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Intravenous ozonized saline therapy as prophylaxis for healthcare workers (HCWs) in a dedicated COVID-19 hospital in India – A retrospective study

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Abstract. – OBJECTIVE: In the current pandemic, Health Care Workers (HCWs) are at a high risk of developing COVID-19. Preventive methods like the use of personal protective equipment, isolation, social distancing, and chemoprophylaxis show limited benefit. Despite standard prophylaxis, many of the HCWs develop COVID-19. Medical ozone therapy has immunomodulatory, antioxidant and antiviral effect, and, therefore, it can be explored as prophylaxis for COVID-19.

PATIENTS AND METHODS: We conducted a retrospective controlled cohort study. IV ozonized saline was administered once a day for a total of 4 days in one month in addition to standard prophylaxis for COVID-19 to HCWs in a dedicated COVID hospital. Fresh ozonized saline was prepared for every administration and was given over 1 hour.

RESULTS: There were 235 HCWs, 64 received the ozone prophylaxis and 171 did not. The incidence of COVID-19 was significantly (p=0.04) lesser in HCWs that received ozone prophylaxis (4.6%) as compared to those who did not (14.03%). The benefit was seen irrespective of the risk of exposure. In the red zone, 8.69% of the HCWs who received ozone prophylaxis tested positive as opposed to 15.3% of those who did not. In the orange zone, 4.34% of the HCWs who received ozone prophylaxis tested positive, remarkably lesser than those who did not (20%). In the green zone, none of the HCWs who received ozone prophylaxis tested positive; however, 3.4% of the HCWs who did not receive ozone prophylaxis tested positive. No major adverse events were noted.

CONCLUSIONS: IV ozonized saline can be used in addition to the standard prophylactic regimen for the prevention of COVID-19 in HCWs. Prospective larger studies are required to establish the potency of IV ozonized saline as prophylaxis.

Key Words:
Ozone, COVID-19, Sars-Cov 2, Antiviral, Coronavirus, Oxygenation.

Introduction

Currently, the world has been facing the biggest pandemic since a century caused by a novel strain of Coronavirus, Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV 2)[1]. SARS-CoV 2 leads to a pulmonary disease called COVID-19 characterized by viral pneumonia with symptoms, such as cough, fever, dyspnea, anosmia, ageusia, loss of appetite, generalized fatigue, diarrhea, sore throat, and pleuritic chest pain[2]. The disease has proven to be highly contagious and can be fatal in its severe forms[3]. Frontline workers, such as healthcare workers (HCWs), ancillary and administrative professionals working in COVID care facilities are at a higher risk of exposure to the virus and subsequent infection[4]. HCWs like doctors, nurses, and caretakers are in close contact with the

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patients and partake in many aerosol-generating procedures. Aerosols are microdroplets emitted by COVID-19 patients while speaking, sneezing, coughing, and during medical procedures like intubation, nebulization, suctioning, etc. Aerosols can remain suspended in air for a long time and may travel over some distance. Aerosol generating procedures can increase the risk of airborne transmission, as aerosols when inhaled, can cause infection[5]. There have been several incidences of healthcare professionals contracting COVID-19, and the consequences have been fatal for some of these[6]. In India, 5% of the HCWs were found to be COVID-19 positive[7]. In Italy, 12,252 HCWs were tested positive for COVID-19, which was approximately 10% of the total COVID cases, and 80 medical workers and 25 nurses died[8]. It is therefore of immense importance to protect the healthcare professionals from contracting this infection. Prevention methods like the use of personal protective equipment, isolation, and social distancing have limited benefit in healthcare workers as they are in direct contact with patients while providing care. Many of the HCWs have contracted the infection despite taking these precautions[9]. It is therefore important to explore other preventive strategies like chemoprophylaxis and vaccine. Hydroxychloroquine (HCQ) has been used widely as a chemoprophylactic drug and has shown benefit in reducing the incidence of COVID-19 in HCWs taking HCQ[10,11]. National guidelines in India recommend the use of HCQ as chemoprophylaxis for contacts of COVID-19 patients, frontline workers at risk of exposure to COVID-19 patients, and healthcare workers[12,13]. At the moment, there is no other chemoprophylactic agent approved apart from HCQ. However, several publications have highlighted the risks of using HCQ and the potential cardiotoxicity of the drug[14,15]. Earlier experiences with vaccine development have shown that it requires years, optimistically about 12-18 months, before an effective vaccine can be made available[16]. Although the vaccine is now available, immunization of the whole population may take months or years. Therefore, in the interim, safe prophylactic agents are required to be explored that have lesser adverse effects to protect HCWs.

