

Clinical and Inflammatory Benefits of Nebulized Furosemide with Salbutamol–ipratropium in COPD Exacerbations: A Randomized Controlled Trial

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Received: 1 October 2025; Received in revised form: 9 December 2025; Accepted: 7 February 2026

ABSTRACT

Exacerbations of chronic obstructive pulmonary disease (COPD) are a leading cause of morbidity, mortality, and healthcare burden. While standard bronchodilator therapy alleviates airway obstruction, its efficacy is often limited. This study evaluated nebulized furosemide, which has bronchodilatory and anti-inflammatory effects, as an adjunct to salbutamol–ipratropium in hospitalized COPD patients.

Ninety-two patients with exacerbated COPD were randomly assigned to two equal groups (46 each). The intervention group received nebulized salbutamol–ipratropium plus furosemide (20 mg), and the control group received salbutamol–ipratropium, both every 8 hours for 10 minutes over 5

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consecutive days. Demographic and clinical variables, pulmonary function indices (FEV₁, FVC, FEV₁/FVC), clinical outcomes (COPD Assessment Test (CAT), Modified Medical Research Council (mMRC) scores, and quality of life by St. George's Respiratory Questionnaire (SGRQ)), arterial blood gases, and inflammatory biomarkers (TNF- α , IL-6, IL-8, CRP, ESR, neutrophil %, WBC) were measured before and after treatment.

Demographic characteristics and baseline indices did not differ significantly between the groups. Dyspnea and respiratory symptoms (mMRC and CAT scores) decreased significantly, while quality of life, improved markedly in the intervention group compared to the control group. Pulmonary function also showed significant enhancement, with the FEV₁/FVC ratio increasing. Arterial blood gas analysis showed higher PaO₂ and lower PaCO₂ in the intervention group. IL-6 and IL-8 decreased significantly, and no adverse events were reported.

Nebulized furosemide enhances standard therapy in COPD exacerbations, improving lung function, relieving symptoms, and reducing systemic inflammation. Its safety, accessibility, and low cost make it a promising adjunct treatment.

Keywords: Exacerbations of chronic obstructive pulmonary disease; Furosemide; Inflammation; Ipratropium; Salbutamol

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is among the most common and clinically important chronic respiratory diseases worldwide. It is marked by chronic airway inflammation, irreversible airflow obstruction, and persistent symptoms including chronic cough, sputum production, and dyspnea.^{1,2} Exacerbated COPD represents an acute surge of airway and systemic inflammation in which neutrophilic infiltration, mucosal edema, epithelial disruption, and heightened neurogenic responsiveness rapidly intensify. These episodes are marked by substantial increases in inflammatory biomarkers such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-8 (IL-8), alongside elevations in systemic biomarkers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) changes that directly drive the sudden escalation of dyspnea, reduced exercise capacity, and worsening gas exchange.³ Although inhaled bronchodilators such as salbutamol and ipratropium remain the backbone of management, their therapeutic effects are largely confined to smooth-muscle relaxation and provide only limited influence on the acute inflammatory and epithelial injury that dominate the pathophysiology of exacerbations.⁴⁻⁹ This mismatch between the inflammatory profile of exacerbated COPD and the pharmacologic scope of standard bronchodilators underscores a critical therapeutic gap during these episodes.

In this context, nebulized furosemide has gained attention as a potentially valuable adjunctive therapy with mechanisms directly relevant to the pathophysiology of COPD exacerbations. Beyond its classic renal diuretic effects, nebulized furosemide produces distinct local actions in the lungs,^{10, 11} including reducing airway epithelial edema, inhibiting the sodium-potassium-chloride cotransporter Sodium Potassium Chloride Cotransporter 1 (NKCC1) in airway epithelial cells, which helps stabilize membrane potential and reduce epithelial swelling,¹² modulating vagal afferent signaling to decrease reflex bronchoconstriction,¹³ and suppressing proinflammatory cytokine release.¹⁴ Collectively, these mechanisms reduce airway hyperresponsiveness, sensory nerve irritation, and both local and systemic inflammation, addressing pathophysiological aspects that conventional bronchodilators do not. These findings provide a rationale for evaluating nebulized furosemide specifically during COPD exacerbations rather than in stable disease. Notably, clinical observations suggest that when nebulized furosemide is administered alongside standard bronchodilators, improvements in airflow parameters and symptomatic relief may exceed those achieved with bronchodilator therapy alone.⁸ Such findings reinforce the rationale for evaluating furosemide specifically during exacerbated COPD, where its anti-inflammatory, neuromodulatory, and epithelial-stabilizing properties may address pathologic components that conventional bronchodilators do not effectively target.

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Given the acute inflammatory burden, epithelial edema, and the need for therapies with rapid onset during COPD exacerbations, evidence regarding the efficacy of nebulized furosemide remains limited and inconclusive. While some studies suggest potential benefits in reducing airway inflammation and improving pulmonary function, others report minimal or no effect.⁴⁻⁹ To address this gap, this study was designed as a randomized controlled trial to evaluate whether adding nebulized furosemide to standard therapy could provide additional benefits in hospitalized patients with COPD exacerbations. Specifically, we aimed to assess its effects on lung function, arterial blood gases (ABG), and systemic inflammatory biomarkers, while also capturing patient-reported outcomes, including symptom burden and health-related quality of life, using the COPD Assessment Test (CAT), the Modified Medical Research Council (mMRC) dyspnea scale, and the St. George's Respiratory Questionnaire (SGRQ). By systematically evaluating these outcomes, this study seeks to generate evidence that may inform more effective and comprehensive management strategies for patients experiencing COPD exacerbations.

