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Safety and efficacy of ozone therapy in mild to moderate COVID-19 patients: A phase 1/11 randomized control trial (SEOT study)[☆]

Mili Shah^a, Jignasha Captain^b, Vidyadhar Vaidya^c, Arvind Kulkarni^d, Kedar Valsangkar^e, Pradeep M.K. Nair^{f,*}, Gayatri Ganu^g

^a Training and Education Department, President of Ozone Forum of India, Mumbai, India

^b Head of the Clinical Department, Director of Ozone Forum of India, Mumbai, India

^c Trustee in Department of Ozone Therapy, Lokmanya Medical Research Centre, Pune, India

^d Department of Oncology, Integrated Cancer Treatment and Research Centre, Wagholi, Pune, India

^e Department of Ozone Therapy, Lokmanya Medical Research Centre, Pune, India

^f Indian Academy for Scientific Writing and Research, Pune, India

^g Clinical Research, Department of Ozone Therapy, Lokmanya Medical Research Centre, Pune, India

ARTICLE INFO

Keywords:

Ozone therapy
COVID-19
SARS-COV-2
Anti-viral
Integrative medicine
Oxygen therapy

ABSTRACT

Introduction: The Corona virus disease 19 (COVID-19) has accounted for multiple deaths and economic woes. While the entire medical fraternity and scientists are putting their best feet forward to find a solution to contain this deadly pandemic, there is a growing interest in integrating other known alternative therapies in to standard care. This study is aimed at evaluating the safety and efficacy of ozone therapy (OT), as an adjuvant to the standard of care (SOC).

Methods: In the current randomized control trial, 60 patients with mild to moderate score NEWS score were included in two parallel groups (n = 30/group). The interventional group (OZ) received ozonized rectal insufflation and minor auto haemotherapy, daily along with SOC, while the control group (ST) received SOC alone. The main outcome measures included changes in clinical features, oxygenation index (SpO₂), NEWS score, Reverse transcription polymerase chain reaction(RT-PCR), inflammatory markers, requirement of advanced care, and metabolic profiles.

Results: The OZ group has shown clinically significant improvement in the mean values of all the parameters tested compared to ST Group. However, statistical significance were only observed in RT-PCR negative reaction (P = 0.01), changes in clinical symptoms (P < 0.05) and requirement for Intensive care (P < 0.05). No adverse events were reported in OZ group, as against 2 deaths reported in ST group.

Conclusion: OT when integrated with SOC can improve the clinical status and rapidly reduce the viral load compared to SOC alone, which facilitate early recovery and check the need for advanced care and mortality as demonstrated in this study.

1. Introduction

Corona Virus infection (COVID-19) has bedevilled the common public, health care providers, researchers and policy makers to a great extent having been declared as a pandemic by World Health Organization in March 2019. COVID-19 is clinically characterized with fever and cough, breathing difficulties and along with other nonspecific symptoms, like headache, vomiting, diarrhoea etc [1]. Since the first case reported in Wuhan in December 2019, by June 2020, as it stands

now, 213 countries have reported to have COVID-19 cases in their respective countries, of which United States of America, Brazil, Russia, India and United Kingdom are the most affected countries [2]. Prevention and quarantine are considered as a major resort against this deadly virus in the absence of any effective vaccine or anti-viral drugs [3,4].

A wide range of strategies like anti-viral dosages, oxygen supplementation, plasma therapy are being used for managing the symptoms [3]. Due to this uncertainty around management of COVID-19, there has been a lot of interest in exploring the role of adjuvant therapies that can

[☆] This trial is registered in Clinical Trial Registry of India with registration number CTRI/2020/07/026354

* Corresponding author at: Indian Academy for Scientific Writing and Research, A-1102, Shanti Elixir, Keshav Nagar, Pune 411036, India.

E-mail addresses: vgvaidya178@gmail.com (V. Vaidya), director@iaswar.com (P.M.K. Nair).

