ORIGINAL RESEARCH

Prospective Randomized Double-blind Placebo-controlled Study to Assess the Effects of Nano-ozonized Hydrogen Peroxide Nebulization on Results of RTPCR for Novel Coronavirus thus Infectivity and Clinical Course among Moderately Sick COVID-19 Patients

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Abstract

Importance: Given the high mortality and cost of health care, especially in isolation settings, the idea of using nebulized hydrogen peroxide may play a very significant role in inactivation of coronavirus, thus reducing the infectivity period leading to reduced requirement of isolation and improving morbidity and mortality in people suffering with coronavirus disease-2019 (COVID-2019).

Aim and objective: Objective of this study was to determine the efficiency of nebulized hydrogen peroxide (H_2O_2) in reducing the viral load and disease severity of patients suffering with COVID-19.

Design: Double-blinded randomized control trial. HOPE in COVID-19 study.

Setting: Tertiary care COVID hospital (single center).

Participants: Moderate sick COVID-19-positive patients were included in the study after they qualified the inclusion criteria.

Intervention: Patients were nebulized using 1 mL of ozonized H_2O_2 after diluting with 4 mL of normal saline three times a day for 5 days. The control group was nebulized with normal saline only.

Main outcome: Outcome was assessed for reduction in oxygen requirement (number of days on oxygen), symptoms resolution (dyspnea, cough, and fever), and number of days it took to be RT-PCR negative for COVID-19.

Results: The early data from trial showed promising trends toward a better outcome. The study showed that in the case group who were nebulized with hydrogen peroxide resulted in better outcome in terms of parameters assessed in the study and the differences from the control group were statistically significant ($p \leq 0.001$, CI 95%). Outcome in the form of mortality (odds ratio 0.29, 95% CI 0.02–3.14, $p = 0.31$, $z = 1.007$) was statistically insignificant. The number needed to treat for our study was 10.

Keywords: COVID-19, Hydrogen peroxide, Nebulization.

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Introduction

Coronavirus disease-2019 (COVID-2019) is an infectious respiratory disease caused by a newly discovered single-stranded (positive-sense) RNA virus. This pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak was first identified in Wuhan, China, in the month of December 2019 and was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020. The spread of this COVID-19 pandemic is quick and has resulted in total global deaths of more than 847,040 and 63,000 in India at the time of preparation of this study.[1,2]

For diseases like COVID-19, where natural history of disease is evolving and still under evaluation, and only methods for controlling spread being social distancing and isolation, it becomes important if some methods are identified that can reduce the viral load, infectivity, and poorer outcomes in this ongoing pandemic of COVID-19. Also, managing a patient in isolation practices is cumbersome and costly, so if infectivity is reduced, the overall cost of managing patients can be reduced thus reducing burden on already

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stressed system. Coronavirus has been identified to spread via respiratory secretions as shed from infected individuals, even when the infection is asymptomatic. COVID-19-positive patients can have variable infectivity period ranging from 8 to 10 days, rarely more.[3] There have been instances of patient remaining positive for prolonged time beyond 3 weeks too in our institutional experience as well.

We intend to demonstrate via this study that severity of infection and cost of health care can be reduced in COVID-19 pandemic using very simple solution like nebulized hydrogen peroxide (H_2O_2); also its use can be extended to controlling other respiratory viruses as well.

The COVID-19 is an enveloped virus, meaning that it has an outer envelope composed of proteins and fatty material (lipid). Due to this outer layer, the enveloped viruses are relatively easy to eliminate by disinfectants, compared to nonenveloped viruses.[4] Besides type, also the virus size influences the difficulty in virus elimination: smaller viruses are more difficult to eliminate. This is shown in Flowchart 1.[5] It shows, for example, that the coronavirus is relatively easy to inactivate (rank 4 of 10, where 10 mean "very difficult to eliminate").