MATERIALS AND METHODS

Study Design and Participants

This study was designed as a randomized, double-blind, parallel-group controlled clinical trial conducted at Dr. Masih Daneshvari Hospital, Tehran, Iran, in 2024. Ninety-two eligible patients were enrolled following written informed consent.

Inclusion criteria were patients aged 20 to 65 years with stable vital signs at admission and confirmed COPD exacerbation based on clinical and paraclinical criteria according to GOLD 2023, including chronic cough, sputum production, dyspnea, history of risk exposure such as smoking or air pollution, and post-bronchodilator FEV1/FVC (Forced Expiratory Volume in 1 second / Forced Vital Capacity) ratio < 70%.¹⁵ Exacerbation was defined as worsening respiratory symptoms requiring additional therapeutic intervention such as new medications, emergency visit, or hospitalization.

Exclusion criteria included patients with underlying diseases such as moderate to severe heart failure, chronic renal or hepatic disease, any chronic condition requiring continuous medication, or respiratory tract malignancies. Physiologic and functional conditions

such as pregnancy, lactation, or severe gastrointestinal symptoms including nausea and vomiting led to exclusion. Patients who changed their medication regimen during the study or withdrew consent were also excluded. Regarding the intervention drug furosemide, absolute contraindications included hypersensitivity to furosemide or other protocol medications, while relative contraindications included severe hypotension with systolic blood pressure below 90 mmHg or diastolic below 60 Millimeters Of Mercury (mm Hg), hypokalemia with serum potassium below 3.5 milliequivalents per litre (mEq/L), and hypovolemia defined as hematocrit above 55 percent, urine output below 0.5 milliliters per kilogram per hour (mL/kg/h), or weight loss over 10 percent due to fluid loss.

Randomization and Blinding

Eligible participants were randomly assigned in a 1:1 ratio to the intervention or control group using a computer-generated sequence created with Random Allocation software (version 1.0.0.0). Block randomization (block size of four) ensured balanced allocation. Treatment allocation was concealed until patient enrolment, and the trial was conducted in a double-blind manner.

Interventions

Patients in the intervention group (n=46) received routine therapy together with nebulized salbutamol- ipratropium (2.5 mg + 0.5 mg in 2.5 mL) combined with 20 mg of nebulized furosemide, administered every 8 hours for 10 minutes over five consecutive days. The control group (n=46) received standard treatment plus nebulized salbutamol- ipratropium (2.5 mg + 0.5 mg in 2.5 mL) without furosemide, following the same administration schedule.

All patients in both groups received standardized routine therapy for exacerbation of COPD in accordance with GOLD recommendations. The treatment protocol was identical in both groups and included the following:

Oxygen therapy in case of O₂ saturation ≤ 90%, with oxygen given via Venturi mask 30%.

Non-Invasive Ventilation BiPAP (Bilevel Positive Airway Pressure) with inspiratory positive airway pressure (IPAP) of 12 cmH₂O, expiratory positive airway pressure (EPAP) of 6 cmH₂O, and a respiratory rate of 12 breaths/min, indicated when partial pressures of carbon dioxide (PaCO₂) > 45 mmHg and pH < 7.35.

Nebulized 0.5 mg budesonide twice daily for 5 days.

50 mg prednisolone tablet once daily for 5 days (or equivalent IV injection if oral administration is not possible).

750 mg levofloxacin tablet or injection once daily for 5 days.

600 mg N-acetylcysteine effervescent tablet twice daily for 5 days.

40 mg enoxaparin injection once daily for 5 days.

40 mg pantoprazole tablet once daily for 5 days.

Sample Size

G*Power 3.1.10 was used to calculate sample size, based on data from previous studies,⁸ with $\alpha=0.05$, 80% power, and equal allocation of participants. The calculation was based on the primary outcome (oxygen saturation, O₂Sat), yielding a required sample of 92 patients (46 per group).

Data Collection and Outcome Assessment

Baseline information, including sex, age, educational level, place of residence, marital status, height, weight, body mass index (BMI), family history of COPD, history of smoking, number of COPD exacerbations during the previous year, and duration of COPD, was collected using a standardized questionnaire at enrollment. Data collection was conducted at two predefined time points: at baseline (day 0) and after completion of the intervention (day 5). In addition, all patients completed three validated questionnaires recommended by GOLD 2023 for COPD evaluation: the CAT (an 8-item questionnaire, score range 0–40), where higher scores indicate more severe symptoms and poorer health status. SGRQ: A validated Persian version was used to assess disease-specific health-related quality of life. It consists of 50 items covering symptoms, activity, and psychosocial impact. Scores are expressed on a scale from 0 to 100, with higher values reflecting worse health status. For interpretation, scores were categorized as follows: 0–25: very good respiratory health, 26–50: good respiratory health, 51–75: moderate impairment, and 76–100: poor respiratory health. mMRC (Dyspnea Scale): A single-item, 5-point scale (0–4) assessing activity limitation due to breathlessness.

Physiological and laboratory evaluations were also performed. O₂Sat was measured by pulse oximetry (ChoiceMMed, China) and pulmonary function was assessed by digital spirometry (BIONET, Korea) according to ATS/ERS 2019 standards, reporting FEV₁ (Forced Expiratory Volume in 1 second), FVC (Forced

Vital Capacity), and FEV₁/FVC. ABG analysis was performed from radial artery samples collected to determine partial pressures of oxygen (PaO₂), PaCO₂, and pH. Venous blood samples were collected for complete blood count (CBC) using ethylenediaminetetraacetic acid (EDTA) tubes and an automated cell counter. CRP was quantified by turbidimetric assay, while ESR was determined using the standard Westergren method.