CONSORT Flow Diagram

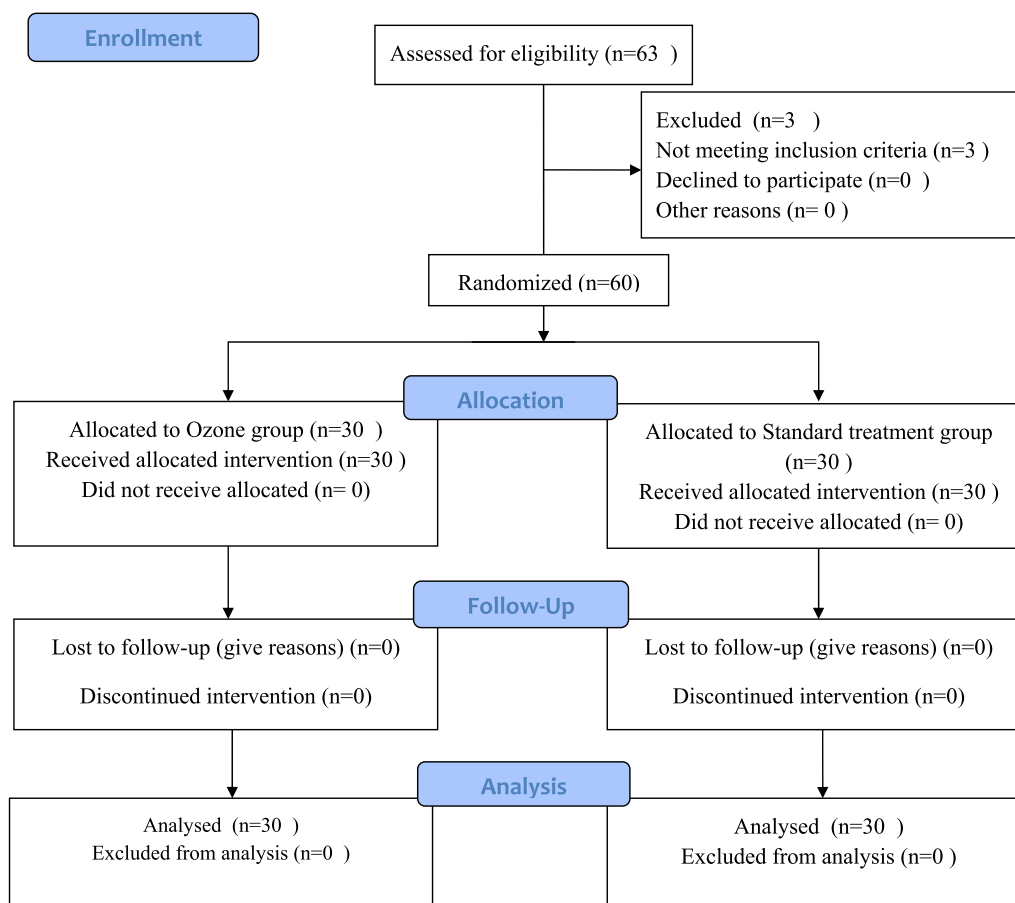


Fig. 1. CONSORT Flow chart of the trial events.

complement mainstream care [5–8]. Medical Ozone therapy is one such complementary therapy which is reckoned to have strong immunomodulator, anti-oxidant and germicidal effect on humans [7,9–11]. The common mode of ozone applications are Ozone autohemotransfusion, direct injection via the intramuscular/intradiscal/paravertebral, rectal,nasal, oral, vaginal insufflations, Cutaneous exposure of the body in a chamber or bag and saline [12].

Brief reports exploring the use of ozone therapy as an adjuvant/potential therapeutic tool in treating COVID-19 suggests a possible antagonizing action of ozone against Corona virus [7,13–17]. One of these studies has hinted on a possibility of early recovery and reduction in length of hospital stay on patients who underwent ozone therapy compared to others [16]. Barring a few clinical/observational studies, most of the studies in Ozone and COVID-19 are reviews that warrant more clinical studies to strengthen the recommendation of Ozone as a therapy in COVID-19. This study evaluates the safety and effectiveness of the ozone therapy as an adjuvant treatment for patients displaying mild to moderate stage of COVID-19.

2. Materials and methods

2.1. Study design

The study was a randomized control trial comprised of patients who were enrolled for COVID care in a Dedicated COVID care setting in India. The study was approved by the Institutional Ethics Committee and was

registered with Clinical Trial Registry of India with registration number CTRI/2020/07/026354. The CONSORT flow of the entire study is depicted in Fig. 1

2.1.1. Inclusion criteria

Adults of age 30 to 60 of both sex with positive Reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swab test result presenting mild to moderately severe disease (NEWS score ≤ 8) [18] and willing to provide informed consent were included in the study.