Therapies that help to enhance the immune system of the body are also being investigated as prophylactic agents. Medical ozone therapy (MOT) has been successfully used since the 20th century as an antiseptic means. Technological advances post 1970s have made it easy to use them in the common clinical practice. Medical ozone therapy can be applied through various routes. Medical ozone therapy provided in the form of intravenous (IV) ozonized saline administration is an immunity enhancing therapy that may be considered as a prophylaxis to reduce/prevent the incidence of COVID-19 in healthcare professionals. IV ozone therapy has been of interest to clinicians due to its immune-modulating, anti-inflammatory, antioxidant, and antiviral properties[17-19]. IV ozone administration also alters the immune response by activating neutrophils, platelets, and lymphocytes[20,21]. Ozone also has an antiviral effect, which is not organism-specific and can be seen across various genotypes making it especially useful in the case of multiple strains of coronaviruses[19]. We investigate IV ozonized saline as a prophylaxis to reduce the incidence of COVID-19 in HCWs working in a dedicated COVID-19 hospital.

Patients and Methods

We conducted a retrospective cohort study to compare the incidence of COVID-19 in healthcare professionals who took prophylactic IV ozone therapy and those who did not. Sampling was convenient. The study was conducted between 1st June 2020 and 31st August 2020 (3 months).

Inclusion Criteria

HCWs of both genders working in all departments of the hospital were included.

Exclusion Criteria

Employees who had exposure to the work environment of our DCH for less than 1 month were excluded.

Prophylaxis Protocol

All HCWs were trained in the appropriate infection control protocols and provided with appropriate personal protective equipment based on their risk of exposure.

Hospital Zones

The study was conducted in 75 hospital with 20 ICU beds. It was divided into various zones based on the risk of exposure, namely Red, Orange, and Green zone. The red zone included areas where HCWs were in direct contact with COVID-19 patients and, therefore, were at a high risk of exposure. These were triage area, hospital wards,

step down ICU, and ICU. Orange zone included areas where the COVID-19 patients were in transit and where HCWs were in direct contact with the relatives and contacts of COVID-19 patients; therefore, they had a moderate risk of exposure. These included reception areas, hospital canteen, admission area, and billing area. In contrast, the Green zone included areas where HCWs were not in contact with patients or their relatives and had minimal risk of exposure. These included administrative staff offices, human resource department offices, routine laboratory services, research development department, and accounts and finance department.

All the HCWs, irrespective of the risk of exposure, were prescribed standard chemoprophylaxis, including HCQ (400 mg twice a day on Day 1, followed by 400 mg once weekly for the next 7 weeks; to be taken with meals), multivitamin (one tablet once a day), Vit. C (1 g once a day) and Zinc (50 mg once a day). These vitamins were given for 15 days. They were also provided a steam inhaler and were advised to take steam inhalation twice a day. In addition, all of them were prescribed prophylactic IV Ozonized saline administration once a day for 4 days in one month.

