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Hydrogen Peroxide as an Adjuvant Therapy for COVID-19: A Case Series from Mexico

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Introduction

The Declaration of Helsinki states in Article 37 that when there are no known or effective interventions a physician can use unproven methods, if it is their judgement that these methods could save lives, restore health and alleviate suffering, and provided they've been advised by experts and have informed consent from the patient. Furthermore, the Declaration states that it is their duty to record their intervention and publish new information to the public in case it merits further investigation.

Between May 11th and July 19th, 2020, during the first wave of the Coronavirus disease 2019 (COVID-19) pandemic in Mexico, our group treated 23 ambulatory patients diagnosed with COVID-19, using an unproven intervention consisting of an adjuvant therapy of hydrogen peroxide (H_2O_2), administered PO, by mouth rinses (oral gargles), and inhalation routes. We hypothesized that hydrogen peroxide, an antiseptic agent, could play a pivotal role in reducing the severity and duration of the illness in patients, and in preventing transmission among caregivers and close contacts. This Brief Report describes our main findings, aimed at gaining wider dissemination and sparks the interest of the scientific community.

A recently published literature review on hydrogen peroxide and viral infections, pertaining to the current COVID-19 pandemic, has identified invitro and invivo observational studies that indicate that oropharyngeal washing with hydrogen peroxide may enhance the host's local innate responses to viral infections and help protect against SARS-CoV-2 [1]. Applying hydrogen peroxide to the epithelial cells of the nose, mouth, and throat, has been described as "extremely effective" against viruses, including SARS-CoV-2 [2]. Since the start of the century it has been used in dentistry, alone or combined with other salts [3,4]; it is possible that pre-procedural mouth rinses containing oxidative agents such as 1% H_2O_2 could be effective for reducing the salivary viral load of SARS-CoV-2 and other viruses when in close contact with infectious individuals [3-5]. Even after a 2 year follow up there were scarce side effects reported on soft tissue using 1%-1.5% H_2O_2 as a daily rinse, making it a potential prophylactic agent in vulnerable populations. Nasal washes with peroxide twice a day have also been proposed for the disinfection of COVID-19 from the oral and nasal cavities and it has been proposed that "the effectiveness of hydrogen peroxide based therapeutic regimen would be verifiable by a significant reduction in the rate of hospitalizations and respiratory complications in patients positive to SARS-CoV-2" [1,2]. Elsewhere, the nebulization of hydrogen peroxide has also been reported to have a clear viricidal effect on different viral strains [6]. Successful nebulization with oxidizing solutions for the symptomatic treatment of airway infections has also been recently reported for COVID-19 cases [7].

The effects of hydrogen peroxide on immune system response have been described and could explain the therapeutic mechanism of the molecule. Among these are: the stimulation of monocytes and T-Helper cells; the production of interferon gamma; the role in immunoregulation; the inhibition of B cell activity; and its role in up-regulating the inflammatory response [1,8]. All are plausible biological mechanisms that could be at play in improving clinical outcomes on COVID-19 patients. Furthermore, recent invitro studies have found that 3% H_2O_2 effectively inactivated many virus types, where "coronaviruses and influenza viruses were the most sensitive" [4]. Despite possible analogies being made between hydrogen peroxide and chlorine dioxide, given that both are strong oxidizing agents commonly used for antiseptic purposes in the medical field, these substances are entirely different. Only hydrogen

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peroxide is known to be safe for oral, vaporized or intravenous administration. Chlorine dioxide has serious side effects and an untested efficacy in humans. Unlike hydrogen peroxide's metabolism, when the molecule decomposes it can be harmful to humans: the product Cl2 can either react with organic matter to form trihalomethane (a carcinogen) or form chloroxy anions like ClO2- and ClO3- [9]. The U.S. Food and Drug Administration have also received reports of severe side effects after its oral ingestion such as methemoglobinemia, QT prolongation, dehydration, acute liver failure and hemolytic anemia [10]. Results

