with CDS (Table 1).

TABLE 1. Covid19-lik symptoms (mild, moderate and severe) that were reported by relatives

	n	%
Relatives that reported covid19-like symptoms		
Total (non-success cases)	112	9.63
Female	67	59.82
Male	41	36.61
No informed sex	4	3.57
Covid19-like symptom (sporadic-mild)		
Headache	36	3.10
Throat pain	24	2.06
Cough	23	1.98
Fever	22	1.89
Malaise	14	1.20
Diarrhea	12	1.03
Dizziness	11	0.95
Abdominal Pain	10	0.86
Fatigue	10	0.86
Nasal Congestion	10	0.86
Nasal Secretion	10	0.86
Nausea	9	0.77
Chest Pain	8	0.69
Dyspnea	7	0.60
Ageusia	4	0.34
Vomit	4	0.34
Anosmia	3	0.26
Gastritis	3	0.26
Appetite Loss	3	0.26
Joint Pain	3	0.26
Myalgia	1	0.09
Disorientation	1	0.09

Sneeze	1	0.09
Relatives that reported moderate covid19-like symptoms and suspended CDS		
Total	2	0.17
Covid19-like symptom (moderate)		
Headache	1	0.08
Gastritis	1	0.08
Relatives that reported severe covid19-like symptoms		
Total	0	0
Relatives that reported secondary effects after CDS consumption		
Total	13	1.12

Thirteen relatives (1.12%) reported secondary effects (diarrhea, headaches, gastritis, nausea, dizziness or throat pain) posterior to CDS intake, and two of the non-success cases (1.78%) suspended the prophylactic management due to moderate headaches and gastritis. In those 112 ill relatives, the CDS consumption dosage was increased immediately after the symptom onset was reported to a therapeutic dose (0.6 mg/kg) until symptoms' resolution (between two and four days). None of the relatives who presented covid19-like symptoms died.

The reported comorbidities were not statistically significant for covid19-like symptoms development (P = 0.092). There was no statistical evidence that relative's sex and sick patient's disease severity contributed independently and were associated with the presence of symptoms (P = 0.351 and P = 0.574). However, both variables were added to the model to adjust for confounding. Adjusting for sex and sick patient's diseases severity, relatives of all age categories had higher odds of present covid19-like symptoms compared to younger patients, but only statistically significant in those of 35-64 years (aOR = 4.22, 95%CI: 1.71, 10.41, P = 0.002) and more than 64 years (aOR = 3.64, 95%CI: 1.30, 10.16, P = 0.014). When comparing the prophylactic effectiveness of Ivermectin (average 86%[5]) against CDS, we observed that relatives who consume CDS are 31% less likely to develop covid19-like symptoms (RR = 0.69, 95% CI = 0.54-0.89, P = 0.003).

No parameters analyzed of the complete blood count (Table 2) were outside the average values before or after. The Mean Cell Volume (MCV) was different (Wilcoxon rank-sum test, $P < 0.02$), being greater after prophylactic management with CDS, although it was not outside the normal upper limit. In the metabolic test (Table 2), blood glucose was above expected values before and after (mean, 102.65 mg/dL and 103.79 mg/dL, respectively). Nevertheless, there were no differences between both periods, neither in this metabolite nor in the others evaluated. The mean QTc was 400.08 ms (95% CI: 394.34 ms, 405.76 ms), and no ECG showed prolonged QTc (Fig. 1). Although, one male's ECG showed a QTc = 442 ms. QTc interval of relatives was significantly lower (ANOVA, $P < 0.001$) compared to the QTc of patients treated with conventional COVID19 treatment (Hydroxychloroquine and Azithromycin).[29,30]

TABLE 2. Complete blood count and metabolic parameters of 27 relatives before and after the CDS prophylactic management to prevent covid19-like symptoms development