2.1.2. Exclusion criteria

Participants requiring Intensive Care Unit (ICU) admission and or artificial ventilation or any other co-morbidity (which were at critical stage at screening), were excluded from the study. Participants with chronic constipation for more than 7 days at the time of screening or with glucose-6-phosphate-dehydrogenase deficiency (G6PD) deficiency, were excluded from the study. Participants from the vulnerable group like pregnant and breastfeeding women were excluded from the study.

2.1.3. Groups

We screened 63 participants of which 60 participants were enrolled into the study. They were randomized using a computer generated randomization sheet, either in the standard treatment arm (ST Group) where the patients were provided with conventional care as recommended in Clinical management protocol for COVID 19 advocated by Indian Council of Medical Research (ICMR), Ministry of Health and

Family Welfare, Government of India [19] or to the treatment arm where the patients were treated with ozone therapy along with the standard protocol (OZ group). See Fig. 1 for the flow of event this trial.

2.1.4. Sample size

The trial was designed as a superiority trial assuming the number of RT-PCR negative patients in the ST group as 66% and in OZ group as 90%. To achieve this difference (d) of 24% and level of significance (α) 0.05 for a superiority margin (δ) of 5% and for a power (β) of 80%, the sample size required was calculated as 30 ($n = 30$) per arm and total number of samples required for the whole study was 60.

2.1.5. Interventions

As mentioned the control group received Standard of care (SOC) which was provided for 10 days or till a negative report is received via RT-PCR test, whichever was earlier, starting from the patient's hospitalization date (after confirming positive RT-PCR for COVID 19). SOC treatment was continued as per the ICMR protocol. Each patient from the OZ group received SOC and Ozone therapy. The ozone therapy included 40 $\mu\text{g}/\text{ml}$ ozone in the dose of about 150 ml twice daily as a rectal insufflation [20] and 2–3 ml venous blood along with 5 ml Ozone at 25 $\mu\text{g}/\text{ml}$ [minor auto haemotherapy (MiAHT)] [21] once daily along with SOC. The ozone/oxygen mixture was generated from an ozone generator for medical use (O3-Ozonics generator, Ozone Forum of India), which is automated and standardized for time, volume and concentration.

The total duration of treatment per patient was kept as 10 days, which is excluding 2 days screening period. A screening window of 2 days was kept, in case of delay in availability of tests reports or in case few tests needed to be repeated. Day 0 was considered as baseline visit and day 1 to 9 was considered as intervention period. End of study visit was at day 10 or negative report form RT-PCR tests whichever was earlier.

2.1.6. Outcome measures

This study looked at a variety of outcome variables related to the prognosis of COVID 19. The primary outcome measures were,

1. Changes in oxygenation index: SpO₂.
2. Changes in serum Lactate dehydrogenase (LDH), Ferritin and C-reactive protein (CRP)
3. Changes in NEWS (National Early Warning Score)
4. Number of days for negative RT-PCR test for COVID 19. RT-PCR test was repeated on day 5 and 10.

Additionally we evaluated,

1. Change in clinical symptom presentation (for symptomatic patients only) in Cough, breathlessness, persistent pain and pressure in the chest on 5 point ordinal scale: None (1), mild (2), moderate (3), severe (4), extremely severe (5)
2. Requirement of admission to intensive care unit
3. Duration of hospital admission
4. Clinical status expressed in percentage of subjects reporting each severity rating on a 6-point ordinal scale:
 - Death (1)
 - Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (2)
 - Hospitalized, on non-invasive ventilation or high flow oxygen devices (3)
 - Hospitalized, requiring supplemental oxygen (4)
 - Hospitalized, not requiring supplemental oxygen (5)
 - Not hospitalized (6)

2.2. Data analysis

The efficacy analysis was performed in the per-protocol (PP) population defined as those patients who had good treatment compliance, who did not take any prohibited medications (Other than Ozone therapy and SOC treatment, any other health supplements, nutraceuticals, Ayurvedic, Homeopathic, Siddha, Unani drug(s) or any other traditional or folklore medicine or therapy during the study period) and whose CRF was complete as requested. Both descriptive and inferential analyses were used in inferring the data.

2.2.1. Demographic and baseline information

Continuous variables that are Age and other demographic characteristics were summarized by using summary statistics i.e. the number of observations, mean and standard deviation. Categorical values like gender and clinical Examination were summarized using frequencies and percentages.