Serum levels of cytokines, including TNF- α , IL-6, and IL-8, were quantified using commercial Enzyme-Linked Immunosorbent Assay (ELISA) kits (R&D, USA) following the manufacturer's instructions. Blood samples were centrifuged at 3,000 \times g for 10 minutes at 4°C, and the serum was then aliquoted and stored at –80°C for subsequent analysis. For ELISA, pre-coated microplates were incubated with patient samples and standards, followed by enzyme-conjugated secondary antibodies. Following the incubation and washing procedures, the substrate solution was added, and the reaction was halted using a stop solution. Absorbance was measured at 450 nm with a microplate reader, and cytokine concentrations were determined by comparison to standard curves. All assessments (questionnaires, physiological tests, and laboratory analyses) were repeated on day 5 to enable within-group and between-group comparisons of clinical and biochemical changes.

Statistical Methods

All statistical analyses were performed using SPSS software version 27 (IBM Corp., Armonk, NY, USA). The normality of quantitative variables was assessed using the Shapiro–Wilk test. Based on the distribution of the data, appropriate parametric or non-parametric tests were applied.

For between-group comparisons (intervention vs. control), an independent samples t-test was used when the data were normally distributed with homogeneous variances; otherwise, the Mann–Whitney U test was applied. For within-group comparisons (pre- and post-intervention), a paired t-test was used for normally distributed difference scores, and the Wilcoxon signed-rank test was used for non-normal distributions. Ordinal variables, which inherently follow non-normal distributions, were analyzed using non-parametric rank-based tests. The Mann–Whitney U test was used for between-group comparisons, and the Wilcoxon signed-rank test was used for within-group comparisons. Categorical variables were analyzed using the Chi-square

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(χ^2) test. Data are presented as mean \pm standard deviation (SD) for normally distributed quantitative variables, median and interquartile range (IQR) for non-normal quantitative variables, and frequency (percentage) for ordinal or categorical variables. A two-tailed p -value < 0.05 was considered statistically significant.

Ethical Considerations

All procedures in this study adhered to the ethical principles established by the Declaration of Helsinki and national guidelines for human research. The study protocol was approved by the Research Ethics Committee of the School of Medicine, Shahid Beheshti University of Medical Sciences (Approval No. IR.SBMU.MSP.REC.1402.364) and the trial was registered in the Iranian Registry of Clinical Trials (IRCT20240118060726N1). Written informed consent was obtained from all participants, who were also made aware of their right to withdraw at any time without impacting their care. Personal and clinical data were kept confidential and coded to ensure privacy.

RESULTS

Patient Demographics and Clinical Features in Study Groups

Baseline characteristics, including height, weight, age, and BMI, were compared between the control and intervention groups, as shown in Table 1. No significant differences were observed between the groups in height ($p=0.579$), weight ($p=0.170$), age ($p=0.200$), or BMI ($p=0.070$). These findings indicate that the control and intervention groups were homogeneous at baseline, ensuring the validity of subsequent interventional analyses and suggesting that any post-intervention differences could be attributed to the intervention.

Moreover, demographic variables, including gender, marital status, residence, and education level, were analyzed. No significant differences were observed between the groups regarding gender ($p=1.000$), marital status ($p=0.395$), residence ($p=0.189$), or education ($p=0.565$), as presented in Table 2, confirming statistical homogeneity and indicating that these factors are unlikely to influence study outcomes.

Comparison of Disease History and Smoking Status between Groups

The prevalence of comorbidities and smoking habits was compared between the two groups, and the outcome

is provided in Table 3. No significant differences were observed in recent COPD exacerbations ($p=0.646$), family history of COPD ($p=1.000$), smoking history ($p=1.000$), or disease duration ($p=0.916$). These results confirm homogeneity between groups regarding these factors.

Effect of Nebulized Furosemide on CAT, mMRC, and SGRQ Scores in Intervention vs. Control Groups

No significant baseline differences were observed between the groups before treatment for CAT ($p=0.56$), mMRC ($p=0.063$), or SGRQ ($p=0.131$), confirming initial homogeneity (Table 4-6).

As presented in Table 4, within-group comparisons showed that CAT scores significantly decreased from baseline to post-treatment in both groups, control and intervention, with $p < 0.001$. Between-group comparison after treatment revealed that the intervention group achieved significantly lower CAT scores than the control group ($p < 0.001$).

Similarly, as shown in Table 5, mMRC levels showed significant reductions in dyspnea severity within both groups ($p < 0.001$ for each). While the proportion of patients at level 0 increased after treatment in both groups, the intervention group showed a substantially larger increase compared to the control group ($p < 0.001$).

Table 1. Baseline Age, Height, Weight, and BMI in Control vs. Intervention Groups.

Variable	Group	Median (IQR*)	<i>p</i>
Height (cm)	Control	160 (153–165)	0.579
	Intervention	157 (152–165)	
Weight (kg)	Control	65 (55–75)	0.170
	Intervention	68 (62–74)	
Age (years)	Control	60 (53.5–64)	0.200
	Intervention	54.5 (47.75–63)	
BMI	Control	25.49 (21.15–28.13)	0.070
	Intervention	28.04 (24.23–29.90)	

IQR: Interquartile Range, representing the middle 50% of data (Q1–Q3); BMI: body mass index.

Table 2. Distribution of demographic characteristics in the control and intervention groups.