Parameter	BEFORE CDS			AFTER CDS			*p-value*	Reference values
	mean±SD			mean±SD			α = 0.05	
Red blood cells (10^6/µL)	5.02	±	0.59	4.69	±	0.89	0.22	4.39 - 6.10
Hemoglobine (gr/dL)	17.44	±	7.26	14.11	±	2.69	0.13	13.80 - 18.50
Hematocrit (%)	45.59	±	12.80	42.73	±	7.85	0.36	35.40 - 49.40
MCV (fL)	80.05	±	22.56	90.36	±	8.23	0.02*	84.40 - 100.00
MCH (pg)	36.82	±	17.50	30.97	±	2.40	0.45	27.10 - 33.5
MCHC (gr/dL)	30.79	±	5.44	32.11	±	1.45	0.84	31.60 - 34.80
Platelets (10^3)	264.21	±	59.78	239.62	±	39.11	0.27	147 - 384
MPV (fL)	9.47	±	1.75	9.60	±	1.39	0.73	9.60 - 13.40
White blood cells (10^3)	6.93	±	1.73	6.94	±	1.81	0.79	3.84 - 9.79
Neutrophils (%)	62.31	±	7.29	61.05	±	7.77	0.39	39.60 - 76.10
Lymphocytes (%)	29.42	±	6.37	29.51	±	8.48	0.73	15.50 - 48.60
Monocytes (%)	5.43	±	2.13	5.97	±	1.81	0.43	3.40 - 10.10
Eosinophils (%)	2.21	±	2.43	1.88	±	1.70	0.91	0.30 - 4.50
Basophils (%)	0.56	±	0.56	0.41	±	0.48	0.35	0.00 - 1.60
Lactic Dehydrogenase (UI/L)	147.43	±	24.30	194.95	±	72.57	0.22	139 - 205
Aspartate aminotransferase (UI/L)	26.21	±	8.43	27.41	±	9.47	0.34	12 - 35
Alaline aminotransferase (UI/L)	31.08	±	13.27	26.72	±	13.09	0.22	9 - 47
Gamma-glutamyl Transferase (UI/L)	33.77	±	21.88	43.18	±	29.18	0.28	13- 82

Sodium (mmol/L)	139.24	±	1.56	138.78	±	1.72	0.79	136 - 145
Chloride (mmol/L)	104.00	±	3.78	103.94	±	4.11	0.69	102 - 112
Potassium (mmol/L)	4.37	±	0.38	4.48	±	0.48	0.44	3.70 - 5.20
Glucose (mg/dL)	102.65	±	15.76	103.79	±	20.40	0.73	< 100
Urea (mg/dL)	34.57	±	16.91	45.18	±	47.43	0.16	19 - 58
Blood Urea Nitrogen (mg/dL)	19.19	±	8.61	18.87	±	15.54	0.04	9 - 27
Creatinine (mg/dL)	0.90	±	0.20	0.90	±	0.23	0.74	0.77 - 1.32
Cholesterol total (mg/dL)	191.25	±	66.91	174.09	±	58.41	0.76	< 200
Triglycerids (mg/dL)	151.78	±	75.02	141.71	±	63.80	0.28	< 150
Total Bilirubin (mg/dL)	0.64	±	0.39	0.73	±	0.36	1	0.22 - 1.04
Direct Bilirubin (mg/dL)	0.16	±	0.13	0.31	±	0.20	0.64	0.12- 0.42
Indirect Bilirubin (mg/dL)	0.48	±	0.37	0.42	±	0.32	1	0.09 - 0.65
Alkaline phosphatase (UI/L)	79.94	±	30.42	78.55	±	29.11	0.48	40 - 130
Total Protein (g/dL)	7.03	±	0.66	6.99	±	1.14	0.26	6.50- 8.10
Seric Albumin (g/dL)	4.14	±	0.53	4.19	±	0.85	0.71	3.50 - 5.20

Abbreviations: MCV, mean cell volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelets volume; SD, standard deviation.
*Statistical significance

Discussion

This retrospective study collected information from 1,163 relatives who lived with sick patients and who consumed CDS prophylactically. In this study, the incidence of the covid19-like symptoms was 9.63%, which is lower than the estimated overall household secondary attack rate reported (16.6%, 95% CI: 14.0%, 19.3%).[4] It is clear that people commonly take protective measures in public places such as washing their hands and wearing face masks, but neglect personal protection at home because they consider it a “safe” place, which has generated a high incidence of infection among relatives.[4] This is why researchers are making a great effort to find an effective prophylactic alternative against COVID19.

A few studies had proof of the COVID19 prophylaxis effect. Vitamin D supplementation during the COVID19 pandemic has been suggested as a preventive measure due to its beneficial effect on the immune system.[31] However, the effectiveness was only about 40%.[6] On the other hand, Ivermectin has been studied extensively to prove its prophylactic efficiency against SARS-CoV-2 infection.[32–34] The results of a meta-analysis were used to compare the effectiveness of CDS against Ivermectin. We show that CDS prophylactic effectiveness was slightly higher than the reported for Ivermectin (90.4% vs 86%, respectively). Despite using similar exposure and outcome variables, the conditions and design of the compared studies were different. Due to the few available evidence of ClO_2/CDS in humans, we consider it necessary to carry out randomized control trials or prospective cohorts to compare the effect of these two substances in analogous groups.