Virus Inactivation with H_2O_2

A 3–6% concentration of H_2O_2 is very effective in inactivating certain human viral pathogens.[6–11] It has been reported that H_2O_2 is also effective in inactivation of bacteria.[12–16] The disinfectant mode of action of H_2O_2 has been shown to result from the formation of a free hydroxyl radical that causes oxidation of membrane lipids, nucleic acids, and other cell components.[17] Recent utilization of H_2O_2 disinfection in the poultry industry has shown promising results against bacteria, yeasts, and molds when aerosolized onto hatching eggs.[18] Alternative application procedures to micro aerosolization have also proven effective.[19,20]

Source of support: Nil
Conflict of interest: None

Hydrogen peroxide is known to be effective against viruses because of its strong oxidizing properties.[21] Often 0.5% H_2O_2 is recommended for corona virus inactivation. The 0.5% hydrogen peroxide is able to inactivate corona virus within a contact time of 1 minute. The reduction of viral elimination that corresponds to this time and dosage was >log 4.[22] This translates into 99.99% viral inactivation. Another recently published review article effectively summarized that human corona viruses can be efficiently inactivated by surface disinfection procedures with 0.5% H_2O_2 within 1 minute.[23] In addition to virus inactivation studies, H_2O_2 has also been successfully tested at 1% against several bacteria according to test standard EN 13697.[24]

As far as safety of H_2O_2 nebulization is concerned, the concentration proposed in our study is 0.6% only, which is widely used worldwide in otolaryngology without any reported side effects. The Government of Italy has adapted and recommended the use of H_2O_2 in control of COVID infection.[25,26]

Materials and Methods

Patients were recruited after obtaining informed consent, by following matched pair randomization process (with pair matching, patients were paired in terms of their potential confounders, i.e., comorbidity and disease severity; then within each pair, one patient was randomized to receive H_2O_2 nebulization and the other one received normal saline nebulization), using free to use software online (Table 1). This was done by principal investigator. Double

Flowchart 1: Consort 2010 flow diagram

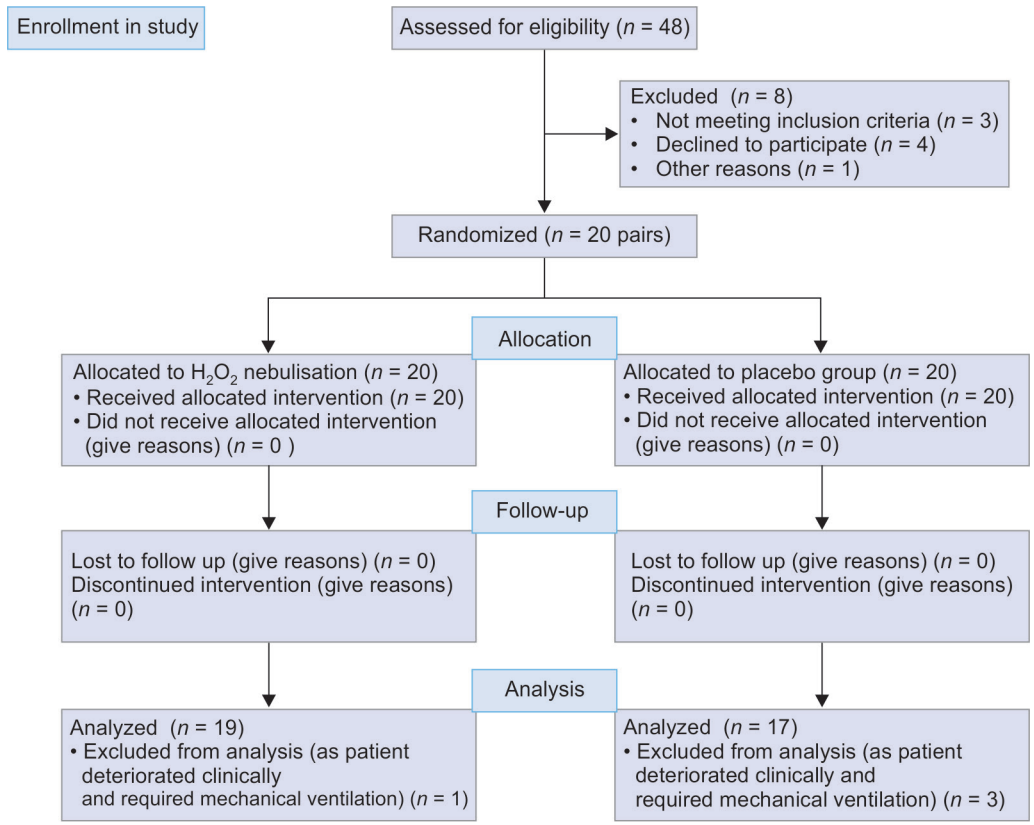

Table 1: Inclusion and exclusion criteria

Inclusion criteria	*Exclusion criteria*
All newly diagnosed positive patients above 18 years of age who gave informed consent	Patient not giving consent
Not requiring mechanical ventilation	Patient not tolerating the nebulization
On oxygen therapy	Patients with comorbid respiratory illnesses
Tolerating hydrogen peroxide nebulization	Patients requiring mechanical ventilation during course of study