Methods

A concentrated solution of tri-distilled or ultra-pure hydrogen peroxide at a concentration of 35% was used. The PO dosage was a 0.06% hydrogen peroxide solution, administered every 8 hours, for up to 16 days depending on the clinical course of the disease. Our enteral supplementation of hydrogen peroxide at 0.06% was based on the 2 fold assumption that (1) the SARS-CoV-2 attacks the gastrointestinal system of many patients and (2) the gastrointestinal (GI) system may become a modulator for circulating oxygen in the body. The GI tract is about 40% more efficient at assimilating oxygen than the lungs, thus the oral administration of hydrogen peroxide is a very effective way of getting therapeutic oxygen into the body [11]. The nebulized dosage was 0.2% hydrogen peroxide in purified or distilled water, nebulized for 5 to 15 minutes as tolerated, every 4 to 8 hours for up to 16 days. Caregivers and family members in close contact with patients who consented to a prophylactic regimen were prescribed with a 1.5% dilution of hydrogen peroxide mixed in clean tap water, gargling in the oral cavity and then the back of the throat for 30 seconds each, 2 or 3 times a day. All patient consultations were provided in an ambulatory care setting by telemedicine, using traditional telephone calls and WhatsApp messaging.

The clinical response was assessed and graded according to disease progression, evaluated based on clinical criteria: First improvement (or feeling of improvement endpoint) was defined as the positive change that each of the patients refers to the clinical monitor during the daily follow up interview. Clinical monitors were trained to recognize this positive change when the patient, during the interview, in addition to spontaneously reporting a feeling of improvement, reported a decrease in the following symptoms: headache, asthenia/adynamic, general discomfort and dyspnea/shortness of breath. Completely better or clinical remission of symptoms endpoint was defined as the total or almost total absence of any of the following symptoms during the daily follow up interview for each case: headache, asthenia/adynamic, general discomfort and dyspnea/shortness of breath. This second endpoint entails the clinical remission of symptoms and therefore allows the clinical monitor to declare the end of the acute period of the disease.

Results

23 patients ranging from 8 months to 70 years of age with a mean age of 39 years were included. 6 patients were female (26%) and 17 were male (74%). 3 patients were active smokers and 2 were passive smokers. 7 patients (30%) were overweight and 2 (9%) were obese; body measurements weren't available for the rest of the patients. The major comorbidities included systemic arterial hypertension (22%), diabetes mellitus (17%), and gastroesophageal reflux (17%). 7 of the 23 patients were responsible for their own care. Of the other 16 patients, there were a total of 28 caregivers or people in close contact with the COVID-19 patients (living within the same household).

The most common clinical symptoms were cough, headache, and weakness (asthenia/adynamia), reported by 87, 83, and 83% of patients respectively. Malaise, myalgias or arthralgias, and chills were the second group of most common symptoms; followed by fatigue, fever, dyspnea, and GI symptoms. Diagnostic and imaging studies performed on the 23 patients. Twelve patients were tested for COVID-19 with RT-PCR and 92% were positive. 14 had imaging (chest X-Ray or CT scan) studies. 2 patients presented deteriorating conditions and were hospitalized. None of the 23 patients died.

Antipyretics and non-steroidal anti-inflammatory drugs were used as each clinical case required. Concomitant medications for comorbidities were also continued as managed by their usual health care providers. Additional medications used by patients included antivirals (7 patients), antibiotics, corticosteroids, vitamin supplements, and in 2 cases hydroxychloroquine. 22 patients (96%) used oral hydrogen peroxide and 17 (74%) used hydrogen peroxide nebulization therapy.

In the case of inhalation therapy, most patients reported immediate relief of respiratory symptoms and documented improved oxygenation as measured by pulse oximeter. In addition to the reduction in duration (compared to clinical progress and outcomes for Mexican patients), we observed a possible reduction in the severity of the disease, and a perceived reduction in symptoms by most patients. In the case of oral administration, a frequent complaint was that it caused nausea, sometimes dizziness and vomiting. Incremental dosing was instructed in such cases.