One of the most studied drugs proposed as prophylactic is Hydroxychloroquine.[7,35] However, it has not shown statistically significant hazard reduction (HR =0.72, 95% CI: 0.44, 1.16; P = 0.18).[7] Furthermore, hematological alterations, liver[36] and kidney[37] function changes, and prolonged QTc interval[29,30,38] have been reported using this drug. Contrary to what we report in the present study, blood tests did not reveal any systemic alteration after CDS consumption, similar to previously reported.[21,22] Regarding cardiac function, the use of Hydroxychloroquine combined with azithromycin in COVID19 patients, induces a longer QTc interval (459 ± 36 ms[29] and 463 ± 32 ms[30]). In this study, only one relative presented the QTc interval (442 ms) in the borderline (431-450 ms), a limit established as usual for 1% of the population.[38] In the rest of the relatives, the QTc interval was within normal ranges during prophylactic management with CDS. COVID19 infection has been associated with prolonged QTc, regardless of various clinical factors related to QTc prolongation. It has been reported that the risk of having prolonged QTc, increases in patients treated with Hydroxychloroquine and Azithromycin, regardless of the presence or absence of SARS-CoV-2 infection,[39] and could lead to a high risk of malignant arrhythmia.[38] We did not find alterations in the QTc interval in healthy individuals who consumed CDS prophylactically. The design of clinical trials in which a detailed follow-up is carried out is recommended to evaluate any possible effect of Chlorine Dioxide on the QTc interval.

Concerning the risk associated with sex, women are the primary caregivers of other household members, which could put them at risk in the event of a sick familiar.[40] It has been reported a higher risk of infection for COVID19 in females than in males (RR= 1.66, 95% CI: 1.39, 2.00) being the wife the most affected compared with a non-spouse family member because of intimacy or direct contact (e.g. sleeping in the same room) with her husband.[3] However, in this study, no evidence was found that women have a higher risk of infection than men. Regarding age, we did not find statistical evidence on covid19-like symptoms development in younger age groups. Relatives older than 35 were at higher risk, being those with the highest probability of developing COVID19 worldwide.[3,4]

Even though comorbidities such as diabetes and hypertension have been recognized as risk factors for COVID19 development,[3] we did not find statistical differences in the present study. This may be due to incorrect clinical data or due to CDS prophylactic effect. However, this remains to be clarified in additional specific-designed studies.

This study shows that non-success cases started with covid19-like symptoms between 4-5 days after the request for prophylactic management. This is consistent with previous studies where the highest transmissibility rate is at the end of the first week of infection.[41] Non-success cases reported sporadic and mild symptoms, mainly: headache, throat pain, cough, fever, malaise, diarrhea, dizziness, abdominal pain, and fatigue, which have already been reported as COVID19 symptoms in other studies.[1,4] Nonetheless, without a confirmatory COVID19 diagnostic, it is impossible to ensure that the relatives were infected with SARS-CoV-2.

ClO_2 in other application forms and dosage have been categorized as a hazard compound due to a few reported side effects. Additionally, some reported cases have been due to sodium hypochlorite ($NaClO_2$) instead of ClO_2. In general, social networks have been flooded with misinformation through unjustified news about ClO_2. Even health authorities have issued erroneous information (without scientific basis) about this compound in different media. While some of this information may be harmless, another portion may be dangerous and may affect the development and implementation of possible treatments,[42] such as this compound. Our results show that CDS in the used dosage is safe and does not have severe side effects, even if used in higher doses (none of the non-success cases reported secondary effects after dose increase). This also is supported since no blood parameter was out of the normal range after 14 days of prophylactic management. In this study, we only report thirteen relatives with secondary effects, which disappear after dosage adjustment.

Limitations

Our study has some limitations. The first of all is that this is a retrospective observational study, which means that conclusive evidence of the effectiveness of the CDS cannot be established because we could only use the information available in the medical records of the relatives, and we could not have any control over the variables. Second, misinformation bias exists since baseline and clinical information is reported by relatives. Third, many relatives did not undergo diagnostic or confirmatory tests for SARS-Cov-2 due to the economic situation and the high cost of these in Mexico. Therefore, it was impossible to establish with certainty that the relatives who reported any covid19-like symptoms had COVID19. Fourth,

the studies' results used to compare our results are obtained from different populations and were collected under other conditions, so these comparisons should be interpreted with caution. Fifth, the overall interpretation of the findings may be restrained due to the lack of additional information (e.g. personal care, eating habits, proximity and relationship with patients, etc.). These and other variables should be taken into account in future studies.