blinding was done, both at level of person doing nebulization and patient level to reduce bias and placebo effect. Institutional ethical clearance was obtained vide no. SNMC/EC/2020-12 and registered with clinical trial registry, India vide no. CTRI/2020/08/027038. The trial has shown promising results in early assessment of parameters; the results will be submitted for further evaluation as it is an ongoing trial. Patients were recruited from August 1 to 31, 2020 and followed up for 3 months post recovery.

For the purpose of the study, SARI was defined as acute respiratory infection with history of fever or measured fever of ≥38 C° and cough with onset within the last 10 days, and requires hospitalization.

Primary drug TRIOZON used in the study had a heterogeneous catalyst thus releasing nascent oxygen molecules gradually for effective results. Around 1 mL of TRIOZON was mixed with 4 mL of normal saline (0.9%) making 5 mL solution (single dose) which was used for nebulizing the cases thrice a day for 5 days. The controls were nebulized three times a day consecutively for 5 days using 5 mL of 0.9% normal saline as placebo. Normal saline is not known to exert any effect over virus replication and is devoid of any side effects.

Any patient not able to maintain blood oxygen saturation above 92% on room air was considered to be on oxygen therapy. Patient's oral temperature was recorded using digital thermometer thrice daily. Temperature readings below 98.6 F were considered afebrile when not using any antipyretic. Dyspnea was assessed using modified Borg scale (Table 2).[27] Patients reporting 0, 0.5, and 1.0 were considered to be symptomatically improved and values ≥2 were considered symptomatic. Cough was assessed using cough symptom score (Table 3),[28] score ≤1 was considered to be free of cough. RT-PCR tests were conducted on patients third day onwards every 24 hours until they turned negative for COVID-19. Also, serum ferritin and CRP were measured on days 1, 5, and 10. Total leukocyte count was done on alternate day. All the patients' standard of care and treatment was as per the institutional protocol devised in line with the WHO and the national guidelines.

Objectives: Primary objective of this study was to determine the efficiency of nebulized H_2O_2 in reducing the viral load as assessed by RT-PCR and secondary objective was to assess the decrease in disease severity of patients suffering with COVID-19.

Outcome was assessed for reduction in oxygen requirement (number of days on oxygen), symptom resolution (dyspnea, cough, and fever), and number of days it took to be RT-PCR negative for COVID-19.

Statistical analysis: Data were entered into Microsoft Excel sheet and analyzed using SPSS software ver. 25. Paired *t* test was conducted for the parameters under assessment for cases and control groups and odds ratio (OR) was calculated. The number needed to be treated was also evaluated to assess the perceived benefit.

Table 2: Modified Borg scale

0	*None*
0.5	Extremely mild
1	Very mild
2	Mild
3	Moderate
4	Intense
5	Rather intense
6	
7	Very intense
8	
9	Almost unbearable
10	Unbearable

Table 3: Cough symptom score

Score	*Daytime*	*Nighttime*
0	No cough during the day	No cough during night
1	Cough for one short period	Cough on waking only
2	Cough for more than two periods	Wake once or early due to cough
3	Frequent coughing which didn't interfere with usual daytime activities	Frequent waking due to coughs
4	Frequent coughing which interfere with usual daytime activities	Frequent coughs most of the night
5	Distressing coughs most of the day	Distressing coughs preventing any sleep

Results

In total, 20 patients were recruited in each arm as cases and controls after randomization, but one patient had to be removed from the cases and three from the control group, as patients required mechanical ventilation during the course of study after recruitment in the study.

The cases group had seven female and 13 male with mean age of 47 years with age range from 18 to 70 years, in comparison the control group had nine female and 11 male with mean age of 43 years ranging from 23 to 65 years. The mean SpO_2 on admission to the hospital was 87.57 ± 2.65 for the cases and 88.29 ± 2.54 for the control group, which is comparable without any significant difference.

The various comorbid conditions that the patients suffered from are tabulated in Table 4. Majority of the patients were SARI patients and most leading comorbidity was type 2 diabetes.