The Figure illustrates the disease course for the 23 consecutive patients, ranked by length of the SARS-CoV-2 disease duration. The vertical axis is the patient number and the horizontal axis is the days since clinical onset of the disease. Patients are ordered by duration of disease and not by consecutive appearance. Patient #1 was the first to enter the series on May 1st, and patient 23 is the last to enter the series on June 20th. Patient #23 is the last to exit the series on July 20th. On average, most patients felt the first improvements within the first two and a half days since starting the experimental treatment. Patients were "mostly better" at an average of 6.2 days, and patients were "completely better" in an average of 9.5 days. Most frequently patients reported feeling either mostly better within 2 or 11 days and feeling completely better within 3 and 15 days.

The Figure displays in shades of grey the presence or absence of clinical symptoms as well as the start and end of the hydrogen peroxide treatment. It also illustrates additional clinical events of relevance. Key milestones for the evolution of each case are also presented and include: presence or absence of clinical symptoms (gray shading), start and end of hydrogen peroxide treatment (arrows), day of first improvement (triangle) and day of feeling "completely better" (circle), hospitalization days (letter H), confirmatory RT-PCR exam (dot), positive serum antibody exam (diamond), and confirmatory CT Scan or X-ray (plus sign). Overall, most patients had a disease that lasted between 15 and 30 days and 3 patients had a disease that lasted more than 31 days. The lengthiest duration was a patient with 53 day clinical history, of which the first thirty are not shown in the graphic. They were prior to the patient's hospitalization. The shortest duration was 10 days in patient #8. In 4 patients the duration was 14 days or less. Patient #11 came to us after being in the hospital for 5 days and was admitted considering his first day when he received the positive result of the RT-PCR result. The duration of his disease was 53 days. The start of his disease was much longer than is reflected in the Figure 1.

