Original Article

Efficacy of lignocaine nebulization in patients with COVID-19 respiratory infection: An exploratory randomized double-blinded controlled trial

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Abstract

Background and Aims: Coronavirus disease (COVID-19)-related pneumonia is proposed to be an inflammatory process. The treatment currently includes supportive therapy and low-dose steroids. Anti-inflammatory drugs have been proposed to prevent cytokine storms and improve oxygenation in such cases. The study aimed to assess the efficacy of nebulized lignocaine in COVID-19 patients with pneumonia.

Material and Methods: This was an exploratory randomized double-blinded control trial conducted in COVID-19 patients with respiratory failure requiring oxygen therapy either by face mask or non-invasive mechanical ventilation. Patients included were of the age of more than 18 years of either gender. The patients were randomized to receive either lignocaine or distilled water nebulization. The outcomes assessed were PaO_2/FiO_2 ratio, hemodynamics, respiratory parameters, and sequential organ failure score (SOFA).

Results: The two groups were comparable concerning demographic variables. The PaO_2/FiO_2 were significantly higher in the lignocaine group from day 2 onward. The SPO_2 was significantly higher on day 3 in the lignocaine group and thereafter there was no significant difference. Other hemodynamic, respiratory parameters, and SOFA scores showed no difference in both the groups.

Conclusion: Lignocaine nebulization improved oxygenation in COVID-19 patients and can be used as adjunctive therapy along with other supportive medications.

Keywords: COVID-19, nebulized lignocaine, pneumonia

Introduction

Coronavirus disease 2019 (COVID-19) caused by the novel coronavirus was declared a pandemic by the World Health Organization in early 2020.[1] It has presented varied symptomology affecting various parts of the body, of which pneumonia is one major concern to physicians.[2] It has resulted in high mortality and morbidity in the past 2 years. As the presentation and disease progression was very sparsely understood, the mainstay of treatment was supportive measures such as oxygenation, ventilation, and fluid management along with critical care support for patients needing mechanical ventilation. Many treatment modalities have been explored but very few have proven their efficacy definitively in the control of disease progression. These include antivirals, antimicrobials, low-dose steroids, and anticoagulants.[3]

One of the proposed and proven mechanisms of disease pathophysiology in patients presenting with pneumonia is the inflammatory process induced by the virus. Abnormal

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activation of T cells is the main cause of the excessive immune response.[4] Many drugs have been proposed for the same, and combinations of such non-specific treatments have been used to prevent cytokine storms during the course of the disease, which often turns out to be fatal.

Lignocaine is a local anesthetic agent and class-3 antiarrhythmic drug. Its primary site of action is on the voltage-gated sodium and calcium channels. It was observed that some of these receptors are also involved in the activation of T cells. The current exploratory study aimed to study the effect of nebulization of lignocaine in patients having lung involvement due to COVID-19 infection, with the hypothesis that it will lead to better oxygenation parameters in such patients compared to control. The primary objective was to compare oxygenation parameters on days 1 to 4 and secondary objectives were to compare hemodynamic, respiratory parameters and sequential organ failure score (SOFA) on days 1to 4.

Material and Methods

This was a randomized, double-blinded exploratory controlled trial, done at the COVID-19 intensive care units in our institute over a period of 5 months. The study protocol was approved by the institutional ethics committee (AIIMS/IEC/20/560 dated 22.08.2020) and was registered in clinical trials (CTRI/2020/11/029170 dated 17.11.2020). Patients were recruited after written informed consent, between November 2020 and March 2021. All necessary patient information explaining the study protocol, risks, and benefits was provided to all patients before signing the consent form. The healthcare personnel while caring for these patients wore standard personal protective equipment (PPE). The manuscript was prepared in accordance with the CONSORT statement for reporting trials.

Patients older than 18 years of both gender with RT PCR documented COVID-19 infection with respiratory distress (presence of hypoxia with SpO_2<93% or radiographic evidence of pneumonia, any single organ failure, sepsis) requiring supplemental oxygenation or non-invasive mechanical ventilation, irrespective of the day of illness were included in the study. Patients who refused to participate in the study, patients with a known allergy to lignocaine, and patients requiring invasive mechanical ventilation/septic shock during the study period were excluded from the study.

