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Effect of Inhaled Corticosteroids in Mild COVID Cases: A Prospective Study

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Abstract: Inhaled corticosteroids are well established for the long-term treatment of inflammatory respiratory diseases such as asthma or chronic obstructive pulmonary disease. They have been investigated for the treatment of coronavirus disease 2019 (COVID-19). The anti-inflammatory action of inhaled corticosteroids might have the potential to reduce the risk of severe illness resulting from hyper-inflammation in COVID-19. Hence we undertook this study to assess the effectiveness of corticosteroids in reduction of COVID-19–related cough.

Keywords: COVID-19, corticosteroids, Budesonide

Introduction: The coronavirus disease 2019 (COVID-19) pandemic has resulted in an unparalleled effect on global health. Caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it led to three consecutive waves. Due to the initial lack of effective vaccines or their restricted availability, social distancing and use of masks were the major means of preventingthe snowballing of this highly infectious disease. Among the various symptoms, dry cough is the key symptom of this viral infection during the acute phase in the majority of the hosts, and in some,it continues after the infective phase. More than two-thirds of the symptomatic patients infected with SARS-CoV-2 suffer from persistent cough. Grant *et al.*[1] in their systematic review which included data from more than 21,000 infected patients reported cough in 57%. An attempt to understand the mechanism deeper has revealed increased bronchial reactivity during this acute viral infection, which leads to impaired airflow. Cough, which is major manifestation in acute bronchitis,

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can thus be a result of this increased bronchial reactivity. A retrospective study found that median time was a single day from the onset of the disease to cough. The mean duration of cough was 19 days, and it persisted for an average of 19 days.[2] Besides, cough is a wearisome and exasperating symptom affecting the daily life of the infected patient. Apart from the morbidity associated with cough, it also enhances transmission of this viral infection through droplets. Therefore, curbing cough is crucial to limit its spread. Patients often administer over-the-counter products and antitussive agents which have no proven benefit. Moreover, insufficient effective antitussive agents are available for virus-mediated cough; besides, these are not often used clinically.[3] Inhalational corticosteroid like budesonide, helps in reducing cough symptoms by reducing inflammatory mediators in the airway.[4] Budesonide is a corticosteroid and can contain the inflammatory reaction regionally in the respiratory tract[5]. We, therefore, proposed that cough associated with COVID-19 and other indicative clinical outcomes may be alleviated with budesonide and undertook this study to assess the effectiveness of budesonide in reduction of COVID-19–related cough.

Materials and Methods: A prospective, observational study was conducted in mild COVID-19 patients who presented with a cough score ≥8 at presentation. The study was conducted in Tertiary care hospital, Bangalore from June 2020 to December 2020. The institutional ethics committee's approval was obtained before the commencement of the study. Demographic data using a pre-structured data collection form was obtained from the participants before their enrolment. The study included COVID-19 real-time polymerase chain reaction (RT-PCR)-positive patients who presented with a cough score ≥8 at presentation and had symptoms for 5 to 10 days. Patients were followed up till 28th day from the symptoms' onset. A convenience sampling strategy was considered. Patients who were initiated on budesonide MDI were observed as group A and those not initiated on budesonide were observed as group B. For those in group A, patients were advised to take two puffs twice daily for 7 days, with each puff containing budesonide 400 mcg. As a part of usual care, both groups were getting Indian Council of Medical Research (ICMR) COVID-19 guideline- directed therapy on SOS basis. Each group was matched for gender, age, history of allergic diseases and other comorbidities. The cough symptom score (CSS), proposed by Hsu *et al.*[6] in 1994, which was prepared based on patient's intuitive perception and oral expression of cough, was used. The CSS has a two-part questionnaire including both daytime and night-time symptoms. Depending upon the frequency, intensity and influence of cough on daily activities and sleep, cough symptoms were scored from 0 to 5, with 0 indicating no cough and 5 indicating the most severe cough. We calculated both night-time and daytime CSS together; a score of 10 was maximum, whereas 0 was the minimum

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score.[6] CSS (at baseline and on day 3 and day 7), the incidence of hospital admission and/or death, and need for mechanical ventilation were documented. Prescribing patterns of anti-cough medications were also noted and analysed. Data were checked for completeness and statistically analysed. Descriptive data was represented as mean or percentage as applicable. Where applicable, hypothesis testing was done using Student's *t*-test and measures of association were analysed using Chi-square test and Pearson's correlation coefficient. Different levels were expressed at 95% confidence interval. A *P* value of less than 0.05 has been considered statistically significant. All statistical analyses for various measures were performed using various statistical software packages like Statistical Package for the Social Sciences (Windows version 21.0; SPSS Inc, Chicago, IL, USA) and Microsoft Excel.

Results: A total of 100 adults diagnosed with COVID-19 were included in the study. Group A consisted of50 patients prescribed budesonide MDI, and group B consisted of 50 COVID-19 patients not initiated on any MDI. The demographic data of the patients is presented in Table 1. There was no significant difference in the demographic characteristics between both groups.

