RESEARCH PAPER

Comparative Efficacy of Nebulized Budesonide Versus Systemic Corticosteroids in Acute Exacerbation of COPD

Bashir Ahmed Memon[1], Ganiyev Sardor Saminjonovich[2], Saima Alam[3], Waqas Rasheed[4], Abdul Majeed Akhtar[5], Ihsan Ullah[6]*

[1]Senior Registrar, Department of Internal Medicine, Akhtar Saeed Medical College Rawalpindi, Farooq Hospital, Rawalpindi, Punjab, Pakistan.
[2]Assistant Teacher, Department of Endocrinology, Hematology and Faziatryia, Fergana Medical Institute of Public Health, 2A Yangi Turon Street 150100 Uzbekistan.
[3]Associate Professor, Department of Pulmonology and Allergy, Rehman Medical Institute, Peshawar, KP, Pakistan.
[4]Assistant Professor of Pulmonology, Department of Medicine & Allied, Jinnah Medical and Dental College, Medicare General Hospital, Karachim Pakistan.
[5]Professor University Institute of Public Health, The University of Lahore, Pakistan.
[6]Associate Professor Pharmacology, Saidu Medical College, Swat, Pakistan.

***Corresponding:** Ihsan Ullah,
Associate Professor Pharmacology, Saidu Medical College, Swat, Pakistan. Email: drahsanz@gmail.com

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ABSTRACT

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) have been shown to have significant morbidity and healthcare utilization. Systemic corticosteroids are commonly used and can have significant side effects. The nebulized budesonide may offer an alternative with lower systemic uptake.

Objective: To compare the efficacy and safety of nebulized budesonide versus systemic corticosteroids in patients with AECOPD.

Methods: This was a comparative interventional study that recruited 160 patients with AECOPD, with 80 patients in each group. Group A was given nebulized budesonide, and Group B was given systemic corticosteroids. The clinical improvement, respiratory parameters, treatment success, hospital stay, and adverse events were compared.

Results: Both groups demonstrated improvement in clinical and respiratory parameters. Mean CAT score reduction was 8.7 ± 3.1 in Group A and 9.6 ± 3.3 in Group B (p=0.08). Success in treatment was 87.5% and 90.0% (p=0.61), and median hospital stay was five days in both groups (p=0.41). Nebulized budesonide had significantly fewer overall adverse events than budesonide (17.5% versus 36.3%, respectively, p=0.007). Hyperglycemia occurred in 6.3% versus 17.5% (p=0.027).

Conclusion: Nebulized budesonide achieved similar short-term clinical benefits and fewer adverse events than systemic corticosteroids.

Keywords: COPD; Acute Exacerbation; Budesonide Nebulisation; Systemic Steroids; Treatment Effectiveness

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INTRODUCTION

The condition is chronic obstructive pulmonary disease (COPD), which is a heterogeneous disorder of the lungs in which airflow limitation is permanent, the lesions are chronic respiratory symptoms, and the lesions are progressive.[1] An acute exacerbation of COPD (AECOPD) is a clinically significant illness in which symptoms of dyspnea, cough, and sputum production deteriorate beyond the usual day-to-day variation in COPD and necessitate pharmacological interventions or hospitalization.[2] These attacks play a significant role in disease burden, reduced quality of life, health service utilization, and mortality.[3] According to the World Health Organization, COPD remains one of the leading causes of death worldwide, accounting for approximately 3.5 million deaths in 2021, representing nearly 5% of all global deaths.[4] The increasing burden of COPD, particularly in low- and middle-income countries, highlights the importance of identifying effective and safer treatment strategies for acute exacerbations.

