Section: Anesthesiology

Original Research Article

# TO ESTIMATE THE EFFICACY OF INHALED CORTICOSTEROID IN-PATIENT OF MODERATE COVID -19 PNEUMONIA- RANDOMIZED CONTROLLED STUDY

**Sangeeta Dhanger[1], Pratheeba Natrajan[2], Ravindra Bhat[2], Bhavani Vaidiyanathan[1]**

[1]Associate Professor, Department of Anesthesiology, Indira Gandhi Medical College &Research Institute, Puducherry, India
[2]Professor, Department of Anesthesiology, Indira Gandhi Medical College &Research Institute, Puducherry, India

*Received* : 16/07/2023
*Received in revised form* : 26/08/2023
*Accepted* : 07/09/2023

*Keywords:*
*SARS-CoV-2, pneumonia, inhalational, steroids.*

Corresponding Author:
**Dr. Bhavani Vaidiyanathan,**
Email: bhavanivaidiyanathan@gmail.com

DOI: 10.47009/jamp.2023.5.5.101

Source of Support: Nil,
Conflict of Interest: None declared

*Int J Acad Med Pharm*
2023; 5 (5); 517-521

## Abstract

**Background:** Systemic corticosteroids have been found to reduce the mortality in patients with moderated and severe COVID-19 pneumonia in the first and second waves of the pandemic but had the unwanted effects which can be avoided when the corticosteroids are given via the inhalational route (ICS). Therefore in this study, we aimed to investigate whether Inhaled Corticosteroid MDI – Budesonide could reduce the morbidity in patients with moderate COVID-19 pneumonia. Our primary objective was to study the time to clinical improvement in days (Time Frame: Up to 14 days), defined as the resolution of all systemic and respiratory symptoms (SPO2 > 92% in room air, RR 14-16/min, for ≥2 consecutive days). **Materials and Methods:** After obtaining approval from Institute Research and Ethics committee and following CTRI registration, this randomized controlled study was carried out from January to March 2022 in a covid dedicated hospital. Eighty participants were enrolled and written informed consent was obtained. The study interventions began within 6–12 h of confirmation of diagnosis with RT PCR report and CT scan of thorax (CORAD Score 2-3) of moderate COVID 19. Participants were randomized by the computer-generated random number table and were divided in to two groups: S (Intervention) group and C (control) group. Both the groups received the Covid 19 care as per the hospital treatment protocol. In addition, participants of Group S received Inhaled Budesonide MDI (metered dose inhaler) 2 puff (400mcg) two times in a day for 14 days. All patients were hourly monitored and following parameters were recorded daily for 14 days: GCS, HR, NIBP, SPO2, HR, Temperature, mode of Oxygen therapy: (FM/ VM/ NRBM/ NIV/ IV) and FIO2. Study end point may be before 14 days incase of patient was shifted to ICU due to requirement of mechanical ventilation or incase of adverse outcome within 14 days. **Result:** The results of this study showed that budesonide nebulization significantly reduced morbidity as there were significant difference between both the group in the number of days requirement of oxygen in Group C 31± 5 days and Group S 7 ± 4 days, number of patient shifted to ICU in Group C 23 and Group S 5 and number of patients expired in Group C 13 and Group S only 4. Discussion is Budesonide is an inhaled glucocorticoid, which inhibits a variety of inflammatory cells, reduces the production of inflammatory mediators and consequently has a significant anti-inflammatory effect. Compared to systemic glucocorticoids, budesonide inhalation has the following advantages; high concentration primarily in the lungs, high hepatic clearance, and high glucocorticoid receptor affinity. During nebulization, the nebulizer unit breaks the liquid into micro-particles, which are directly inhaled into the lower respiratory tract and rapidly absorbed by the pulmonary mucosa, thus increasing the local drug concentration. **Conclusion:** Inhaled budesonide in patient with moderate covid pneumonia improved oxygenation and significantly reduced hospital stay without any side effect.