Screening for IV Ozonized Saline Prophylaxis

Hyperthyroidism and G6PD deficiency are contraindications for the administration of IV ozonized saline; therefore, all the HCWs were screened for the same. All HCWs were prescribed the ozone prophylaxis protocol. An informed and documented consent was obtained from HCWs that consented to IV ozonized saline administration. HCWs that consented to the protocol, adhered to it and completed 4 sessions in the period of 1 month and were included in the group of HCWs that received ozone prophylaxis. All other HCWs were included in the group that did not receive ozone prophylaxis.

IV Ozone Therapy Procedure

Ozone generation: Ozone generator for medical use (O3-Ozonics generator, Ozone Forum of India) was used for preparing ozone gas. Feed gas used was 100% pure medical grade oxygen with a variable flow. The ozone generator can provide various concentrations between 5 μg/mL to 60 μg/mL and is automated and standardized for time, volume, and concentration (tested and certified using ozone analyzer). It can deliver these concentrations persistently and precisely.

Ozonized saline preparation: Saline (200 ml 0.45% NaCl) was saturated with ozone by bubbling ozone gas at 5 μg/ml concentration in a glass bottle for 20 mins. It was immediately administered intravenously over 1 hour at 60 drops per minute. Fresh ozonized saline was prepared for every HCW at each dose of administration.

Comparison of Incidence of COVID-19

HCWs were considered COVID-19 positive on the basis, qRT-PCR testing or Chest HRCT findings suggestive of COVID-19[22,23]. Demographic data with respect to age, gender, co-comorbidities were collected and tabulated.

The incidence of COVID-19 was calculated in the whole population and separately for each zone. Percentage incidence was compared between HCWs that received IV ozonized saline as prophylaxis and those who did not. Statistical analysis was done using the Chi-Square test.

Adverse Effect Monitoring

All the HCWs were monitored for major and minor adverse effects (AE). Major AE monitored were allergic reaction, anaphylactic reaction, pulmonary embolism, life-threatening adverse events, and death. Minor adverse events like pain at the site of injection, bleeding at the site of injection, thrombophlebitis, mild headache, and fatigue were also monitored.

Results

There were 235 HCWs included in the study; out of these, 64 HCWs received IV Ozonized saline as prophylaxis, and 171 HCWs did not. HCWs included were all of the hospital employees, including Doctors, Nurses, Therapists, other non-clinical staff, administrative staff, and housekeeping employees. Demographic data of these HCWs are showed in Table I. Mean age of HCWS across both groups was comparable (Table I). The percentage of males in the group that received ozone prophylaxis was considerably higher than the group that did not receive ozone prophylaxis. The percentage of comorbidities like diabetes mellitus, hypertension, hypothyroidism was comparable. During the baseline comparison of the two groups HCWs that received the ozone prophylaxis exhibited other comorbidities like epilepsy, migraine, PCOD, and hysterectomy, whereas HCWs that did not receive IV ozonized saline prophylaxis exhibited comorbidities like a history of hysterectomy, asthma,

Table I. Demographic details of health care workers.

Parameter	HCWs that received IV Ozonized saline as prophylaxis	HCWs that did not receive IV Ozonized saline as prophylaxis
Mean age (SD)	31.8 (7.4)	29.1 (6.1)
No. of males (percentage)	37 (57.8)	73 (42.7)
No. of females (percentage)	27 (42.2)	98 (57.3)
No. HCWs with diabetes (percentage)	2 (3.1)	6 (3.5)
No. HCWs with hypertension (percentage)	1 (1.6)	7 (4.1)
No. HCWs with hypothyroidism (percentage)	0 (0)	10 (5.9)
No. HCWs with other comorbidities (percentage)	13 (20.3)	18 (10.5)

umbilical hernia, implant pacemaker, Polycystic Ovarian Disease (PCOD), epilepsy, cholecystectomy, and polycystic kidney disease.

59% of the HCWs worked in the red zone, 18% in orange zone and 23% in green zone (shown in Figure 1). The distribution of HCWs in different zones based on the status of their ozone prophylaxis is given in Table II.