Side effects reported by patients in the cases group were irritation in throat, hawking sensation, dryness of throat, tingling sensation, headache, and dizziness, but all patients tolerated them well and no one dropped out from the study on account of these side effects. Control group patients did not report any side effects to nebulization.

The study showed that the cases who were nebulized with H_2O_2 resulted in better outcome in terms of parameters assessed in the study and the differences from control group were statistically significant ($p \leq 0.001$) (Table 5).

The inflammatory markers also showed improvement but only in later stages of disease nearing day 10 of admission after an initial increase in their levels around day 5, thus suggesting that inflammation processes going on in the body showed a lag with positivity for COVID-19. However, it was found that the resolution of inflammatory markers for cases group was more noteworthy but statistically nonsignificant than controls *vis a vis* day of admission (Table 6). Only one patient from cases group (SARI) required mechanical ventilation who finally expired, in comparison with three patients (SARI, DM, CAD, one each) from the control group. This is 5% vs 15%, OR 0.29, 95% CI 0.02–3.14, p =0.31, and z = 1.007, which is statistically insignificant for poor outcome in the form of disease outcome as far as mortality is concerned.

The NNT for our study was 10.0, estimating that 10 number of patients need to be treated with the new treatment rather than the standard treatment (or no treatment) for one additional patient to benefit.

Table 4: Distribution of comorbidity

Cases		*Controls*	
Diabetes mellitus DM + HTN (1) DM (2) DM + hypothyroid (1) DM + CKD (1)	**5**	Diabetes mellitus DM + HTN (1) DM + HTN + hypo thyroid (1) DM (4)	**6**
Malignancy (oral cavity)	**1**	Nephrotic syndrome (on steroid)	**1**
CLD + portal HTN	1	CKD	**1**
SARI	10	SARI	**8**
Hypothyroid	1	HTN	**2**
CAD CAD/post CABG (1)	2	CAD CAD/post PTCA (1)	**2**

DM, diabetes mellitus; CKD, chronic kidney disease; CLD, chronic liver disease; CAD, coronary artery disease; HTN, hypertension; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty

Discussion

Nebulization as a method of drug delivery is in use for very long time. Aerosol therapy is defined as drug administration in the form of an aerosol into a patient's airways or lung. Its efficiency depends on the type of drug used and aerosol's physical and chemical properties, the aerosol device as well as patient's breathing pattern, lung anatomy, and physiology. Currently, inhalation therapy is the best option for lung diseases like asthma, cystic fibrosis, and chronic

Table 5: Comparative analysis of study parameters

Parameters	*Case (N = 19) (mean ± SD)*	*Control (N = 17) (mean ± SD)*	*t value (CI 95%)*	*p value*
Number of days on O_2	4.74 ± 1.62	8.82 ± 1.59	7.60	0.001
RT-PCR negative (no. of days)	5.16 ± 1.21	9.41 ± 1.97	7.89	0.001
Dyspnea	4.58 ± 1.12	7.12 ± 1.05	6.97	0.001
Cough	4.79 ± 1.84	6.82 ± 1.51	3.59	0.001
Fever	2.84 ± 1.01	4.65 ± 1.22	4.84	0.001

Table 6: Comparative data of inflammatory markers

	Group	*N*	*Mean*	*Standard deviation*	*Standard error Mean*
Ferritin-I	Case	19	996.9211	592.76951	135.99065
	Control	17	762.3529	453.75171	110.05096
Ferritin-II	Case	19	1085.3053	604.65317	138.71695
	Control	17	997.5882	592.07285	143.59876
Ferritin-III	Case	19	661.2263	417.28965	95.73281
	Control	17	975.3412	647.60401	157.06704
CRP-I	Case	19	101.0900	48.26216	11.07210
	Control	17	98.8588	38.10136	9.24094
CRP-II	Case	19	100.1068	45.17442	10.36372
	Control	17	111.3824	34.88532	8.46093
CRP-III	Case	19	68.8384	47.39794	10.87383
	Control	17	87.8824	30.48336	7.39330
TLC-I	Case	19	13473.1579	3831.68378	879.04855
	Control	17	12164.7059	2802.21813	679.63773
TLC-II	Case	19	12023.6842	2927.10173	671.52319
	Control	17	11529.4118	2796.82067	678.32865
TLC-III	Case	19	10344.7368	2366.95390	543.01647
	Control	17	8947.0588	3018.50908	732.09599