In moderate-to-severe AECOPD, systemic corticosteroids are a known part of pharmacologic therapy due to their potent anti-inflammatory properties.[5] They decrease airway inflammation, enhance lung function, quicken recovery, and shorten hospital stays.[6] The systemic administration is, however, correlated with clinically relevant side effects such as hyperglycaemia, hypertension, gastrointestinal troubles, mood disorders,

and an increased risk of infections.[7] These issues are especially significant in the older patient and in those with diabetes mellitus, cardiovascular disease, and other comorbidities.[8] There is a tendency to give systemic corticosteroids in short courses, but there has been interest in exploring alternative methods of corticosteroid delivery which might achieve similar clinical responses while minimizing systemic exposure.[6]

The use of nebulized budesonide is becoming a possible alternative as the drug provides high local anti-inflammatory activity, with minimal systemic exposure.[9] Budesonide decreases the inflammation of the airway mucosa, the recruitment of inflammatory cells, and the cytokine-mediated responses, which all contribute to the improvement of airflow and respiratory symptoms.[10] Nebulized administration may be especially beneficial if the patient is very short of breath or unable to coordinate the use of an inhaler.[11] A 2022 systematic review and meta-analysis of 22 studies and 5,764 patients found similar benefits of forced expiratory volume in 1 second (FEV1), arterial levels of oxygen and carbon dioxide and oxygen saturation with nebulized and systemic corticosteroids.[12] Moreover, systemic corticosteroid treatment was linked to an increased risk of gastrointestinal symptoms and hyperglycemia, suggesting the possible safety benefits of nebulized therapy.[12]

More recent studies have reinforced the desire to compare these two therapy options. In a systematic review and meta-analysis published in the European Respiratory Review in 2024, which included 20 randomized and quasi-randomized studies with 2,140 patients, there was no clear evidence of superiority of systemic corticosteroid therapy over inhaled corticosteroid therapy for key clinical outcomes, such as treatment failure, breathlessness and serious adverse events.[13] There was also a trend towards fewer overall adverse events, less hyperglycaemia, and less certainty of evidence for this with inhaled corticosteroids. However, systemic corticosteroid therapy is the standard treatment for moderate to severe exacerbations, and is recommended by current GOLD guidelines for a short course of prednisolone 40 mg per day for 5 days.[6] These results indicate the nebulized budesonide may represent a clinically effective alternative for selected patients, but additional comparative clinical data are needed.

Although systemic corticosteroids are well established in the treatment of AECOPD, the potential for adverse effects is another major concern in clinical practice, especially with patients suffering from diabetes mellitus and associated comorbidities who are susceptible to steroid-induced side effects. Furthermore, there is no definite evidence that nebulized budesonide is as clinically effective as systemic corticosteroids in general hospital settings. Thus, a direct comparison of these treatments is clinically relevant, of special importance in resource-limited health care settings where the number of complications associated with treatment and the number of hospitalizations are of concern. The present study aimed to compare the efficacy of nebulized budesonide versus systemic corticosteroids in patients presenting with acute exacerbation of COPD.

METHODS

The study was a comparative interventional study, which was conducted at the Department of Pulmonology of Farooq Hospital, Rawalpindi, Pakistan for 6 months period from 1st December 2025 to 30th May 2026. Non-probability consecutive sampling was used. Patients presenting with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) at the Department of Pulmonology, Farooq Hospital, Rawalpindi, during the study period.

Sample size was determined using the OpenEpi online sample size calculator to compare two independent proportions. Considering the 95% confidence level, 75% statistical power, and allocation ratio of 1:1, it was assumed that 4.5% of patients receiving nebulized budesonide and 16.8% of patients receiving systemic methylprednisolone would experience hyperglycemia as a treatment-related side effect from the previous study conducted by Ding et al. (2016).[14] The calculated sample size in each group was around 80 patients, and the total sample size was 160 patients.

Patients aged 40–80 years of either gender with a previously established diagnosis of COPD, according to GOLD criteria, who presented with an acute exacerbation characterized by worsening dyspnea, cough, and/or sputum production requiring hospital admission were included. Patients who had clinically appropriate mild to moderate exacerbations and moderate to severe exacerbations were included. Patients with a history of bronchial asthma, bronchiectasis, active pulmonary tuberculosis, pneumonia, or any other acute respiratory diseases presenting like COPD exacerbation were not included. Patients who needed immediate invasive mechanical ventilation, who had life-threatening respiratory failure, were recently receiving systemic corticosteroid treatment, were known to be hypersensitive to corticosteroids, or had contraindications to either of the study medications were also excluded. Patients with severe hepatic or renal impairment and pregnant women were excluded.