Variable	Group	n (%)	Total (%)	<i>p</i>
Gender				
Male	Control	16 (34.8%)	32 (34.8%)	1.000
	Intervention	16 (34.8%)		
Female	Control	30 (65.2%)	60 (65.2%)	
	Intervention	30 (65.2%)		
Marital status				
Single	Control	4 (8.7%)	7 (7.6%)	0.395
	Intervention	3 (6.5%)		
Married	Control	31 (67.4%)	66 (71.7%)	
	Intervention	35 (76.1%)		
Divorced	Control	2 (4.3%)	6 (6.5%)	
	Intervention	4 (8.7%)		
Widowed	Control	9 (19.6%)	13 (14.1%)	
	Intervention	4 (8.7%)		
Residence				
Urban	Control	27 (58.7%)	60 (65.2%)	0.189
	Intervention	33 (71.7%)		
Rural	Control	19 (41.3%)	32 (34.8%)	
	Intervention	13 (28.3%)		
Education				
Below diploma	Control	29 (63.0%)	56 (60.9%)	0.565
	Intervention	27 (58.7%)		
Diploma	Control	7 (15.2%)	11 (12.0%)	
	Intervention	4 (8.7%)		
Associate degree	Control	7 (15.2%)	15 (16.3%)	
	Intervention	8 (17.4%)		
Bachelor	Control	2 (4.3%)	8 (8.7%)	
	Intervention	6 (13.0%)		
Master	Control	1 (2.2%)	2 (2.2%)	
	Intervention	1 (2.2%)		

n: number of participants.

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Table 3. Frequency and percentage of disease history and risk factors in the control and intervention groups.

Variable	Status	Control n (%)	Intervention n (%)	Total (n=92)	<i>p</i>
History of COPD Exacerbation in the Past Year	No	44 (95.7%)	43 (93.5%)	87 (94.6%)	0.646
	Yes	2 (4.3%)	3 (6.5%)	5 (5.4%)	
Family History of COPD	No	43 (93.5%)	43 (93.5%)	86 (93.5%)	1.000
	Yes	3 (6.5%)	3 (6.5%)	6 (6.5%)	
Smoking History	No	38 (82.6%)	38 (82.6%)	76 (82.6%)	1.000
	Yes	8 (17.4%)	8 (17.4%)	16 (17.4%)	
Duration of COPD	<2 years	15 (32.6%)	16 (34.8%)	31 (33.7%)	0.916
	2–10 years	27 (58.7%)	27 (58.7%)	54 (58.7%)	
	>10 years	4 (8.7%)	3 (6.5%)	7 (7.6%)	

COPD: Chronic obstructive pulmonary disease. n: number of participants.

Table 4. Distribution of CAT Questionnaire Scores (Median and Interquartile Range) Before and After Treatment in Control and Intervention Groups.

Parameter	Group	Before Treatment Median (IQR)	After Treatment Median (IQR)	Median Difference (95% CI)	<i>p</i> (within group)
CAT	Control	21.5 (19–26)	7 (5–11)	-14 (-15, -13)	<0.001
	Intervention	21 (18–25)	3.5 (2–5)	-18 (-19, -17)	<0.001
Median Difference (95% CI)		-1 (-4, 2)	-10 (-13, -7)		
<i>p</i>-value (between groups)		0.560	<0.001		

IQR: Interquartile Range, representing the middle 50% of data (Q1–Q3); CAT: COPD Assessment Test.

Table 5. Frequency and Percentage Distribution of mMRC Levels Before and After Treatment in Control and Intervention Groups.

Group	mMRC Level	Before Treatment n (%)	After Treatment n (%)	<i>p</i> (within group)
Control	0	0 (0.00%)	8 (17.40%)	<0.001
	1	2 (4.30%)	19 (41.30%)	
	2	8 (17.40%)	12 (26.10%)	
	3	21 (45.70%)	7 (15.20%)	
	4	15 (32.60%)	0 (0.00%)	
	Total	46 (100%)	46 (100%)	
Intervention	0	0 (0.00%)	24 (52.20%)	<0.001
	1	2 (4.30%)	18 (39.10%)	
	2	16 (34.80%)	2 (4.30%)	
	3	19 (41.30%)	2 (4.30%)	
	4	9 (19.60%)	0 (0.00%)	
	Total	46 (100%)	46 (100%)	
<i>p</i> (between groups)		0.063	<0.001	

mMRC: Modified Medical Research Council. n: number of participants.

Table 6. Frequency and Percentage Distribution of SGRQ Quality Levels Before and After Treatment in Control and Intervention Groups.

Group	SGRQ Level	Before Treatment n (%)	After Treatment n (%)	<i>p</i> (within group)
Control	Very Good	0 (0.00%)	17 (36.96%)	<0.001
	Good	4 (8.70%)	25 (54.35%)	
	Moderate	29 (63.04%)	4 (8.70%)	
	Poor	13 (28.26%)	0 (0.00%)	
Intervention	Very Good	0 (0.00%)	32 (69.57%)	<0.001
	Good	8 (17.39%)	13 (28.26%)	
	Moderate	32 (69.57%)	1 (2.17%)	
	Poor	6 (13.04%)	0 (0.00%)	
<i>p</i> -value (between groups)		0.131	0.006	

SGRQ: St. George's Respiratory Questionnaire. **n**: number of participants.

In terms of SGRQ, both groups exhibited significant within-group improvements in quality-of-life categories after treatment ($p < 0.001$). Notably, the proportion of patients classified as “very good” increased, while those in “medium” and “poor” categories decreased in both groups. Between-group analysis post-treatment indicated that the intervention group showed a significantly greater improvement than the control group ($p = 0.006$), demonstrating enhanced effectiveness of the intervention in improving overall patient quality of life, as presented in Table 6.

Overall, these results show that furosemide markedly reduced symptom severity and enhanced health-related quality of life compared to baseline, and these improvements were greater than those observed in the control group receiving standard care, as measured by CAT, mMRC, and SGRQ scores.