2.2.2. Analysis of primary efficacy parameters

In this study Percentage of patients having negative RT-PCR test on Day 5 and day 10 was analyzed and compared between ST group and OZ group by using Fischer Exact Test. Other Primary efficacy variables that are changes in clinical symptoms and Clinical status as per protocol at each visit from baseline were estimated by Fischer Exact test. Mean changes in Serum levels of CRP, LDH and Ferritin were analyzed at each follow up from baseline within and between groups by using Student T test.

2.2.3. Secondary efficacy parameters

Secondary variables that are mean change in the NEWS score compared to the baseline on day 5 and 10 day were analyzed and compared by using Wilcoxon sign rank test for with in changes and Mann Whitney U test to compare the change between two groups. Other Laboratory data and vital parameters were analyzed and compared by using student t test.

2.2.4. Safety analysis

Adverse events (AEs) and serious adverse events (SEs) will be summarised, counting both the number of separate events and the number of subjects experiencing events occurring during the study period will be provided overall, per system organ class and preferred term by presenting. All p-values were reported based on two-sided significance test and all the statistical tests were interpreted at 5% level of the significance level.

3. Results

There were total of 63 subjects screened of which 3 were screen failure having uncontrolled diabetes and not on stable medication. The mean age of participants in the ST group (22 males; 8 females) was 43.60 ± 9.72 years and 44 ± 8.66 years in OZ group (26 males; 4 females). Out of 30 randomized subjects from ST group, two subjects met with fatality as a result of progression of disease. Around 10% of the cases from ST group had Diabetes mellitus, which was comparable with 10% among OZ group having diabetes and hypertension and thus difference was not significant.

3.1. Profile of RT-PCR negativity in both the groups

On day 5, 77% of cases from OZ group and 53% in ST group showed RT-PCR negative result. At the end of Day 10, 100% of the cases showed PCR negativity in OZ group which is significantly more as compared to 70% in standard treatment group. The changes were statistically significant ($P = 0.01$) in OZ group compared to ST group.

Table 1
Comparison between different parameters in Ozone and standard group.

Parameter studied	Pre Mean (±) SD	Post Mean (±) SD	P value
NEWS score			
ST Group	3.06 ± 1.85	2.80 ± 1.13	0.12
OZ Group	3.20 ± 1.70	2.00 ± 0.98	
C-Reactive Protein			
ST Group	1.00 ± 0.59	1.05 ± 0.38	0.0518
OZ Group	0.98 ± 0.68	0.85 ± 0.36	
Lactate dehydrogenase			
ST Group	956.67 ± 989.1	669.2 ± 763.29	0.2085
OZ Group	944.0 ± 910.10	752.6 ± 416.39	
Ferritin			
ST Group	218.11 ± 220.91	163.5 ± 164.0	0.4027
OZ Group	217 ± 199.85	198.2 ± 176.03	
SpO₂			
ST Group	94 ± 4.55	97 ± 1.5	0.9293
OZ Group	96.4 ± 2.78	97 ± 1.8	

ST Group- Standard Treatment Group; OZ Group- Ozone Group; SD- Standard Deviation

3.2. Comparison of changes in cough between the groups

In OZ group by the end of Day 5, 30% of patients were relieved of cough which were significant from baseline and the same trend continued till day10. 100% subjects from OZ group were relieved of cough on day 10, whereas 75% cases from ST were showing mild cough. The shift from mild cough to no cough was statistically significant (P < 0.05) in OZ group compared to ST group.

3.3. Comparison of changes in breathlessness between the groups

In OZ group, 90% of cases were relieved of breathlessness on day 5, which were significant from baseline and the same trend was continued till day 10. On day 10, test group demonstrated 100% subjects with relieved breathlessness which was 91% in standard group. There was significant difference (P < 0.05) in breathlessness score between the OZ and ST groups.

3.4. Comparison of inflammatory markers between the groups

In the present study, within ozone treated group, there was reduction in all three inflammatory biomarkers from baseline to end of study. There was 21.29%, 30% and 25% decrease in mean levels of CRP, LDH and ferritin respectively at end of the study compared to baseline. The same was observed in ST group as well, however, the magnitude of change was predominant in OZ group. The results are tabulated in [Table 1](#). The changes were statistically not significant.