After obtaining approval from the institutional ethical review committee, eligible patients were enrolled after obtaining written informed consent. A structured proforma was used to record baseline demographic and clinical information, such as age, gender, smoking history, COPD duration, comorbidities, previous exacerbations, current medications, respiratory rate, heart rate, blood pressure, oxygen saturation, and presenting symptoms. COPD severity was determined using the COPD Assessment Test (CAT), and pulmonary function and arterial blood gas parameters were recorded.[15]

Patients were allocated into two treatment groups using a computer-generated randomization sequence. Group A received nebulized budesonide at a dose of 2 mg

three times daily, while Group B received intravenous methylprednisolone 40 mg once daily. The treatment regimens were based on the comparative clinical study by Ding et al. (2016), which reported comparable clinical improvement with nebulized budesonide and systemic methylprednisolone. All patients in both groups received conventional treatment for COPD exacerbation with bronchodilators, supplemental oxygen as clinically indicated, antibiotics as clinically indicated, and other supportive care as per institutional protocols. The treatment response was evaluated at baseline and during follow-up, especially on the 3rd and 5th day of treatment. Changes in CAT score, respiratory rate, oxygen saturation, pulmonary function parameters, and arterial blood gas measurements were documented. Hospitalization time, treatment failure, requirement for escalation of respiratory support, and treatment-related adverse effects including hyperglycemia, gastrointestinal side effects, and oral candidiasis were also documented.

Data collected were analyzed using IBM SPSS Statistics version 26. Data were presented as mean ± standard deviation or median with interquartile range as appropriate according to the distribution of quantitative variables such as age, respiratory rate, oxygen saturation, CAT score, pulmonary function parameters, arterial blood gas parameters, and hospital stay. The Shapiro–Wilk test was used to determine normality. The categorical variables such as gender, smoking status, comorbidities, treatment failure, and adverse effects were presented in the form of frequencies and percentages. Comparisons of continuous variables between two groups were done using the independent-samples t-test and Mann–Whitney U test. Chi-square and Fisher's exact test were used to compare categorical variables. Confounding variables were evaluated by stratification, and a p-value of <0.05 was regarded as statistically significant.

RESULTS

In total, 160 patients were enrolled, 80 in each treatment arm. There were no statistically significant differences between the groups in demographic characteristics, smoking status, duration of COPD, prior exacerbations, or comorbidities (Table 1).

The baseline respiratory rate, heart rate, oxygen saturation, CAT score, FEV_1 and arterial blood gas parameters also showed no significant difference between the two groups (Table 2).

Both groups demonstrated improvement by day 5. The median (interquartile range) by-group difference in CAT was 8.7 ± 3.1 points in nebulized budesonide and 9.6 ± 3.3 points in systemic corticosteroid, which was not statistically significant (p=0.08). Other respiratory outcomes were also comparable (Table 3).

Median hospital stay was 5 days in both groups. There was no difference between the clinical treatment success rate for patients receiving nebulized budesonide (87.5%) and those receiving systemic corticosteroids (90.0%) (p=0.61). Treatment failure and escalation of respiratory support were comparable (Table 4).

The rate of at least one AE recorded was approximately 17.5% in the nebulized budesonide group and 36.3% in the systemic corticosteroid group (p=0.007). Systemic corticosteroids were associated with a higher prevalence of hyperglycemia (17.5% vs. 6.3%, p=0.027); there was a numerical increase in oral candidiasis with nebulized budesonide (Table 5).

Stratified exploratory analyses revealed no statistically significant treatment failure differences between age, diabetes, or smoking subgroups. These findings should be interpreted cautiously because of the small number of events (Table 6).

Table 1

Baseline demographic and COPD-related characteristics

Variable	Budesonide (n=80) n (%)/mean ± SD	Systemic steroid (n=80) n (%)/mean ± SD	p-value
Age (years)	66.2 ± 8.1	65.4 ± 8.6	0.54
Male	58 (72.5)	60 (75.0)	0.72
Female	22 (27.5)	20 (25.0)	
Current smoker	34 (42.5)	36 (45.0)	0.75
Former smoker	39 (48.8)	37 (46.3)	
Never smoker	7 (8.7)	7 (8.7)	
COPD duration (years)	7.1 ± 3.8	7.4 ± 4.1	0.64
Exacerbation in previous year	46 (57.5)	49 (61.3)	0.62
Diabetes mellitus	21 (26.3)	23 (28.8)	0.72
Hypertension	32 (40.0)	35 (43.8)	0.62
Ischemic heart disease	13 (16.3)	15 (18.8)	0.68