Pulmonary Function Improvements Following Nebulized Furosemide

As seen in Table 7, Changes in lung function indices (FEV1, FVC, and the FEV1/FVC ratio) were measured pre- and post-treatment in both study groups. Initially, baseline values were compared to ensure homogeneity between the groups. Baseline measurements indicated no measurable differences between the control and intervention groups for FEV1 ($p = 0.95$), FVC ($p = 0.46$), and FEV1/FVC ($p = 0.16$), confirming initial homogeneity. After treatment, the intervention group showed a significant increase in FEV1 and FVC compared to their baseline values (FEV1: $p < 0.001$; FVC: $p = 0.008$), while no meaningful changes occurred

in the control group (FEV1: $p = 0.07$; FVC: $p = 0.71$). The intervention group exhibited a marked rise in FEV1/FVC relative to baseline ($p = 0.02$), whereas the control group exhibited negligible change ($p = 0.35$). Moreover, post-treatment comparisons between groups revealed a significant difference in FEV1/FVC in favor of the intervention group ($p = 0.01$), while differences for FEV1 and FVC were not statistically significant (FEV1: $p = 0.08$; FVC: $p = 0.57$). Altogether, the results indicate that the intervention led to marked improvements in pulmonary function, particularly in the FEV1/FVC ratio, demonstrating greater effectiveness than routine care.

3.5 Effects of Nebulized Furosemide on ABG Parameters and Oxygenation

As demonstrated in Table 8, baseline measurements of ABG parameters and O₂Sat showed no significant differences across the two groups (O₂Sat: $p = 0.19$; PaCO₂: $p = 0.06$; PaO₂: $p = 0.2$; pH: $p = 0.86$), confirming initial homogeneity. After treatment, both groups demonstrated a significant increase in O₂Sat relative to their baseline values ($p < 0.001$); however, post-treatment comparisons between groups did not reveal a significant difference ($p = 0.38$), indicating similar improvements in oxygen saturation in both groups.

For PaCO₂, no significant change was observed in the control group compared to baseline ($p = 0.76$), whereas the intervention group experienced a significant reduction ($p = 0.02$). Furthermore, after treatment, the intervention group showed significantly lower PaCO₂ levels compared to the control group ($p = 0.012$), highlighting the intervention's superior effect in

improving ventilation and reducing carbon dioxide levels. Additionally, a significant rise was observed in both groups for PaO₂ relative to baseline ($p < 0.001$). Importantly, post-treatment PaO₂ was markedly higher in the intervention group versus the control group ($p = 0.002$), demonstrating greater efficacy of the intervention in enhancing arterial oxygenation.

Changes in pH were not significant within either group (control: $p = 0.53$; intervention: $p = 0.75$) or between groups post-treatment ($p = 0.6$), indicating that the intervention did not substantially affect acid–base balance.

Overall, the intervention resulted in significant improvements in PaCO₂ and PaO₂, showing superior effectiveness over routine care, while O₂Sat increased similarly in both groups and pH remained stable.

3. Effect of the Intervention on Inflammatory Markers and Blood Cells Before and After Treatment

As shown in Table 9, the effects of the intervention on inflammatory and hematological parameters including ESR, white blood cells (WBCs), Polymorphonuclear neutrophils (PMN), and CRP were evaluated before and after treatment in both the control and intervention groups. Baseline comparisons indicated no statistically significant differences between the control and intervention groups for ESR ($p = 0.271$), WBC ($p = 1.000$), PMN ($p = 0.200$), or CRP ($p = 0.11$), confirming initial homogeneity.

Following treatment, both groups demonstrated a significant reduction in ESR ($p < 0.001$ for each), and WBC counts increased significantly in both groups ($p < 0.001$ for each), with no significant between-group differences (ESR: $p = 0.833$; WBC: $p = 0.600$).

However, more specific immune responses showed differential effects. PMN percentages increased significantly only in the intervention group ($p = 0.013$), while no significant change was observed in the control group ($p = 0.450$).

CRP levels significantly decreased after treatment within each group ($p < 0.001$). In both groups, the proportion of patients with CRP < 1 mg/L increased markedly following treatment. However, no statistically significant difference was observed between the two groups, either at baseline ($p = 0.112$) or after treatment ($p = 0.190$) (Table 10).

Beneficial Effects of Furosemide on Key Inflammatory Cytokines (TNF- α , IL-6, and IL-8)

According to Table 11, baseline comparisons indicated no statistically meaningful differences between control and intervention groups for TNF- α ($p = 0.279$), IL-6 ($p = 0.621$), or IL-8 ($p = 0.734$), confirming similar initial inflammatory status between groups. Following treatment, both groups demonstrated significant reductions in IL-6 (control: $p = 0.059$; intervention: $p < 0.001$) and IL-8 ($p < 0.001$ for both), while TNF- α decreased significantly only in the intervention group ($p = 0.005$), with the change in the control group remaining non-significant ($p = 0.053$). Between-group comparisons after treatment demonstrated that the intervention group experienced a significantly greater decrease in IL-6 ($p = 0.030$) and IL-8 ($p = 0.040$) compared to the control group, whereas the difference in TNF- α reduction was not statistically significant ($p = 0.169$).

Safety Outcomes

No clinically significant changes were observed in serum electrolytes (potassium, sodium), renal function (Blood urea nitrogen (BUN), creatinine), blood pressure, or hearing status. No serious adverse events occurred during the study (Table 12).

Table 7. Changes in respiratory function indices before and after treatment in control and intervention groups.