3.5. Comparison of ICU admission between the groups

In this study 0% of cases from OZ group required ICU admission whereas there were 10% participants who required ICU admission in ST group due to poor prognosis. There was no supplemental oxygen requirement in Ozone group and not a single fatality in ozone treated group. However, 2 fatalities were reported in the ST group due to progression of COVID-19. Comparison between the two groups on Fisher Exact Test indicated a statistically significant (P < 0.05) change. ([Table 5](#))

3.6. Comparison of mean SpO₂ between groups

In both ST and OZ group the mean SpO₂ improved in magnitude from baseline to end of study. However, the changes were not statistically significant (P > 0.05). Results are tabulated in [Table 1](#).

Table 2
Comparison of Lipid profile between Ozone Group and standard group.

Parameters studied	OZ Group		ST group		P value
	Baseline (Mean ± SD)	Post treatment (Mean ± SD)	Baseline (Mean ± SD)	Post treatment (Mean ± SD)	
Bilirubin Total	0.69 ± 0.24	0.69 ± 0.23	1 ± 0.25	0.688 ± 0.14	0.6277
Bilirubin Direct	0.25 ± 0.14	0.3 ± 0.14	0 ± 0.13	0.32 ± 0.09	0.5069
Bilirubin Indirect	0.44 ± 0.14	0.38 ± 0.16	0 ± 0.18	0.34 ± 0.12	0.7549
SGOT	33 ± 13.46	27.13 ± 19.49	33 ± 21.84	25.76 ± 9.74	0.1382
SGPT	37 ± 16	39.06 ± 21.41	37 ± 28.94	27.88 ± 10.58	0.0168
Alkaline Phosphatase	102.9 ± 42.16	111.43 ± 32.82	110 ± 26.65	129.8 ± 15.49	0.1269
Total Proteins	7.27 ± 0.80	10.74 ± 23.87	7 ± 0.59	11.83 ± 26.08	0.8287
Serum Albumin	3.39 ± 0.38	3.12 ± 0.62	3.0 ± 0.30	3.36 ± 0.32	0.4651
Serum Albumin/ Globulin Ratio	0.86 ± 0.12	1.13 ± 0.53	1.0 ± 0.17	1.0 ± 0.27	0.7805

SD- Standard Deviation; OZ Group- Ozone Group; ST group- Standard Treatment Group; SGOT-Serum glutamic oxaloacetic transaminase; SGPT-Serum glutamic pyruvic transaminase

Table 3
Comparison of Renal profile between Ozone Group and standard group.

Parameters studied	Ozone Group		Standard Treatment Group		P value
	Baseline (Mean ± SD)	Post treatment (Mean ± SD)	Baseline (Mean ± SD)	Post treatment (Mean ± SD)	
Serum Calcium	9.253 ± 0.43	9.414 ± 0.41	10 ± 0.36	9.27 ± 0.48	0.4620
Serum Uric Acid	3.78 ± 0.60	5.14 ± 0.95	5 ± 0.89	4.49 ± 0.89	0.2558
Blood Urea Nitrogen	9.13 ± 0.95	16.14 ± 3.91	13 ± 3.84	15.60 ± 4.16	0.0630
Serum Creatinine	0.78 ± 0.27	0.77 ± 0.17	1 ± 0.14	0.80 ± 0.13	0.5488

Table 4
Comparison of Lipid profile between the Ozone and standard treatment groups.

Parameters Studied	Ozone Group		Standard Treatment Group		P Value
	Baseline (Mean ± SD)	Post treatment (Mean ± SD)	Baseline (Mean ± SD)	Post treatment (Mean ± SD)	
Total Cholesterol	166.4 ± 9.51	167.62 ± 11.12	164 ± 11.69	169.36 ± 10.11	0.4483
Cholesterol HDL Direct	49.23 ± 6.65	44.79 ± 6.73	45 ± 5.16	48.52 ± 7.19	0.0067
Triglycerides	97.56 ± 9.17	117.48 ± 17.57	96 ± 6.17	98.64 ± 6.24	0.0613
LDL Cholesterol	99.46 ± 7.61	94.17 ± 7.88	110 ± 12.18	99.6 ± 3.48	0.7835
VLDL Cholesterol	21.18 ± 4.54	22.22 ± 4.97	20 ± 1.36	20.84 ± 2.29	0.1279
TC/HDL Ratio	3.41 ± 0.41	3.78 ± 0.46	4 ± 0.38	3.51 ± 0.47	0.1356
LDL/HDL Ratio	2.037 ± 0.32	2.084 ± 0.28	2 ± 0.42	2.04 ± 0.29	0.5111

Table 5
Comparison of changes in clinical status between the groups.