Patients were randomized into one of two groups: The lignocaine nebulization group or the control group (sterile water nebulization). Randomization was done by a computer-generated random numbers table and allocation concealment using serially numbered, sealed, opaque envelopes to minimize selection bias. The allocation ratio was 1:1. Patients randomized to lignocaine nebulization (Group L) group received lignocaine hydrochloride nebulization with 2 mL of 4% lignocaine mixed with 2 mL of distilled water in a nebulizing machine and supplemental oxygen was continued as per requirement. Patients randomized to the sterile water nebulization (Group C) received 4 mL of sterile water nebulization using a nebulizing machine and supplemental oxygen was continued as per requirement. Patients in both groups received interventions after 15 min of bronchodilator nebulization, which was given eighth hourly daily.

The study drugs were prepared by nursing personnel not involved in the study and were given a sealed envelope to open and prepare the appropriate intervention in a 5 mL syringe. This was handed over to the health care personnel who was administering the nebulization. The patient, the person administering the drug, and the outcome assessor were blinded to the group allocation.

As there was no similar study at the time of performing this study, an exploratory study was planned with the intent to do a *post hoc* power analysis after the documentation of the results. Approximately 20 participants were planned to be taken in each group (sample size of 40) based on the feasibility and institutional infrastructure.

The primary outcome was PaO_2/FiO_2 ratio (Horowitz index) on days 1 to 4 of the intervention. The secondary outcomes were systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate, oxygen saturation, and SOFA score from day 1 to day 4 of the intervention. The oxygenation values were taken from arterial blood gas every morning along with measurement of other outcome parameters.

The continuous variables such as age, weight, and height values are presented as mean ± standard deviation (SD) with a 95% confidence interval and analyzed with Student's *t*-test or Mann–Whitney *U* test as appropriate. The qualitative data were analyzed using Chi-square/Fisher's test as appropriate. Data analysis was done using the statistical software package SPSS vs. 20.0 (IBM, SPSS statistics 20.0). $P \leq 0.05$ was considered statistically significant.

Results

A total of 52 patients were assessed for eligibility. Ten ($n = 10$) patients were excluded based on exclusion criteria and one ($n = 1$) patient denied participation in the study. A total of 41 patients were included in this study and they were randomly

assigned to group L (n = 21) and group C (n = 20). Among 21 patients in group L, one patient (n = 1) required endotracheal intubation. In group C, none (n = 0) was excluded from the study. A total of 40 patients were analyzed at the end of the study [Figure 1]. In group L, 15% of patients were on NRBM and 40% were on NIV; in group C, 25% were on NRBM and 55% were on NIV.

The two groups were comparable concerning demographic variables [Table 1]. The oxygen requirement was measured using the fraction of inspired oxygen concentration (FiO_2) delivered by various O_2 delivery devices such as the NIV mask, Hudson mask, and nasal prongs. The average day of illness in both groups was 5 ± 2 days, and the percentage of death in both groups was 55%.

The PaO_2/FiO_2 ratio was used as a measure of lung function. The baseline ratio (P = 0.266) and day 1 (P = 0.407) were similar in both groups. From day 2 onward, the lignocaine group had a significantly higher PaO_2/FiO_2 ratio compared with the control group [Table 2]. Taking the difference in mean values of PaO_2/FiO_2 ratio on day 2, for *post hoc* power analysis, we achieved a power of 0.89 at a two-tailed alpha error of 0.05 taking 20 samples in each group.

Hemodynamic parameters between the two groups were comparable on all days of measurement [Table 3]. SPO_2 was significantly higher in the lignocaine group on day 3; thereafter, there was no significant difference in SPO_2 between the groups [Table 4]. The. SOFA score showed no significant difference in both groups [Table 5].

Discussion

Numerous studies and huge amounts of data on COVID-19 pneumonia have failed to provide definitive results in the

Table 1: Demographic parameters of two groups

Parameters	Group L (n=20)	Group C (n=20)	P
Age (years) Mean±SD	53±10	55±14	0.40
Sex (no/percentage)			
Male	17	11	0.08
Female	3	9	
Weight (Kg) Mean±SD	59±10	61±10	0.52
Height (cm) Mean±SD	149±6	150±8	0.40
BMI* (Kg/m^2) Mean±SD	22.8±2.2	24.0±2.4	0.20
Comorbidities (no/percentage)			0.86
Diabetes	9	11	
Hypertension	4	3	
CAD	3	3	