Parameter	Group	Before treatment Median (IQR)	After treatment Median (IQR)	Median Difference (95% CI)	<i>p</i> (within group)
FEV1 (%)	Control	43.65 (31.33–61.83)	48.40 (37.85–64.10)	5.15 (0.80, 8.65)	0.072
	Intervention	44.00 (29.43–55.90)	53.05 (41.50–86.70)	9.70 (3.50, 18.90)	<0.001
Median Difference (95% CI)		0.35 (-7.15, 9.40)	4.65 (-3.40, 23.15)		
<i>p</i> (between groups)		0.956	0.088		
FVC (%)	Control	48.70 (33.28–73.70)	54.35 (35.88–74.70)	3.00 (-11.10, 12.60)	0.710
	Intervention	45.95 (31.90–62.90)	51.20 (40.53–89.40)	6.85 (1.00, 18.00)	0.008
Median Difference (95% CI)		-2.75 (-17.20, 10.75)	-1.85 (-13.90, 19.60)		
<i>p</i> (between groups)		0.461	0.573		
FEV1/FVC (%)	Control	81.03 (44.71–97.50)	85.44 (62.75–94.34)	0.00 (-1.62, 7.14)	0.350
	Intervention	87.23 (75.52–97.70)	93.57 (78.66–99.17)	2.565 (0.63, 7.51)	0.022
Median Difference (95% CI)		6.20 (-7.92, 21.59)	7.48 (-0.41, 19.84)		
<i>p</i> (between groups)		0.160	0.010		

IQR: Interquartile Range, representing the middle 50% of data (Q1–Q3); FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity.

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Table 8. Changes in ABG parameters and O₂Sat before and after treatment in control and intervention groups.

Parameter	Group	Before treatment Median (IQR)	After treatment Median (IQR)	Median Difference (95% CI)	p-value (within group)
O₂Sat (%)	Control	93.5 (90–96)	96 (95–98)	2.00 (1.00, 3.00)	<0.001
	Intervention	94.5 (91–96)	96.5 (95–98)	2.00 (1.00, 3.00)	<0.001
Median Difference (95% CI)		1 (-1, 3.5)	0.5 (-0.5, 2)		
p (between groups)		0.199	0.383		
PaCO₂ (mmHg)	Control	40.5 (38–44)	40 (37–44)	0.25 (-1.00, 1.30)	0.760
	Intervention	38.85 (36–41)	36.4 (35–41)	-1.65 (-2.00, -1.00)	0.020
Median Difference (95% CI)		-1.65 (-4.50, 0.50)	-3.60 (-5.50, -1.00)		
p (between groups)		0.067	0.012		
PaO₂ (mmHg)	Control	41.5 (38–52)	44.35 (37.32–51.4)	1.75 (1.00, 2.10)	<0.001
	Intervention	48.15 (38–58)	53.5 (44.75–62.25)	7.00 (5.00, 10.00)	<0.001
Median Difference (95% CI)		6.50 (-5.00, 11.00)	11.00 (1.00, 19.00)		
p (between groups)		0.200	0.002		
pH	Control	7.375 (7.35–7.41)	7.38 (7.35–7.4)	-0.01 (-0.01, 0.01)	0.530
	Intervention	7.39 (7.36–7.4)	7.38 (7.36–7.41)	-0.01 (-0.01, 0.01)	0.750
Median Difference (95% CI)		0.01 (-0.02, 0.02)	0.0 (-0.015, 0.01)		
p (between groups)		0.860	0.660		

IQR: Interquartile Range, representing the middle 50% of data (Q1–Q3); O₂Sat: oxygen saturation; PaCO₂: partial pressures of carbon dioxide; PaO₂: partial pressures of oxygen.

Table 9. Comparison of Inflammatory and Hematologic Parameters Before and After Treatment in Control and Intervention Groups.

Parameter	Group	Pre-treatment Median (IQR)	Post-treatment Median (IQR)	Median Difference (95% CI)	<i>p</i> (between-groups)
ESR (mm/h)	Control	21.0 (21.0–39.0)	16.5 (8.0–31.0)	–4.00 (–7.00, –2.00)	<0.001
	Intervention	21.5 (13.0–40.0)	12.0 (8.0–21.0)	–9.00 (–13.00, –6.50)	<0.001
Median Difference (95% CI)		0.50 (–9.50, 10.00)	–4.50 (–11.50, 7.00)		
<i>p</i> (between-groups)		0.271	0.833		
WBC ($\times 10^3/\mu\text{L}$)	Control	7.35 (6.4–9.6)	9.85 (8.6–12.3)	1.90 (1.30, 2.50)	<0.001
	Intervention	7.95 (6.2–9.9)	10.0 (8.3–11.9)	2.00 (1.10, 2.90)	<0.001
Median Difference (95% CI)		0.60 (–0.80, 1.75)	0.15 (–1.95, 1.50)		
<i>p</i> (between-groups)		1.000	0.600		
PMN (%)	Control	70.0 (63.0–72.0)	69.0 (66.0–71.0)	–0.5 (–2.0, 2.0)	0.450
	Intervention	65.0 (61.8–70.0)	69.0 (65.0–73.0)	+2.0 (–0.75, 7.0)	0.013
Median Difference (95% CI)		–5.00 (–6.50, 0.50)	0.00 (–3.50, 1.00)		
<i>p</i> (between-groups)		0.200	1.000		

IQR: Interquartile Range, representing the middle 50% of data (Q1–Q3); ESR: Erythrocyte sedimentation rate; WBC: white blood cell; PMN: Polymorphonuclear neutrophils.

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Table 10. Distribution of CRP Qualitative Levels Before and After Treatment in Control and Intervention Groups.