Duration in Days	Std. Group (N = 30)						Ozone treated group (N = 30)					
	1 No. %	2 No. %	3 No. %	4 No. %	5 No. %	6 No. %	1 No. %	2 No. %	3 No. %	4 No. %	5 No. %	6 No. %
Baseline	-	-	-	0	30	- (-)	-	-	-	0(0)	30	- (-)
	(-)	(-)	(-)	(0)	(100)		(-)	(-)	(-)	(0)	(100)	
1	-	-	01 (3.3)	01 (3.3)	28	- (-)	-	-	-	0(0)	30	- (-)
	(-)	(-)			(93.3)		(-)	(-)	(-)		(100)	
2	-	-	01	00	29	- (-)	-	-	-	01	29	- (-)
	(-)	(-)	(3.3)	(0)	(96.6)		(-)	(-)	(-)	(3.33)	(96.6)	
3	-	-	01	00	29	- (-)	-	-	-	01	29	- (-)
	(-)	(-)	(-)	(3.33)	(96.6)		(-)	(-)	(-)	(3.33)	(96.6)	
4	-	-	03	00	27	- (-)	-	-	-	01	29	- (-)
	(-)	(-)	(10)	(0)	(90)		(-)	(-)	(-)	(3.33)	(96.6)	
5	-	-	02	00	11	- (-)	-	-	-	0	10	- (-)
	(-)	(-)	(15.4)	(0)	(84.6)		(-)	(-)	(-)	(0)	(100)	
6	01	-	01	00 (0)	11	- (-)	-	-	-	01	06	- (-)
	(7.7)	(-)	(7.7)	0 (0)	(84.6)		(-)	(-)	(-)	(14.2)	(85.7)	
7	02	-	01	0 (0)	10	- (-)	-	-	-	- (-)	7	- (-)
	(15.4)	(-)	(7.7)	0 (0)	(76.9)		(-)	(-)	(-)		(100)	
8	02	-	-	0 (0)	10	- (-)	-	-	-	- (-)	07 (100)	- (-)
	(15.4)	(-)	(-)	0 (0)	(83.3)		(-)	(-)	(-)			
9	02	-	-	0 (0)	10	- (-)	-	-	-	- (-)	07 (100)	- (-)
	(15.4)	(-)	(-)	0 (0)	(83.3)		(-)	(-)	(-)			
10	02*	-	-	0 (0)	10	- (-)	-	-	-	- (-)	07 (100)	- (-)
	(15.4)	(-)	(-)	0 (0)	(83.3)		(-)	(-)	(-)			

1 = Death, 2 = Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation, 3 = Hospitalized, on non-invasive ventilation or high flow oxygen devices 4 = Hospitalized, requiring supplemental oxygen, 5 = Hospitalized, not requiring supplemental oxygen, 6 = Not hospitalized.

At baseline all the subjects from both groups were hospitalized and not requiring supplemental oxygen. From the second day one subject from standard group went on to non-invasive ventilation or high flow oxygen devices and got shifted to ICU. On day 5 two subjects from standard group were on non-invasive ventilation or high flow oxygen devices and admitted to ICU. On day 6th there was one fatality in standard group related to progression of disease. On Day 7 there was second subject from standard group in ICU showed bad prognosis resulted in second fatality.

3.7. Comparison of NEWS score between groups

There was significant change in the mean values of NEWS score in both groups compared to the baseline. The change was more predominant in the OZ group; however, the changes were not statistically significant. Results are tabulated in Table 1.

3.8. Comparison of safety parameter between the groups

Neither the OZ group nor the ST group showed any significant changes in lipid profile, liver profile, renal profile and serum electrolytes such as sodium, potassium and chloride. Results are tabulated in Tables 2–5, respectively.

4. Discussion

Our trial has found that Ozone therapy when administered with SOC has significantly improved the time to clinical improvement, mortality, or time to clearance of virus in patients with mild to moderate COVID-19, compared to patients who received only SOC. To our knowledge this is the first trial directly reporting the safety and efficacy of Ozone in mild to moderate COVID 19 patients.