Table 2

Baseline clinical and respiratory parameters

Variable	Budesonide (n=80) Mean ± SD	Systemic steroid (n=80) Mean ± SD	p-value
Respiratory rate (breaths/min)	25.1 ± 3.6	25.4 ± 3.8	0.61
Heart rate (beats/min)	104.2 ± 13.1	105.6 ± 12.8	0.49
SpO_2 (%)	88.6 ± 3.2	88.3 ± 3.4	0.57
CAT score	25.8 ± 4.7	26.1 ± 4.5	0.68
FEV_1 (% predicted)	39.4 ± 8.6	38.8 ± 8.9	0.66
PaO_2 (mmHg)	58.2 ± 7.4	57.6 ± 7.8	0.62
$PaCO_2$ (mmHg)	52.1 ± 8.9	53.0 ± 9.2	0.53
Arterial pH	7.34 ± 0.05	7.33 ± 0.05	0.20

Table 3

Clinical and respiratory parameters at baseline and day 5

Outcome	Time	Budesonide (n=80)	Systemic steroid (n=80)	p-value
CAT score	Baseline	25.8 ± 4.7	26.1 ± 4.5	0.68
	Day 5	17.1 ± 4.2	16.5 ± 4.0	0.36
CAT score change	Baseline–Day 5	−8.7 ± 3.1	−9.6 ± 3.3	0.08

Respiratory rate	Baseline	25.1 ± 3.6	25.4 ± 3.8	0.61
	Day 5	19.2 ± 2.8	18.8 ± 2.7	0.36
SpO_2 (%)	Baseline	88.6 ± 3.2	88.3 ± 3.4	0.57
	Day 5	93.1 ± 2.1	93.4 ± 2.0	0.36
FEV_1 (% predicted)	Baseline	39.4 ± 8.6	38.8 ± 8.9	0.66
	Day 5	45.8 ± 9.1	46.7 ± 9.3	0.53
$PaCO_2$ (mmHg)	Baseline	52.1 ± 8.9	53.0 ± 9.2	0.53
	Day 5	46.8 ± 7.2	46.1 ± 7.0	0.54

Table 4

Treatment response and hospital outcomes

Outcome	Budesonide (n=80) n (%)	Systemic steroid (n=80) n (%)	p-value
Hospital stay (days), median (IQR)	5 (4–7)	5 (4–6)	0.41
Clinical treatment success	70 (87.5)	72 (90.0)	0.61
Treatment failure	10 (12.5)	8 (10.0)	0.61
Escalation to non-invasive ventilation	8 (10.0)	7 (8.8)	0.79
Transfer to intensive care	3 (3.8)	4 (5.0)	1.00
In-hospital mortality	1 (1.3)	2 (2.5)	1.00

Table 5

Treatment-related adverse events

Adverse event	Budesonide (n=80) n (%)	Systemic steroid (n=80) n (%)	p-value
Hyperglycemia	5 (6.3)	14 (17.5)	0.027
Gastrointestinal symptoms	4 (5.0)	10 (12.5)	0.09
Oral candidiasis	5 (6.3)	1 (1.3)	0.21
Fluid retention	2 (2.5)	7 (8.8)	0.10
Sleep or mood disturbance	2 (2.5)	8 (10.0)	0.049
Any recorded adverse event	14 (17.5)	29 (36.3)	0.007

Table 6

Exploratory stratified analysis of treatment failure

Subgroup	Budesonide: failure n/N (%)	Systemic steroid: failure n/N (%)	p-value
Age			
<65 years	3/31 (9.7)	2/34 (5.9)	0.66
≥65 years	7/49 (14.3)	6/46 (13.0)	0.85
Diabetes			
Present	4/21 (19.0)	4/23 (17.4)	0.89
Absent	6/59 (10.2)	4/57 (7.0)	0.54
Current smoker			
Yes	5/34 (14.7)	4/36 (11.1)	0.64
No	5/46 (10.9)	4/44 (9.1)	0.77