**BMI=Body mass index, CAD: Coronary artery disease*

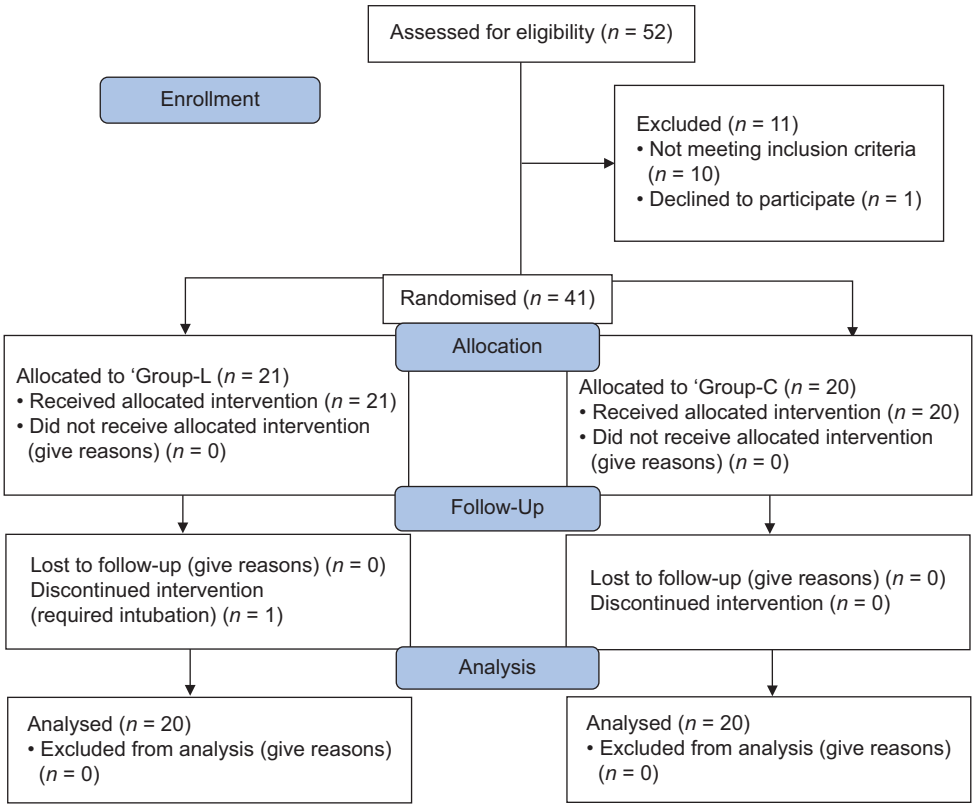

Figure 1: Consolidated standards of reporting trials (CONSORT) flowchart

Table 2: PaO_2/FiO_2 ratio (Horowitz index) of two groups

PaO_2/FiO_2 ratio (Mean±SD)	Group L (*n*=20)	Group C (*n*=20)	*P*
T0 (Baseline)	124.39±63.30	138.19±63.92	0.266
T1 (Day-1)	112.27±46.53	117±59.08	0.407
T2 (Day-2)	187±60.83	128.85±65.41	0.026
T3 (Day-3)	177.08±58.39	125.42±104.98	0.048
T4 (Day-4)	178.9±79.11	132.5±150.95	0.022

Table 3: Hemodynamic parameters of both groups

Parameters	Group L (*n*=20)	Group C (*n*=20)	*P*
Heart Rate (Mean±SD)/min			
T0 (Baseline)	86.21±20.11	86.36±16.93	0.48
T1 (Day-1)	85.89±16.42	83.32±10.81	0.28
T2 (Day-2)	81.12±23.84	85.23±9.33	0.23
T3 (Day-3)	84±23.4	87.90±9.60	0.44
T4 (Day-4)	87.5±20.04	84.24±9.24	0.47
Systolic Blood Pressure (Mean±SD), mm Hg			
T0 (Baseline)	125.95±14.47	125.5±17.05	0.46
T1 (Day-1)	121.05±12.46	121.42±12.41	0.47
T2 (Day-2)	128.59±9.80	125.18±14.77	0.21
T3 (Day-3)	127.65±14.20	127.76±14.77	0.49
T4 (Day-4)	125.81±15.12	125.52±15.95	0.47
Diastolic Blood Pressure (DBP) (Mean±SD), mmHg			
T0 (Baseline)	79.42±8.75	79.56±11.38	0.49
T1 (Day-1)	77.16±9.13	76.18±10.37	0.37
T2 (Day-2)	78.35±6.61	82±11.34	0.12
T3 (Day-3)	84.24±9.95	80.05±10.90	0.12
T4 (Day-4)	78.62±11.65	79.29±10.66	0.43