Conclusion

This is the first study to try to determine the effectiveness of a Chlorine Dioxide aqueous Solution in preventing the development of symptoms similar to COVID19. We demonstrated a 90.4% effectiveness of preventing the outbreak of covid19-like symptoms under the given conditions. The blood test did not reveal any systemic alteration after CDS consumption. Our results suggest that the correct use of ClO2 as a solution is safe for human consumption in an adequate concentration and dosage. Hence, we consider that the recent findings regarding Chlorine Dioxide justify implementing RCTs to evaluate its efficacy against SARS-CoV-2. Furthermore, this may open up a new field of research on the potential use of new compounds to solve current and future public health problems. Finally, we invite more research groups to consider this solution for future studies.

Declarations

The Ethics Committee of the Centro Medico 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.

Author Disclosure Statement

No competing financial interests exist.

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Figures

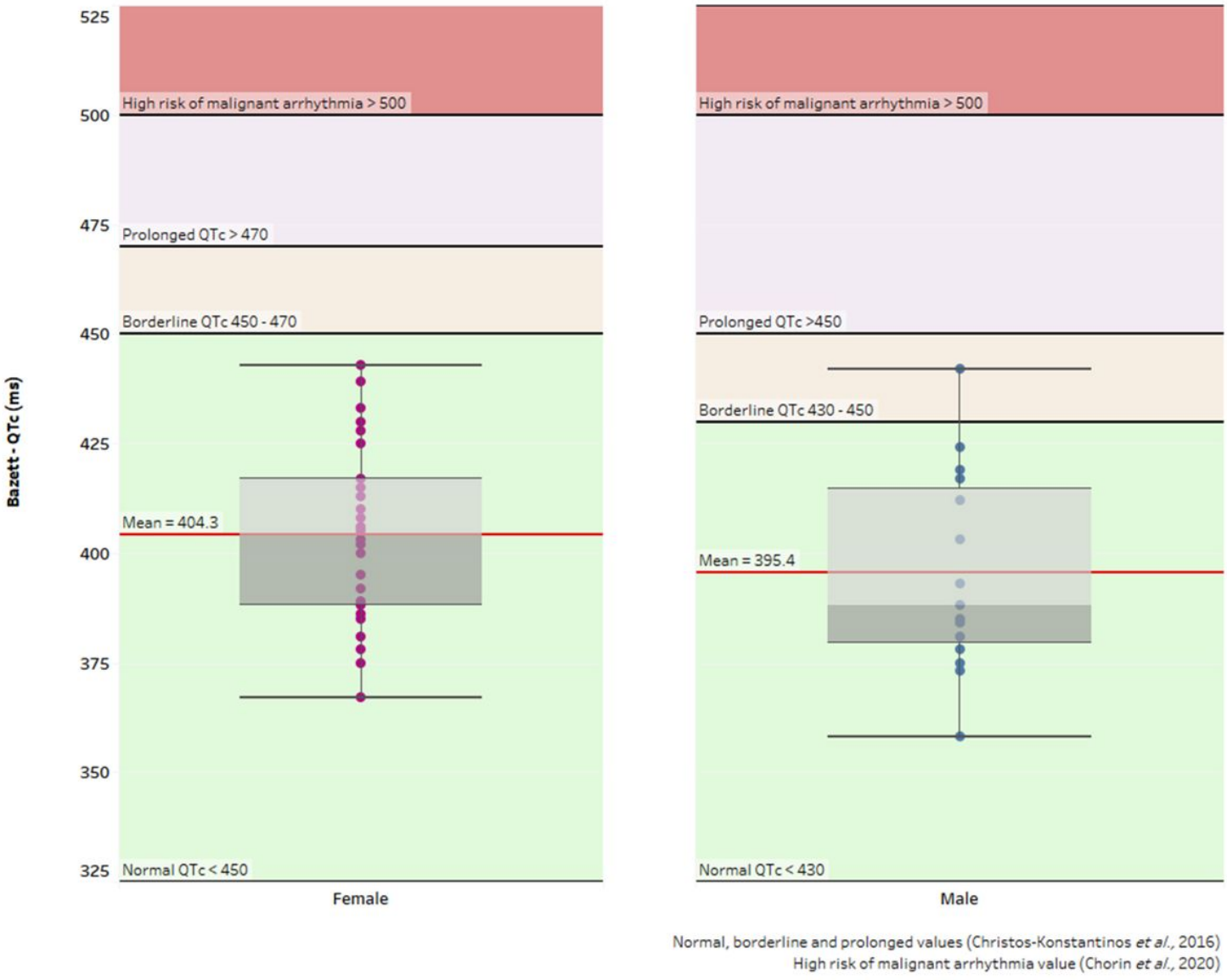

Figure 1

QTc interval (ms) of 50 relatives (females and males) after prophylactic management with CDS to prevent covid19-like symptoms development.