Table 1: Demographic details

Demographics		**Group A (N %)**	**Group B (N %)**	**P value**
Age (in years)	21-40	17 (34%)	20 (40%)	0.3812
	41-60	10 (20%)	12 (24%)	
	> 60	23 (46%)	18 (36%)	
Mean age (years)		34.66 ± 1.12	38.57 ± 1.01	0.3645
Gender	Male	32 (64%)	34 (68%)	0.4812
	Female	18 (36%)	16 (32%)	
History of allergy/atopic disease	Yes	16 (32%)	15 (30%)	0.4165
	No	34 (%)	35 (70%)	
Comorbidities	Hypertension	15 (30%)	12 (24%)	
	Asthma	4 (8%)	4 (8%)	
	Type 2 diabetes	16 (32%)	13 (26%)	
	Hypothyroidism	10 (20%)	11 (22%)	
	Dyslipidaemia	11 (22%)	12 (24%)	
	Nil	14 (28%)	18 (36%)	

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The mean latency of MDI initiation from symptom onset was observed to be 5.98 ± 1.83 days. Cough score was noted for all participants at baseline, and reduction from baseline value was assessed at day 3 and day 7, respectively. Compared to group B, a higher mean cough score reduction was noted for group A at day 3 and day 7 when compared to the baseline, which was significant at $P < 0.001$ [Table 2].

Table 2: Cough score reduction

		Group A	Group B	
Mean cough score	Baseline	9.41 ± 0.50	9.250 ± 0.86	0.5816
	Day 3	4.61 ± 1.43	5.86± 1.13	0.001
	Day 7	1.13 ± 1.04	3.25 ± 1.91	0.001
Mean score reduciton	Baseline versus Day 3	5.89 ± 1.59	4.57 ± 1.75	0.043
	Baseline versus Day 7	7.45 ± 1.52	5.23 ± 2.01	0.012

A significant negative correlation was also observed between mean latency of MDI initiation from the symptom onset and mean cough score reduction (Pearson's correlation = −0.514, $P < 0.01$)

The assessment of other clinical outcomes is represented in Table 3. The obtained results indicate that the incidence of hospitalisation, need for mechanical ventilation and fatal outcomes were numerically higher in group B in comparison to group A. Significantly higher prescribing of medications to treat cough like chlorpheniramine maleate + levodropropizine was observed in group B ($P = 0.015$).

Table 3: Outcome assessment

Outcome	Group A(N %)	Group B(N %)	χ^2	P value
Hospital admission	2 (4%)	12 (24%)	2.9109	0.08
Mechanical ventilation	1 (2%)	4 (8%)	0.2211	0.63
Death	1 (2%)	3 (6%)	0.5324	0.45

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Discussion: The current prospective, observational study on SARS-CoV-2 infected patients showed that they were found to benefit from the use of an inhaled corticosteroid. Use of budesonide inhaler led to significantly greater decreases in cough scores compared to baseline and the group with no such treatment as well. Further, the other clinical outcomes also favored the use of the budesonide MDI.

Al Sulaiman *et al.*,[7] in their recent non-interventional study including 130 patients treated with ICS/LABA, found significantly lower 30-day mortality (−47%, $P = 0.03$). Similar to our study results, the in-hospital mortality and mechanical ventilation days were not statistically significant between the two groups. The STOIC study which included adults with new-onset cough and feveror anosmia or both within 7 days showed that early administration of inhaled budesonide reduced the probability of necessitating imperative hospitalisations compared to usual care. Its use also lessened the time to recovery.[8] A systematic review meta-analysis reported similar reduction in the risk of admission to hospital or death up to day 30.[9]

Studies have shown that ICS controller therapy in patients with chronic respiratory diseases possibly offers protection against viral triggers such as SARS-CoV-2.[10] ICS use in patients with asthma is associated with decreased expression of angiotensin-converting enzyme 2 (ACE2), the receptor of SARS-CoV-2, in induced sputum.[11] Similarly, ICS therapies in COPD diminish the expression of these receptors, largely expressed in the upper respiratory tract of humans as the opening wedge for SARS-CoV-2.[11,12] *In vitro* studies have also shown that ICS block impedes its cytopathogenic effect. Thus, ICS may reduce the risk and intensity of SARS-CoV-2 infection, thereby reducing its manifestations.[13]

Viral invasion of the respiratory epithelium results in the release of pro-inflammatory cytokines including interleukin (IL)-8 and Granulocyte-macrophage colony-stimulating factor (GM-CSF), which recruit, trigger and upregulate immune cells in the airway.[14] Also, the expression of adhesion molecules and immunity-related molecules is increased by respiratory viral infection.[15] Budesonide reduces airway inflammation by its acute anti-inflammatory effect and also limits the excessive stimulation of immune cells.[16] The budesonide has additive effects on the inhibition of cytokine release, adhesion molecule expression and viral replication.

Limitations and future perspectives: Definite findings generally are obtained from randomised controlled studies rather than observational ones. Ours was an observational study conducted in a limited number of patients for a short follow-up period, though it is appropriate and adequate for

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symptomatic relief findings like an acute cough. However, several randomised controlled trials are ongoing to elucidate the role of ICS/LABA in treating COVID-19 patients without chronic respiratory diseases. Until more robust evidence becomes available, we suggest that evidence generated from observational studies should be construed carefully.

Conclusion: Our study showed that patients infected with SARS-CoV-2 COVID-19 treated with budesonide MDI along with usual care benefitted significantly in terms of symptom reduction compared to usual care alone. The symptomatic improvement may translate into a quicker return to normal life.

Ethical approval: The study has been approved by the Ethics Committee vide letter no.

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Conflicts of interest: There are no conflicts of interest.

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