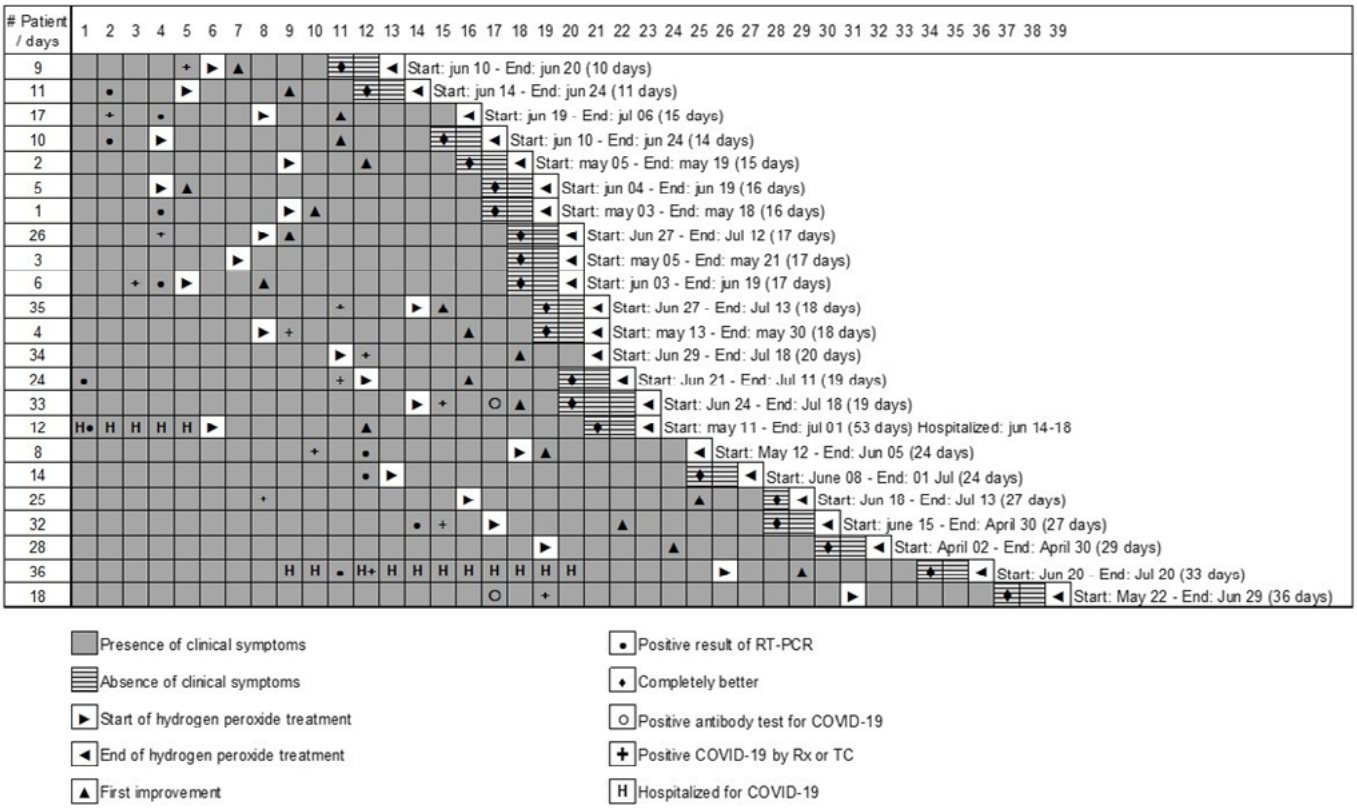

Figure 1. Timeline and disease course of twenty-three consecutive COVID-19 patients with H_2O_2 management.

Figure illustrates the start of H_2O_2 therapy (Forward arrow) and the day of first improvement (triangle). In ten patients "first improvement" was reported by in the first day of treatment with hydrogen peroxide. In many of these cases, the improvements were noted since the first applications of the hydrogen peroxide. On average, the duration of disease starting from the application of hydrogen peroxide to recovery was of 8 days. The minimum days for complete recovery were 4 and the maximum were 14. All patients except number 13, had a complete recovery.

In the case of inhalation therapy, most patients reported immediate relief of respiratory symptoms and documented improved oxygenation as measured by their oxygen saturation by pulse oximeter. In addition to the reduction in the duration (compared to clinical progress and outcomes for Mexican patients), we observed a possible reduction in the severity of the disease, and a perceived reduction in symptoms by most patients. In the case of oral administration, a frequent complaint was that it caused nausea, sometimes dizziness and vomiting, and was not easily tolerated. Incremental dosing was instructed: slowly increasing the concentration of H_2O_2, until the desired dosage was tolerated. With gradual increments, tolerance and acceptance of enteral administration was achieved. As for the caregivers and close family members who accompanied patients, at follow up 1 month after the disease had receded, none who used prophylactic mouth rinsing and gargles with a 1.5% dilution of hydrogen peroxide mixed in clean tap water, twice or 3 times daily reported acquiring the disease [12,13].

Conclusion

We have described the use of 3 concomitant treatment modalities with hydrogen peroxide which have proven to be safe and well tolerated among a group of 23 consecutive COVID-19 patients, and which we believe reduced the duration of the illness by half, considering the natural history of disease. For over 4 decades now, proponents of oral therapies with hydrogen peroxide have existed in the CAM and integrative medicine circles. CAM treatments such as this one, using hydrogen peroxide, may have played a significant role in the rapidly improving clinical characteristics and health outcomes observed among our consecutive patients, and thus deserve further investigation. Among the caregivers, given the possible therapeutic and prophylactic value that has been recently reported in the medical literature, coupled with what we observed in this small number of patients, caregivers, and close contacts, we believe that the molecule merits further scientific scrutiny. Research is needed to determine the full potential of complementary and alternative therapies such as these with hydrogen peroxide, for use in prophylaxis and as adjutant treatment against COVID-19. We strongly encourage the rapid development of randomized controlled trials to study the benefits of oral and nasal lavages, enteral and inhalation administrations of hydrogen peroxide against SARS-CoV-2, in singular use or as therapeutic combinations.

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