Table 4: Respiratory parameters of both the groups

Parameters	Group L (*n*=20)	Group C (*n*=20)	*P*
Oxygen Saturation (SpO_2) (Mean±SD) %			
T0 (Baseline)	94±3.14	95.32±2.12	0.11
T1 (Day-1)	94.11±3.69	93.68±4.58	0.37
T2 (Day-2)	96±4.04	93.67±4.07	0.04
T3 (Day-3)	94.69±4.84	94.86±2.55	0.44
T4 (Day-4)	95.25±2.93	94.86±2.56	0.37
Respiratory rate (Mean±SD)/min			
T0 (Baseline)	24.05±4.79	25.82±5.53	0.14
T1 (Day-1)	26.95±5.59	25.59±5.28	0.09
T2 (Day-2)	24.31±6.93	24.29±3.78	0.49
T3 (Day-3)	26.25±6.32	28.1±3.91	0.53
T4 (Day-4)	25.8±5.23	26.67±2.64	0.52

clinical improvement of such patients.[5] Although many trials have shown early positive results, long-term follow-up has still not proven efficacy. Steroids and other immunomodulatory drugs were found to be efficacious in the early stages and prevented serious disease in patients.[3-5]

Dysregulated inflammatory response plays a key role in the development of acute respiratory distress syndrome (ARDS) in COVID-19 pneumonia. Exacerbated stimulation of T cells and cytokines lead to increased vascular permeability in various organs contributing to the clinical picture of ARDS in these patients.[6,7] Lignocaine is a local anesthetic drug with antiarrhythmic properties and is hypothesized to possess anti-inflammatory properties, which may be utilized in COVID-19 pneumonia patients. As an anti-inflammatory drug, it can prevent cellular damage produced by inflammation in the lungs and other organs. Along with the action on sodium channels, lignocaine in lower concentrations has antithrombotic, antiarrhythmic, and antinociceptive actions.[8,9]

Tanaka *et al*, studied the effect of lignocaine in patients suffering from allergic asthma, which establishes the role of lignocaine as an anti-inflammatory drug.[10] It has been observed that inhaled lignocaine has glucocorticosteroid-sparing properties in atopic asthmatics as demonstrated by a significant reduction in symptoms, bronchodilator use, and blood eosinophilia.[11] In the present study, we have studied the effect of inhalational lignocaine on oxygen saturation and the requirement of oxygen following treatment. Findings corroborated the efficacy in such patients in terms of improvement in oxygenation and reduced requirement of oxygen therapy. Although there is limited literature on the use of lignocaine in the management of COVID-19 pneumonia, intravenous use was found to be beneficial in terms of attenuating the symptoms and pain and improvement in oxygen saturation.[12]

The current study had certain limitations. Contrast-enhanced computed tomography (CECT) chest was not done in all cases, and radiology data, and data on the day of illness could not be collected in other cases. Similarly, data on biological and inflammatory markers were also not accessible for the study, both of which could provide a better pathophysiological insight into the efficacy of our intervention. Our initial sample size was also small with a relatively short follow-up period. Future larger trials can be initiated in such cases with longer follow-ups.

To conclude, lignocaine nebulization is efficacious in improving oxygenation in COVID-19 patients with respiratory failure not requiring invasive ventilation. It has no effect on hemodynamics and no effect on the SOFA score. It can thus be used as an adjunct therapy in the management of COVID-19 patients along with other supportive medication. Larger multicenter trials can help to establish definitive efficacy in such cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have

Table 5: SOFA scores of both groups

SOFA Score (Mean±SD)	Group L (*n*=20)	Group C (*n*=20)	*P*
T0 (Baseline)	2.83±0.89	2.85±0.85	0.45
T1 (Day-1)	2.76±0.87	2.73±0.71	0.44
T2 (Day-2)	2.57±0.72	2.55±0.66	0.52
T3 (Day-3)	2.64±0.71	2.55±0.51	0.55
T4 (Day-4)	2.69±0.60	2.7±0.64	0.43

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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