Group	CRP Qualitative Level	Pre-treatment n (%)	Post-treatment n (%)	<i>p</i> (between-groups)
Control	<1	12 (26.1%)	30 (65.2%)	<0.001
	1	14 (30.4%)	13 (28.3%)	
	2	11 (23.9%)	2 (4.3%)	
	3	9 (19.6%)	1 (2.2%)	
Intervention	<1	20 (43.5%)	38 (82.6%)	<0.001
	1	16 (34.8%)	7 (15.2%)	
	2	4 (8.7%)	0 (0.0%)	
	3	6 (13.0%)	1 (2.2%)	
<i>p</i> (between-groups)		0.112	0.190	

CRP: C-reactive protein. n: number of participants.

Table 11. Comparison of Inflammatory Cytokines Before and After Treatment in Control and Intervention Groups.

Parameter	Group	Pre-treatment (Mean±SD)	Post-treatment (Mean±SD)	Mean Difference (95% CI)	<i>p</i> (between-groups)
TNF-α (pg/mL)	Control	8.67 ± 4.15	7.51 ± 4.15	-1.16 (-2.50, 0.18)	0.057
	Intervention	8.91 ± 3.71	7.08 ± 1.74	-1.84 (-2.96, -0.72)	0.005
Mean Difference (95% CI)		0.24 (-1.34, 1.83)	-0.44 (-1.75, 0.75)		
<i>p</i> (between-groups)		0.279	0.169		
IL-6 (pg/mL)	Control	5.80 ± 4.95	4.37 ± 2.87	-1.44 (-2.67, -0.20)	0.059
	Intervention	6.09 ± 4.75	3.01 ± 1.68	-3.09 (-4.60, -1.57)	<0.001
Mean Difference (95% CI)		0.29 (-1.67, 2.29)	-1.36 (-2.32, -0.42)		
<i>p</i> (between-groups)		0.621	0.030		
IL-8 (pg/mL)	Control	104.41 ± 97.18	56.90 ± 51.55	-47.51 (-76.41, -18.60)	<0.001
	Intervention	102.25 ± 79.95	30.45 ± 26.06	-71.81 (-95.84, -47.77)	<0.001
Mean Difference (95% CI)		-2.16 (-38.52, 34.21)	-26.46 (-43.15, -9.76)		
<i>p</i> (between-groups)		0.734	0.040		

SD: standard deviation; TNF-α: Tumor Necrosis Factor-alpha; IL-6: Interleukin-6; IL-8: Interleukin-8; SD: standard deviation.

Table 12. Safety Parameters Before and After Nebulized Furosemide in the Intervention Group.

Safety Parameter	Pre-treatment (n=46)	Post-treatment (n=46)	<i>p</i>
Serum potassium (mEq/L)	4.34 ± 0.51	4.28 ± 0.43	0.538
Serum sodium (mEq/L)	137.65 ± 3.23	137.78 ± 3.41	0.856
BUN (mg/dL)	17 ± 4.2	15.7 ± 3	0.815
Creatinine (mg/dL)	0.8 ± 0.3	0.7 ± 0.2	0.321
Blood pressure (systolic)	134 ± 10	128 ± 9	0.122
Blood pressure (diastolic)	82 ± 8	78 ± 6	0.200
Hearing / tinnitus	0 (0%)	0 (0%)	1.000
Any serious adverse event	0 (0%)	0 (0%)	1.000

Values are presented as mean ± SD for continuous variables and number (%) for categorical variables. BUN: Blood urea nitrogen.

DISCUSSION

In this study, we evaluated the effect of adding nebulized furosemide to the standard salbutamol-ipratropium therapy in patients with COPD during exacerbation. The intervention led to significant improvements in key clinical outcomes, including reduced dyspnea severity (mMRC), alleviated respiratory symptoms (CAT), and enhanced quality of life (SGRQ). Pulmonary function showed a significant improvement in the FEV₁/FVC ratio, while PaO₂ increased and PaCO₂ decreased. Importantly, the intervention modulated inflammation, as evidenced by significant reductions in IL-6 and IL-8 levels, highlighting both local and systemic anti-inflammatory effects.

Although these results did not directly investigate the molecular mechanism of furosemide in patients, they are consistent with animal and in vitro evidence, shedding light on the potential therapeutic pathways of this drug. In a mouse model, nebulized furosemide was able to modulate the activity of mechanical receptors in the trachea and bronchi, which consequently reduced airway hyperresponsiveness and unnecessary contraction of airway smooth muscles.¹³ Furthermore, in vitro data demonstrated that furosemide decreased airway sensitivity by inhibiting NKCC1 transporters in epithelial and type II alveolar cells. This effect was accompanied by increased infiltration of T lymphocytes into the lungs, while goblet cell numbers and mucus secretion remained unchanged, indicating that the reduction in airway hyperresponsiveness was primarily mediated through modulation of ion channels and

changes in epithelial membrane potential, independent of mucus secretion.¹²

Regarding pulmonary functional capacity and dyspnea severity, the findings of the present study are consistent with those reported by Saba et al (2020). In their clinical trial involving 69 patients with COPD, they investigated the effect of a combination therapy of furosemide (40 mg) and salbutamol and demonstrated that this regimen, compared to monotherapy, significantly improved pulmonary function indices (FEV₁, FVC, and FEV₁/FVC ratio) and reduced clinical symptoms, including dyspnea, as assessed by the mMRC and Borg scales.⁸ The present study, with a larger sample size (92 patients), a longer treatment duration (5 days), and a lower dose of furosemide (20 mg), similarly showed that adding furosemide to standard therapy significantly improved pulmonary function indices, including FEV₁, FVC, and FEV₁/FVC ratio, along with reductions in dyspnea severity measured by CAT and mMRC scores. Similarly, in a study by Ragab et al (2024), 92 patients with stable COPD were randomly assigned to receive either nebulized furosemide (40 mg) or saline in combination with salbutamol-ipratropium. The results showed that furosemide significantly improved FVC, FEV₁, and FEV₁/FVC ratio compared to saline.¹⁶ Furthermore, a systematic review and meta-analysis by Ghaysouri et al (2020) evaluated the effects of nebulized furosemide compared to placebo on cardiovascular and respiratory parameters in patients with COPD. Their results demonstrated that inhaled furosemide significantly influenced respiratory rate, heart rate, and FEV₁, while changes in pH, PaCO₂, O₂ saturation, HCO₃⁻, and PaO₂