CRP, C-reactive protein; TLC, total leukocyte count

obstructive pulmonary disease. These local therapies allow the use of targeted smaller doses and reduced systemic side effects. Nebulizers used in aerosol drug delivery produce a polydisperse aerosol where the drug delivered in the particle size range 1–5 μm in diameter which penetrate to level of alveoli.[29]

In a study by NianlinXie et al., PaO_2 was increased after low molecular weight heparin (LMWH) nebulization treatment, relieving the traumatic acute lung injury in rabbits.[30] In our study likely the free radical formed in degradation of H_2O_2 damaged the viral proteins and nucleic acids thus inhibiting further replication of virus and significantly preventing the progression of disease toward severity in comparison of the control group.

In a study by van Haren et al., it was found that patients infected with SARS-CoV-2 who manifest severe disease have high levels of inflammatory cytokines in plasma and bronchoalveolar lavage fluid and significant coagulopathy. Trial found inhaled LMWH reduced pulmonary dead space, coagulation activation, microvascular thrombosis, and clinical deterioration, resulting in increased time free of ventilator support.[31–33] Similarly, in our study too H_2O_2 has been found to have improved the clinical outcome. Also, being widely available and inexpensive can be widely used for its potential therapeutic properties, particularly in early phase of disease to arrest deterioration and reducing mortalities.

In a study by Breneckke et al., it has been suggested that inhaled furosemide, a small molecule capable of inhibiting IL-6 and TNFα, may be an agent capable of treating the COVID-19-induced cytokine storm. Furosemide not only inhibits the secretion of multiple cytokines implicated in COVID-19, it has also been shown to provide relief of dyspnea via direct inhalation.[34] It is a "repurpose-able" small molecule therapeutics that is safe, easily synthesized, handled, and stored, and is available in reasonable quantities worldwide.[35] In our study, it is hypothesized that the drug used had an indirect effect on cytokines production via inhibition of viral replication and can be used as an off-label drug repurposed for COVID-19 management.

In a study by Moghissi et al., it has been hypothesized that photo dynamic therapy could and should be considered for the treatment of respiratory infection in COVID-19 using the methylene blue nebulization.[36] In a study by Alamdari et al., methylene blue–vitC–N acetyl cysteine (MCN) treatment seems to increase the survival rate of COVID-19 patients. Considering the vicious cycle of macrophage activation leading to deadly NO, oxidative stress, and cytokine cascade syndrome; the therapeutic effect of MCN seems to be reasonable.[37] In current scenario, when multiple repurposed therapies are under evaluation, our study drug H_2O_2 has shown early promise in improved clinical outcome in our experience. As compared with photodynamic therapy, H_2O_2 nebulization does not require specialized costly equipment making it more suitable for low-income countries.

Few studies have shown that patients of COVID-19 may also be harboring bacterial coinfection; the commonest being *Mycoplasma pneumonia, Pseudomonas aeruginosa*, *Hemophilus influenzae, Klebsiella pneumonia,* and *Chlamydia*. Three studies reported fungal coinfections.[38] These findings reiterate that H_2O_2 which has got antibacterial properties also, can be used to control bacterial infection as well thus obviating need for the routine use of antibiotics in the management of confirmed COVID-19 infection thereby reducing the cost of care and chances of propagating antibiotic resistance and creation of superbugs.[24]

Limitations

A small sample size of our study and unavailability of data on long-term follow-up pertaining to adverse effects and safety, if any, of nebulized H_2O_2 is a limitation to our study. Potential biases may have erupted due to unintended deficiencies in pair matching of patients.

Conclusion

Nebulization therapy with H_2O_2 can be a very effective means for controlling COVID-19 among various emerging repurposed therapies. Its low cost, wide availability, and nondependence on specialized equipment make it a very promising repurposed therapy in the current scenario. The cost of health care for a patient in isolation wards for 14 days is approximately USD5000 in India which translates roughly into USD10 billion for a million active cases every day for a month. Our study can have far-reaching implications on the cost of health care being reduced for already stressed economies by reducing the need for isolation facility for patient management. An important application apart from patient management is suggested particularly for healthcare workers working in hospitals managing COVID-19 patients where they are at risk of exposure and catching COVID-19; that if they nebulize themselves regularly as per toleration of side effects at the end of their work shift, it may help in preventing the COVID-19 infection among inadvertently exposed health care workers (HCWs).

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