Comparison of Incidence of COVID-19

The incidence of COVID-19 was significantly low in the group that received IV ozonized saline (4.6%), $p = 0.043$ as compared to the group that did not receive the ozone prophylaxis (14.03%). It was significantly lesser when compared across different zones as well. In red zone, 8.69% of the HCWs who received IV ozonized saline prophylaxis were tested positive compared to 15.3% of the HCWs that did not. In orange zone, HCWs that received ozone prophylaxis showed an incidence of 4.34%, and those who did not show a much larger incidence of 20%. None of the HCWs from the green zone that received tested positive; however, 3.4% of the HCWs that did not receive ozone prophylaxis tested positive (Table III, shown in Figure 2).

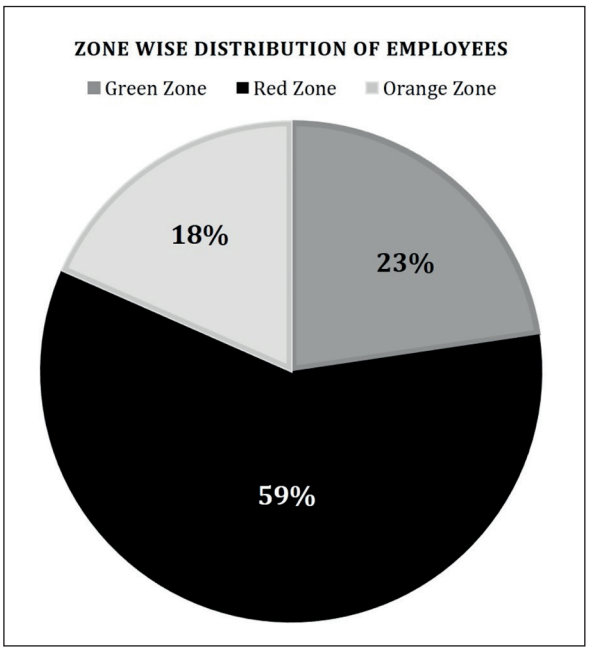

Figure 1. Proportion of HCWs working in different zones of the hospital.

Adverse Effects

None of the HCWs that took IV Ozone as prophylaxis showed any major irreversible adverse events. Some minor adverse events observed were mild pain at the site of injection, fatigue, mild headache, which resolved spontaneously or with one dose of paracetamol.

Discussion

We retrospectively studied IV ozonized saline as prophylaxis for reducing the incidence of COVID-19 in HCWs at risk of exposure. There was a statistically significant reduction (p=0.04) in the incidence of COVID-19 in HCWs who underwent IV ozonized saline as prophylaxis and those who did not. The percentage of HCWs who tested COVID-19 positive was only 5% in the HCWs that received IV ozonized saline as opposed to 14% in those that did not receive the IV ozonized saline. A similar reduction in the incidence was observed when the HCWs were categorized based on their risk of exposure.

Mechanism of Action of Ozone Therapy

Activation of Immune System and Antiviral Effect

Ozone therapy has a well-documented effect of immune modulation through immunoactive

Table II. Distribution of HCWs in different zones.

Ozone prophylaxis status	Received (No. of HCWs)	Not received (No. of HCWs)
Total	64	171
Red zone	22	117
Orange zone	23	25
Green zone	19	29

cytokines[24,25]. When administered in therapeutic dosages, ozone inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway by activating nuclear factor erythroid 2-related factor 2 (Nrf2). Inhibition of NF-κB pathway downregulated pro-inflammatory and stimulated anti-inflammatory cytokine release[26]. Ozone administration leads to the modulation of several anti-inflammatory cytokines[27].

Ozone therapy provides a unique opportunity for host-specific stimulation of the immune system, resulting in the 'autovaccine' effect. This autovaccine effect is due to the release of cytokines that have the capability to reduce the number of virions or modify them structurally so that those are dysfunctional and non-pathogenic. This is achieved through the disruption of the viral capsid. Modification of virions can be structural as well as genomic, providing the diversity of immune response. Therefore, the antiviral immune-stimulating effect is not organism-specific and can be seen across various genotypes making it especially useful in the case of multiple strains of coronaviruses[28,29]. Ozone administration can also prevent the entry of the virus in host cells[29].