## INTRODUCTION

Systemic corticosteroids, which include Injection Dexamethasone and Injection Methyl-prednisolone, have been proved to reduce mortality in patients with severe COVID-19 pneumonia while the first and second pandemic waves.[1-3] But usage of systemic corticosteroids in the treatment of SARS-CoV-2 pneumonia patients has been linked to an increased prevalence of Mucor mycosis.[4,5]

There are too little clinical data to support the use of systemic steroid administration in the treatment of respiratory syncytial virus, influenza, severe acute respiratory syndrome coronavirus (SARS-CoV-2), or Middle East Respiratory syndrome coronavirus (MERS-CoV) respiratory infections, as stated in the WHO guidelines. Next, numerous authors debated whether or not systemic corticosteroids would be effective in treating COVID-19, providing both arguments for and against using them. The inhalational route (ICS) of delivery of corticosteroids, on the other hand, prevents the side effects that occur after systemic administration. When Inhalational Corticosteroid (ICS) was administered to patients at risk for acute respiratory distress syndrome (ARDS), significant physiological improvement and decreased levels of inflammatory markers were noted. Data from in vitro studies have also implicated ICS in blocking the reproduction of coronaviruses (such as SARS-CoV-2) in infected epithelial cells.[6,7] Additional clinical trials evaluating the efficacy of ICS as a standalone treatment intervention in COVID-19 are still warranted. In this study, we wanted to determine whether Inhaled Corticosteroid MDI – Budesonide could reduce morbidity in COVID-19 pneumonia patients with mild to moderate disease severity. Our primary research goal was to determine how long it takes for patients to experience clinical improvement, which we defined as the disappearance of all systemic and respiratory symptoms (SPO2 > 92% in ambient air, RR 14-16/min, for 2 consecutive days). The secondary objectives were 1) To investigate the length of hospitalization [Duration in days from hospital admission to discharge or mortality]. 2) To investigate the proportion of clinical failure (increased oxygen requirement to maintain SPO2 >92%, RR >24/min required admission to the intensive care unit, mechanical ventilation, or death [Duration: up to fourteen days]). 3) Investigate any adverse effects (such as increased blood sugar or a fungal infection on the skin) caused by the study medicine during a period of up to 14 days.

## MATERIALS AND METHODS

This controlled trial was conducted in a Covid dedicated hospital from January to March of 2022. After receiving approval from the Institute's Research and Ethics Committee and registering with the CTRI (CTRI NO. REF/2021/09/046997), 80 participants were enrolled and informed consent was obtained in writing. The research interventions started between 6 and 12 hours after the RT PCR report and CT scan of the chest confirmed a moderate case of COVID 19. Following admission, all patients with moderate COVID pneumonia were treated in accordance with ICMR and MOH & FW (Indian Council of Medical Research and Ministry of Health and Family Welfare) guidelines. Patients (male or female) aged 18 and above who reported with moderate COVID 19 within 7 days of symptom start (fever, cough, cold, diarrhea, and/or breathing problems) and who had been diagnosed with the virus in the lab (SARS-CoV-2 RT-PCR and CT Thorax) were included in the study. The exclusion criteria were patients with mild (does not require hospital admission), moderate (does not require mechanical ventilation), or severe (required mechanical ventilation or Hypoxia (SpO2 92% at room air, Unable to take oral medication, Unable to use inhaler, Pregnancy or breast feeding, Immunocompromised, Participants with moderate or severe renal dysfunction (creatinine clearance (CCL) 30 mL/min) or moderate or severe liver dysfunction (AST or ALT > 5 times upper normal limit) were also excluded, as were those who were unwilling to give informed consent, were younger than 18 years old, or had Pneumonia, COPD, or RFI due to some other condition. Participants were randomly assigned to either the S (Intervention) group or the C (control) group using a computer-generated random number table. The standard hospital care for Covid 19 was administered to both groups. In addition, Group S participants received inhaled Budesonide MDI (metered dose inhaler) 2 puff (400 mcg) twice a day for 14 days (proper methods for using MDI were taught to the patient and patient attender prior to the start of treatment; see [Figure 1]). Patients were constantly monitored (heart rate, oxygen saturation, respiratory rate, and non-invasive blood pressure). Spo2 if decreased to 94% at room air and or RR >20/min, and ABG was performed, and oxygen therapy was initiated with an oxygen mask at a flow rate of 6-8 litres per minute. After 2 hours with no change, we hooked up VM at 50-70% and/or NRBM at 10-15 l/min. Additional oxygen was supplied by non-invasive ventilation (NIV) and invasive ventilation (IV) for patients with a higher oxygen demand. Artificial breathing system. The following parameters were recorded daily for 14 days (for statistical computation) from all patients: GCS, heart rate, NIBP, SPO2, heart rate, temperature, oxygen delivery method (FM, VM, NRBM, NIV, IV), and fiO2. Enteral feeding (when GCS >10) and parental feeding (when GCS 10) were used to keep the patient hydrated (Euvolemia and Euglycemia were maintained, respectively). If the patient required mechanical ventilation or a poor outcome occurred within 14 days, the study may be terminated early.