DISCUSSION

The present study evaluated the efficacy and safety of nebulized budesonide versus systemic corticosteroid therapy in 160 patients with acute exacerbation of COPD. Both treatment groups demonstrated improvement in clinical and respiratory parameters by the fifth day of treatment. There were no statistically significant differences between the groups in the key clinical outcomes, including the reduction in COPD Assessment Test (CAT) score, respiratory rate, improvement in oxygen saturation, or changes in pulmonary function. These results indicate that nebulized budesonide could be a clinically effective treatment option similar to systemic corticosteroids in specific patients hospitalized with AECOPD, but equivalence cannot be concluded based on a non-significant difference.

Hu et al. (2022) did a systematic review and meta-analysis of 22 studies and 5,764 patients. They found no differences in the extent of improvement in FEV_1, predicted FEV_1, PaO_2, $PaCO_2$, or oxygen saturation between nebulized and systemic treatment with corticosteroids. Their results confirm the respiratory benefits found in the current study.[12] In a similar systematic review of 20 randomized trials of inhaled versus systemic corticosteroids, treating 2,140 patients, Papadopoulou et al. (2024) observed no significant difference with regard to treatment failure, breathlessness, or other important efficacy measures. These results confirm the similar clinical outcome that was seen between both treatment groups.[16]

The present study showed that the nebulized budesonide group had a mean decrease in CAT score of 8.7 ± 3.1 points, while the group receiving systemic corticosteroid had a mean decrease of 9.6 ± 3.3 points (p=0.08). The difference between groups was relatively small and consistent with the results of Papadopoulou et al. (2024), who found that there was no clear difference in breathlessness between the two treatment routes (SMD −0.11, 95% CI −0.36 to 0.15). Their findings indicated that inhaled corticosteroids may be an option in select patients; however, the evidence was not assured.[16]

In terms of treatment response, the present study found 87.5% of the patients treated with nebulized budesonide to be successful versus 90.0% of those treated with systemic corticosteroids (p=0.61). Treatment failure was also comparable between groups (12.5% versus 10.0%, respectively). Nguyen et al. (2021) conducted a retrospective cohort study of 128 hospitalized patients and found that treatment with systemic corticosteroid alone was significantly inferior to systemic corticosteroid and nebulized budesonide. They found no differences in escalation of respiratory support, escalation of

corticosteroid dose, mortality, or 30-day readmission. The study also compared combination therapy to conventional systemic therapy, but found no clear advantage to the addition of nebulized budesonide, in routine practice, to systemic therapy in combination.[17]

Another key metric related to treatment response and healthcare burden is hospital stay. There was no significant difference between the two groups in terms of the median hospital stay (5 days, p=0.41). In a systematic review and meta-analysis of 12 RCTs with a total of 1,336 patients, Koarai et al. (2024) found that patients treated with systemic corticosteroids had a mean of 1.57 fewer days of hospitalization than placebo. This comparison was, however, made with placebo and not against nebulized budesonide.[18] A meta-analysis by Zhao et al. (2023), which included short- and long-course systemic corticosteroid treatments, also found that duration had an impact on hospital outcomes, with the effect of the difference between regimens being comparatively small. The findings of these studies highlight the need to take treatment length and clinical severity into account when making hospitalization conclusions.[19]

A key finding of the present study was the difference in treatment-related adverse events. There was at least one adverse event in 17.5% of patients receiving nebulized budesonide versus 36.3% receiving systemic corticosteroids (p=0.007). The systemic corticosteroid group also had more hyperglycemia than the other group (17.5% compared to 6.3%, p=0.027). Johannesmeyer et al. (2022) investigated corticosteroid administration and glycemic outcomes in hospitalized AECOPD patients and found that higher daily corticosteroid doses were associated with increased blood glucose levels, while higher cumulative doses were associated with longer hospital stays. This finding corroborates the higher prevalence of hyperglycemia found in the current study with systemic therapy.[20]