Antioxidant Effects

Ozone administration has been shown to stimulate erythrocyte formation and release, where the functionality of erythrocyte enzymes is also maintained, bringing about an antioxidant effect[30]. In addition, ozone administration brings about mild oxidative stress through various biological interactions and inducing antioxidant response element transcription, rendering ozone therapy an antioxidant and anti-inflammatory properties[31]. Ozone can be considered as a paradoxical oxidative agent. It stimulates free radical scavenger enzymes and cytoprotective enzymes like glutathione peroxidase, catalase, and superoxide dismutase[32].

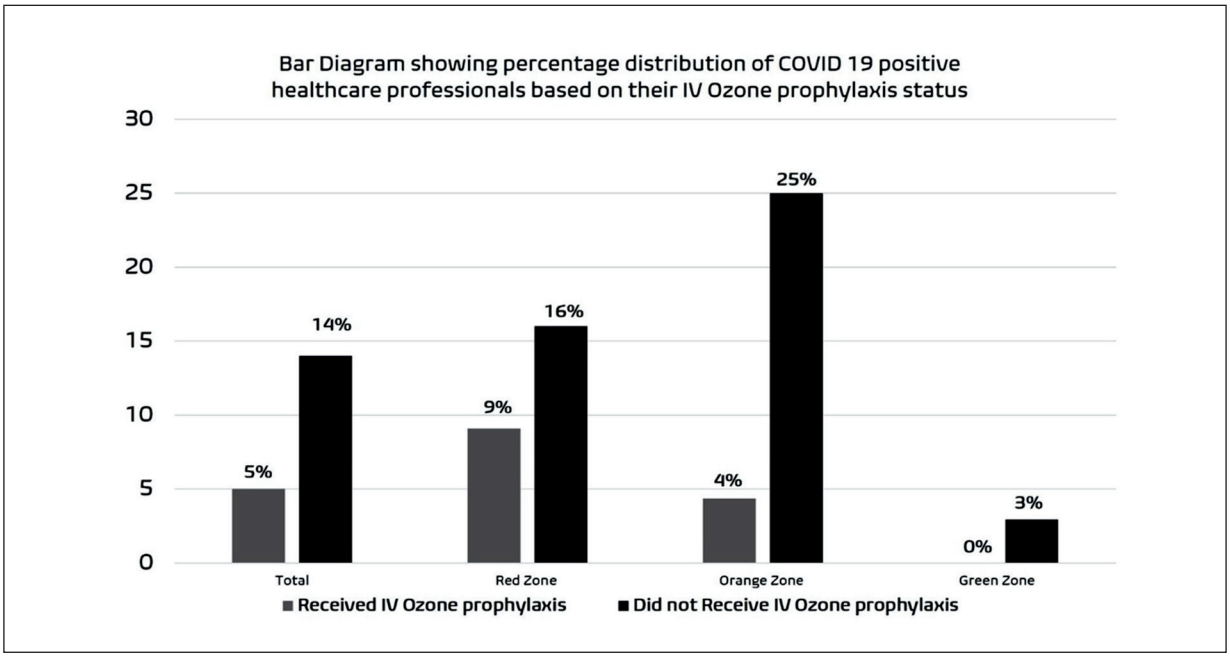

Figure 2. Comparison of percentage incidence of COVID19 in HCWs who received and did not receive.

Table III. Distribution of HCWs in different zones.

Ozone prophylaxis status	Received	Not received
	Number (Percentage)	Number (Percentage)
Total Positive*	3 (4.6)	24 (14.03)
Positive from Red Zone	2 (8.69)	18 (15.30)
Positive from Orange Zone	1 (4.34)	5 (20)
Positive from Green Zone	0 (0)	1 (3.4)

*Statistically significant difference observed on Chi-Square test ($p = 0.04$).