There were few reports suggesting the use of Ozone therapy in COVID-19 treatment prophylaxis [7,13–15,17,22,23]. These reports/studies suggested a potential role of ozone in COVID-19, further it recommended well-designed clinical trials to assess probable ozone concentration, possible routes of administration, safety, stage of the disease in which ozone to be administered, contraindications, concomitant administration of antioxidants etc.

In the present study, Ozone was compared for its safety and clinical efficacy along with standard treatment in COVID 19 patients. The results are promising as it has shown improvement in multiple variables tested compared to the ST group. In COVID-19 though there is multi-organ

involvement, respiratory system is the most affected in which dyspnoea is the most predominant symptom [24,25]. Though statistically not-significant OZ group demonstrated increase in SpO2 levels during the study period compared to baseline, which might be the reason for reduced breathlessness that has reduced the patients risk profile and signifies good prognosis about the disease.

Participants from OZ group didn't show any requirement of supplemental oxygen, ICU admission and mechanical ventilation whereas standard group demonstrated 10% subjects requiring mechanical ventilation, ICU admission and two of which led to two fatalities. The results on mortality and need for advanced care in both groups in our study were comparatively better than the preliminary report published on Ozone safety among COVID-19 patients [26]. This indicates the need to integrate Ozone therapy in to the existing care. Integrating Ozone therapy in COVID-19 care not only reduces the mortality but also will be very strategic to accelerate recovery of COVID 19 patients presenting mild to moderate severity to getting into the advanced COVID-19 stages.

There is strong relationship between symptom regressions and severity of COVID 19 [27]. Our results that subjects in OZ group were relieved of cough, breathlessness more effectively than ST group that can check the severity of COVID-19.

One of the strong correlation to avoid bad prognosis in COVID 19, is to exert faster reduction in viral titre [28]. Antiviral activity can reduce pulmonary infiltrates and pulmonary tissue damage. There were 77% subjects from Ozone treated group showed negative RT-PCR on day 5 and all 100% got negative RT-PCR on day 10. This clearly declares advantage of faster eradication of virus from body which could be attributed to the antiviral potential of Ozone therapy.

In the present study that compared ST group to OZ group, we see a greater magnitude of reduction in mean NEWS score in OZ group, indicating lesser risk profiling, giving patients a fair chance to aster clinical recovery. In addition to the reduction in NEWS score, OZ group has shown significant reduction in all symptoms associated with COVID-

19.

Ozone treated group eventually required reduced hospital stay (Mean duration: ST Group 9 days; OZ group 8 days) as compared to standard, though the change was insignificant. It is a profound fact that there was no ICU admission, supplemental oxygen and mechanical ventilation requirement in ozone treated group. Thus the Ozone treated group has brought the healthcare requirement of above said parameters to zero. Patients subjected to Ozone Therapy showed 100% tolerance at the end of the study.

No significant post treatment change in any of the biochemical investigations was observed in both the groups like liver, kidney, and lipid profiles. This denotes safety of Ozone in management of COVID 19 on extra pulmonary organs as well. There was no abnormality in pulse rate; blood pressure was observed after treatment of Ozone and standard of care, suggesting safety of Ozone.

This efficacy of ozone in COVID 19 may be attributed to its cytokine modulation, [29] direct or indirect oxidation of viruses and by stimulating cellular and humoral responses [17]. The results of our study encourages the use of Ozone as an adjuvant in mild to moderate patients of COVID 19. The present research confirms safety and efficacy of the ozone therapy in COVID 19 patients. However, large scale multi-centric study with larger sample size is warranted.

5. Conclusion

Our study suggests that Ozone therapy is safe and effective to be used in COVID-19 patients who are in mild or moderate stage of the illness. Governments and policy makers should consider including Ozone therapy in the existing level of care which could possibly reduce the requirement of advanced treatment facilities and reduce morbidity and mortality rate. However, future studies are warranted to understand the magnitude of this change in these multiple domains that are affected by COVID-19.

Acknowledgements

The authors would like to thank Prof. (Dr.). K. Satyalakshmi, Director, National Institute of Naturopathy, all the patients and support staff who has supported us in completing this study.

Funding

This study was supported by Bisleri Charitable Trust, India.

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