The sample size was determined using Ly-Mee Yu's et al,[8] research. Early, persistent recovery from ARDS was reported to be 10% higher in the inhaled budesonide group compared to the conventional care


ISSN (O): 2687-5365; ISSN (P): 2753-6556

group. Using a 5% alpha error and 80% research power, the minimum number of subjects needed in each group is 37. 40 people were assigned to each group so that we could account for a 10% attrition rate.

SPSS version 20 was used for the statistical analysis. If the data are regularly distributed, the median (interquartile range) is used to describe the data, but if the data are not normally distributed, the mean standard deviation is used. The unpaired t-test was used to compare regularly distributed data, while the rank sum test was used to examine data that did not follow a normal distribution. The Chi-square test was utilised to compare the two groups' baseline clinical characteristics. P 0.05 was used as the threshold for statistical significant.

## RESULTS

This investigation was conducted on 80 adult patients admitted to the High dependency unit (HDU) of a COVID-dedicated hospital with moderate COVID pneumonia. [Table 1] shows that both groups had comparable demographics. [Table 2] shows that the average time people needed oxygen was much less in the Budesonide inhalation group (Group S) compared to the control group (Group C) (7.3 days vs 31.5 days). There were lesser fatalities and fewer transfers to the intensive care unit for mechanical ventilation among patients in group S compared to group C. After only 2 weeks of treatment, 31 of 40 patients in group S were able to return home, while only 10 of 40 patients in group C were able to do so. The contrast was statistically significant. ($p<0.005$). Clinical progress after 14 days is depicted graphically in Figure 2 for both patient groups. In contrast to the steroid group, the control group spent a median of 32 days in the hospital during their treatment. The log rank test confirmed the significance of the difference.

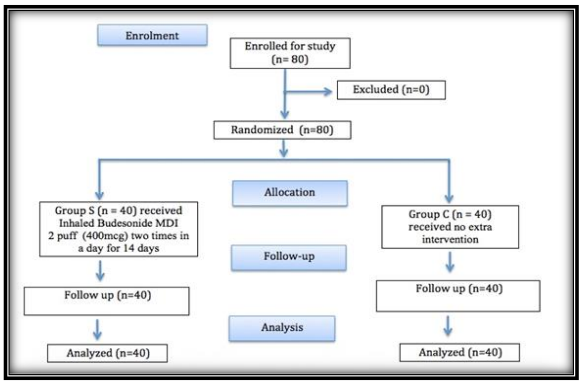


**Figure 1: CONSORT Chart**

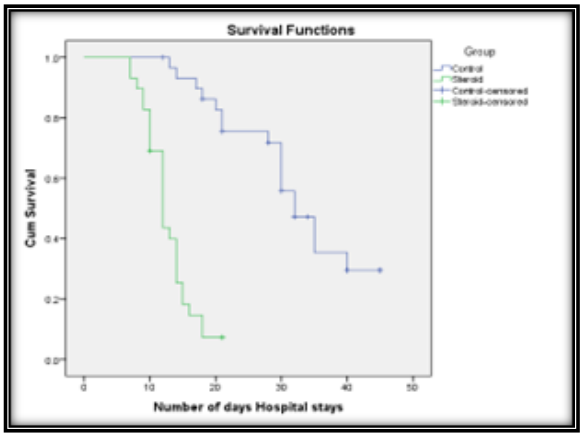


**Figure 2: Graphical representing the comparison between group S and group C in the time to clinical improvement in days.**