Improved Oxygenation

Ozone administration improves blood cell glycolysis stimulating 2,3 diphosphoglycerate, which in turn increases the amount of oxygen released into the tissues[21]. Ozone administration also enhances the production of ATP by influencing Kreb's cycle to increase oxidative carboxylation of pyruvate. The effect of ozone administration on energy metabolism can, therefore, potentially reverse hypoxia[33].

Use of Ozone for Treatment of COVID-19

Ozone therapy has also shown positive results in the treatment of COVID-19[34,35]. Franzini et al[34] conducted on 50 males aged more than 60 years diagnosed with COVID-19 on non-invasive mechanical ventilation showed a remarkable reduction in the inflammatory and thromboembolic markers like C-Reactive Protein (CRP), Interleukin 6 (IL6), and D-dimer after receiving ozone therapy. The oxygenation, respiratory indices, and gas exchange markers also showed an improvement post-treatment. Schwartz et al[35], including 25 patients, showed significant improvements in clinical symptoms like dyspnea, weakness, fever, corroborating with laboratory improvement in D-dimer, fibrinogen, Lactate Dehydrogenase (LDH), and CRP. None of the studies reported any major irreversible adverse effects of ozone therapy. Therefore, ozone administration can play a dual role in preventing the infection of SARS-CoV-2 and treatment of COVID-19 at the same time.

As per the current national recommendation, HCQ is used for chemoprophylaxis of COVID-19 patients. *In vitro,* Liu et al[36] support the findings that Chloroquine and HCQ can inhibit replication of SARS-CoV-2. In a retrospective study of 106 HCWs, Bhattacharya et al[19] showed a statistically significant reduction in the incidence of COVID-19 in HCWs who had taken HCQ prophylaxis as compared to those who had not[10]. The preliminary studies' encouraging results and clinical experience guided the Indian Council of Medical Research (ICMR) to recommend HCQ for chemoprophylaxis[13]. However, administration of these may lead to cardiac side effects[37]. Kulkarni et al[38] on 140 doctors showed that at the end of 1 month of HCQ prophylaxis, 44, i.e., 31% reported adverse effects.

Therefore, there is a need for a prophylactic agent that has good efficacy and less or no adverse effects. Our study elucidates the beneficial effect of IV ozonized saline as prophylaxis in reducing the incidence of COVID-19 in HCWs without any major, irreversible adverse events.

Limitations

This study was retrospective. A larger number of participants were needed. Due to smaller numbers in each zone, statistical analysis for individual zones was not performed.

Conclusions

Positive physiological effects of ozone therapy like immune modulation, improved oxygenation, antiviral, anti-inflammatory and antioxidant effects make it a potential adjuvant tool for prophylaxis of COVID-19. Administration of IV ozonized saline is safe and can reduce the incidence of COVID-19 in HCWs with standard prophylaxis. Larger studies are needed to establish the efficacy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Statement of Ethics

The research was conducted in compliance with World Medical Association Declaration of Helsinki. A documented informed consent was obtained from the HCWs that underwent ozonized saline administration.

Funding Sources
No funding was received for this study.

Authors' Contribution
Alok Sharma – Conceptualization, Supervision, Visualization, Methodology, Resources, Writing-Review & Editing. Milli Shah – Methodology. Hemangi Sane – Conceptualization, Methodology, Data Curation, Project Administration, Supervision, Writing-Review & Editing. Nandini Gokulchandran – Project Administration, Writing-Review & Editing. Amruta Paranjape – Data Entry, Data Curation, Investigation, Writing-Original Draft Preparation, Formal Analysis. Pallavi Khubchandani – Methodology, Data Entry. Jignasha Captain – Methodology. Shruti Shirke – Data Entry, Investigation. Pooja Kulkarni – Methodology, Project Administration..

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