Likewise, Cole et al. (2023) assessed the impact of a corticosteroid stewardship programme in hospitalised patients with AECOPD. They found that 54 patients in their study had a decrease in glucose levels above 180 mg/dL after reducing the dose of corticosteroid, from 38% to 25% (p=0.007). This finding further highlights the relationship between systemic corticosteroid exposure and glycemic complications. Nebulized budesonide was not directly compared with systemic treatment in their study, but it reinforces the need to avoid unnecessary systemic corticosteroid exposure.[21]

The reduced overall rate of adverse events with nebulized budesonide was also similar to that of Hu et al. (2022), who found increased rates of hyperglycemia and gastrointestinal issues in systemic corticosteroid users.[12] Papadopoulou et al. (2024) similarly reported a tendency towards fewer overall adverse events with inhaled corticosteroids, with a relative risk of 0.80 (95% CI 0.64–1.00). Treatment with inhaled drugs, however, was more likely to be reported to have caused oral infections of fungi. Oral candidiasis also occurred more frequently in the nebulized budesonide group in the present study, but this was not statistically significant.[16]

Kleinhendler et al. (2025) studied the use of inhaled corticosteroids (ICS) for systemic steroid treatment in 870 COPD patients hospitalized with exacerbation. After propensity score matching, they did not observe significant differences between patients receiving combined treatment and those receiving systemic corticosteroids alone regarding 30-day mortality, intubation, hospital stay, or readmission. Their results indicate that the role of inhaled corticosteroids in acute exacerbations should be assessed based on the treatment approach, and not by the combination of both routes.[22]

Zhao et al. (2025) performed a real-world retrospective study, comparing nebulized budesonide with systemic corticosteroids in hospitalized patients with AECOPD. In the study, they found that nebulized budesonide treatment was associated with reduced mortality after 6 months, but it is possible that selection of treatment or differences in baseline characteristics affected their results. This lends further clinical interest towards nebulized budesonide as a treatment option, but the results in mortality are not directly comparable with the current study due to the lack of long-term survival data.[23]

Ren et al. (2025) recently compared the various ways glucocorticoids can be administered by using a propensity score matched analysis of a multicenter COPD registry. They analyzed 572 patients in each matched treatment group and concluded that there were no differences in the short-term outcomes in a comparison of inhaled corticosteroid monotherapy and a combination of inhaled and systemic corticosteroid treatment. Systemic corticosteroid monotherapy resulted in greater short-term exacerbation and readmission rates than inhaled corticosteroid monotherapy. However, there were no significant differences in the long-term outcomes. Observational data from these findings support the examination of inhaled CS as an alternative treatment approach, but cannot prove causality.[24]

Overall, the current results were consistent with the literature reviewed on the similar short-term clinical benefits of nebulized and systemic corticosteroids and the possible lower adverse-effect profile of nebulized treatment. Nevertheless, systemic corticosteroids remain an established treatment for moderate-to-severe AECOPD, and the available evidence does not justify their routine replacement in all patients. Consequently, results should be considered in light of the severity of the patients, the presence of comorbidities, treatment response, and the extent of the available comparative evidence.

Limitations

There were some limitations of the study. First, it was carried out in one center, and the results may not be applicable to other health care institutions. Secondly, the limited number of patients and the short follow-up prevented an assessment of infrequent adverse events, the long-term clinical effect, and the recurrence of COPD exacerbations. Thirdly, baseline disease severity, comorbidities, and previous corticosteroid exposure could have affected the treatment response. In addition, not all patients could have spirometry and arterial blood gas

measurements obtained at all assessments. Long-term post-discharge outcomes were not measured. The results in the present multicenter studies are preliminary and should be confirmed by larger studies with longer follow-up.

CONCLUSION

Nebulized budesonide demonstrated comparable short-term clinical and respiratory improvement to systemic corticosteroids in patients with acute exacerbation of COPD. Both treatment groups showed improvement in CAT scores, respiratory rate, oxygen saturation, and pulmonary function parameters, without significant differences in treatment success or hospital stay. Treatment-related adverse events, however, were more common in patients receiving systemic corticosteroids, especially hyperglycemia. In certain patients, nebulized budesonide may therefore be considered as an alternative treatment, especially those with a higher risk of side effects from systemic corticosteroids. Further adequately powered clinical trials are required to establish its comparative efficacy and safety.

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