**Table 1: comparison of demographic Profile between group C and group S.**

| SN | Variables | Group C N= 40 | Group S N=40 | P value |
|---|---|---|---|---|
| | | Median (IQR) | Mean (SD) | |
| 1 | Age (in Years) | 45.77 (39-52) | 49.67 (38-57) | 0.157 |
| 2 | Sex (Female/Male0 | 22/28 | 21/29 | 0.791 |
| 3 | BMI Kg M-2 (median) | 22.5 (19.1-24.5) | 23.1(19.2-25.60 | 0.812 |
| 4 | CORAD Score (median) | 2 (1-3) | 2(1-3) | 0.823 |
| 5 | Comorbidity | | | |
| | Nil | 13 | 10 | 0.986 |
| | DM | 12 | 14 | |
| | HTN | 9 | 10 | |
| | BA | 2 | 2 | |
| | COPD | 1 | 1 | |
| | CAD | 2 | 2 | |
| | Hypothyroid | 1 | 1 | |
| 6 | Duration of illness before hospital admission in days (median) | 3 (2-5) | 4(2-5) | 0.834 |

Foot Note: Values are in Median and Inter Quartile range (IQR)

**Table 2: Comparison of oxygen requirement , stay in ICU and the disease outcome between the two group.**

| SN | Variables | Group C | Group S | P value |
|---|---|---|---|---|
| | | Mean (SD) | Mean (SD) | |
| 1 | Total duration (in days) of O2 therapy requirement | 31± 5 | 7 ± 4 | 0.0001* |
| 2 | Number of patient shifted to ICU | 23 | 5 | <0.001* |
| 3 | Number of patient Discharged home | 10 | 31 | 0.0001* |
| 4 | Number of patients Expired | 7 | 4 | 0.004* |

Foot note: Values are in mean and standard deviation (SD).

* P <0.005 is showing the difference is statistically significant.


ISSN (O): 2687-5365; ISSN (P): 2753-6556

## DISCUSSION

Our research shows that patients with moderate COVID pneumonia benefit greatly from inhaled budesonide without experiencing any negative consequences. Inhalation of budesonide minimizes inflammation by suppressing the activation of several types of inflammatory cells and so decreasing the generation of inflammatory mediators. In addition, it prevents airway remodeling by constricting blood vessels, decreasing mucosal edema, and decreasing cell exudation.[9] Unlike systemic steroids, inhaled steroids are safer because of their rapid hepatic clearance and low concentration in tissues surrounding the liver and kidneys (the effector site).Studies on asthma patients have shown that inhaled steroids with a particle size of 1 m can reach the distal airways and reduce lung inflammation.[10,11] Since SARS-CoV 19 is an emerging illness, scientists are still trying to understand the factors that contribute to its clinical progression. Clinical manifestations of SARS-CoV 19 infection have been described as occurring in three distinct phases: (1) initial infection (viral entry into the body via the nasal cavity); (2) pulmonary involvement with inflammation (epithelial damage; inflammation; and diffuse alveolar damage); and (3) lung fibrosis (typically after 3 weeks) and other organ involvement. The initial phase of virus reproduction is usually eliminated by our specialized and appropriate immune system responses. If not, cytokine storm triggers the hyperinflammatory phase.[12,13] Innate immune cells secrete inflammatory mediators that promote lung fibrosis and other systemic damage, ultimately leading to acute respiratory distress syndrome and death. Patients with COVID pneumonia who received intravenous steroid treatment early on (during the acute phase of the disease) showed considerable clinical improvement, according to two studies.[14,15] The systemic effects of steroids, such as increased blood sugar, inhibition of the hypothalamic-pituitary-adrenal axis, bone demineralization, perforated peptic ulcer, and impaired immunity, are avoided by inhaling budesonide-treatment of human respiratory epithelial cells in vitro with budesonide results in inhibitory activities on replication and cytokine generation of coronavirus HCoV-229E.[16-18] In addition, there is evidence to suggest that ciclesonide prevents the reproduction of SARS-CoV-2 ribonucleic acid in vitro and suppresses its cytopathic action. Reduced disease progression as a result of inhalational steroid treatment was the primary finding of our investigation.[19] In our research, indicators of disease severity and treatment failure included oxygen therapy and mechanical ventilation necessity. Our findings, similar to those of the Cruc study, showed that inhalational steroid treatment dramatically reduced the number of days patients needed oxygen or required mechanical breathing. In a meta-analysis that included trials of both severe and mild cases of community-acquired pneumonia, Brown et al,[20] found that the administration of inhalational steroids during the acute phase of the disease was associated with a reduced risk of death.[21]

## CONCLUSION

Our investigation demonstrated the advantages of using an inhalation steroid during the acute stage of SAR CO-A virus infection. There is no systemic effect from inhalation therapy because the medications go straight to the lungs. It will be important to thoroughly optimize drug and device-related parameters for optimal drug delivery given the difficulty of getting drugs to patients with damaged lungs.

## REFERENCES


1. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA - J Am Med Assoc. 2020 Apr 7;323(13):1239–42.
2. Patel, Vijay K et al. “Corticosteroids for treatment of COVID-19: effect, evidence, expectation and extent.” Beni-Suef University journal of basic and applied sciences vol. 10,1 (2021): 78.
3. Wagner A, Weinberger B. Vaccines to Prevent Infectious Diseases in the Older Population: Immunological Challenges and Future Perspectives. Front Immunol. 2020;11:717
4. Al-Tawfiq JA, Alhumaid S, Alshukairi AN, et al. COVID-19 and mucormycosis superinfection: the perfect storm. Infection. 2021;49(5):833-853
5. Selarka L, Sharma S, Saini D, et al. Mucormycosis and COVID-19: An epidemic within a pandemic in India. Mycoses. 2021;64(10):1253-1260
6. Griesel M, Wagner C, Mikolajewska A, et al. Inhaled corticosteroids for the treatment of COVID-19. Cochrane Database Syst Rev. 2022;3(3):CD015125
7. Kino T, Burd I, Segars JH. Dexamethasone for Severe COVID-19: How Does It Work at Cellular and Molecular Levels?. Int J Mol Sci. 2021;22(13):6764
8. Yu LM, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet ;398(10303):843–55.
9. Papi A, Marku B, Scichilone N, et al. Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. Lancet Respir Med. 2015;3(2):109-119.
10. Pandya D, Puttanna A, Balagopal V. Systemic effects of inhaled corticosteroids: an overview. Open Respir Med J. 2014;8:59-65
11. Berlinski A. 2019 Year in Review: Aerosol Therapy. Respir Care. 2020;65(5):705-712
12. Gao YD, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2021;76(2):428-455
13. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-513.
14. Fiolet T, Kherabi Y, MacDonald CJ etal. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. Clin Microbiol Infect. 2022;28(2):202-221
15. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-613




ISSN (O): 2687-5365; ISSN (P): 2753-6556

16. Omolo CA, Soni N, Fasiku VO, Mackraj I, Govender T. Update on therapeutic approaches and emerging therapies for SARS-CoV-2 virus. Eur J Pharmacol. 2020;883:173348.
17. Eedara BB, Alabsi W, Encinas-Basurto D et al.Inhalation Delivery for the Treatment and Prevention of COVID-19 Infection. Pharmaceutics. 2021;13(7):1077
18. Yamaya M, Nishimura H, Deng X, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. Respir Investig. 2020;58(3):155-168.
19. Song JY, Yoon JG, Seo YB, et al. Ciclesonide Inhaler Treatment for Mild-to-Moderate COVID-19: A Randomized, Open-Label, Phase 2 Trial. J Clin Med. 2021;10(16):3545.
20. Cruciani M, Pati I, Masiello F, Pupella S, De Angelis V. Corticosteroids use for COVID-19: an overview of systematic reviews. Infez Med. 2022;30(4):469-479.
21. Brown SM, Dean NC. Defining severe pneumonia. Clin Chest Med. 2011;32(3):469-479


ISSN (O): 2687-5365; ISSN (P): 2753-6556