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were not significant.⁶ The present study corroborates the findings of Ghaysouri et al showing that nebulized furosemide had a positive and significant effect on pulmonary functional capacity. However, unlike their study, our findings also revealed significant improvements in arterial blood gas parameters, specifically PaCO₂ and PaO₂.

Regarding the anti-inflammatory effects of furosemide, *in vitro* data have shown that furosemide reduces the phosphorylation of p38 mitogen-activated protein kinase (MAPK), leading to decreased accumulation of CD68⁺ macrophages and suppression of inflammatory signaling.¹⁷ Since p38 MAPK phosphorylation is elevated in the airway epithelial cells of COPD patients, resulting in excessive production of inflammatory cytokines such as IL-6, IL-8, and TNF- α ,¹⁸ the observed reduction of these cytokines in the present study is consistent with these findings. It is also important to note that Nuclear factor kappa B (NF- κ B) – regulated cytokines do not respond uniformly in clinical settings. Prior human studies demonstrate that TNF- α often shows smaller systemic fluctuations compared with IL-6 and IL-8, despite being activated through shared upstream pathways. For example, in a cohort of 108 patients with rheumatoid arthritis, IL-6 gene expression levels were higher than TNF- α in more than 80% of cases, illustrating the inherently greater dynamic variability of IL-6 *in vivo*.¹⁹ Furthermore, post-transcriptional regulatory mechanisms help explain the differential cytokine responses observed in our study. TNF- α mRNA is tightly controlled by cell-type-specific RNA-binding proteins such as tristetraprolin (a member of the TPA-inducible sequence 11 (TIS11) family) that actively promote its degradation, limiting the extent to which TNF- α levels change in systemic circulation. In contrast, IL-6 and IL-8 are more strongly influenced by p38-dependent pathways that stabilize their mRNA, making them more responsive to anti-inflammatory modulation.²⁰ Pharmacological studies also show that IL-6 and IL-8 can increase or decrease depending on the activation context, whereas TNF- α typically exhibits more constrained modulation.²¹ Taken together, these data support the biological plausibility of our findings, where IL-6 and IL-8 showed significant between-group reductions while TNF- α did not reach statistical significance.

Additionally, animal studies by Murad et al in a murine model of induced asthma showed that nebulized furosemide reduced IL-6 and TNF- α levels and

potentiated the bronchodilatory effects of salbutamol. In contrast, oral administration of furosemide increased only diuresis, without exerting anti-inflammatory or bronchodilatory effects in the lungs. These findings indicate that the beneficial effects of furosemide in the airways are independent of systemic diuretic activity and are primarily mediated through local pulmonary action.²² Furthermore, in a study by Bryniarski et al (2022), mice received furosemide for 8 days and their macrophages were collected. Furosemide directly influenced macrophages by increasing reactive oxygen species production while simultaneously reducing nitric oxide generation and IL-12 secretion. These changes modulated inflammatory activity and cellular immune responses, demonstrating that furosemide can control chronic inflammation and macrophage activity.²³ Importantly, the reduction in IL-8 levels observed in our study likely influenced neutrophil trafficking. IL-8 is a key chemokine driving neutrophil migration from the circulation into inflamed lung tissue. By attenuating this chemotactic signal, nebulized furosemide may have caused neutrophils that would otherwise accumulate in the lungs to remain in circulation. This mechanism provides a plausible explanation for the observed increase in circulating neutrophil (PMN) percentages in the intervention group. Meanwhile, total WBC counts increased post-treatment in both groups without significant between-group differences, suggesting that the overall leukocyte response likely reflects a generalized systemic effect rather than a direct impact of furosemide.²⁴

Human studies have highlighted the importance of evaluating these biomarkers and their key role in disease prognosis. In a study by Moraes et al, COPD patients exhibited higher levels of IL-6 and IL-8 compared to controls, with these elevations being particularly associated with smoking intensity, the bronchitic phenotype, and the annual frequency of exacerbations.²⁵ Another study demonstrated a stepwise increase in IL-8 levels from healthy individuals to stable COPD patients and then to patients in the exacerbation phase, with significantly higher levels in patients with frequent exacerbations compared to those with infrequent exacerbations.²⁶ Therefore, the reduction of IL-6 and IL-8 observed in the present study may indicate that the intervention modulates key inflammatory pathways associated with poor prognosis and an increased risk of future COPD exacerbations.

The present study demonstrates that adding nebulized furosemide enhances the therapeutic efficacy of standard bronchodilator therapy in patients with COPD exacerbation. Beyond improving clinical symptoms and quality of life, furosemide contributed to significant gains in lung function and meaningful reductions in key inflammatory biomarkers, reflecting its influence on the underlying pathophysiology of the disease. Unlike many previous investigations that focused mainly on respiratory indices, this study provides a more comprehensive evaluation by integrating clinical, functional, and inflammatory outcomes. Given its low cost, wide availability, and favorable safety profile, nebulized furosemide may serve as a practical and effective adjunctive therapy particularly in resource-limited healthcare settings helping to mitigate the clinical and economic burden of COPD exacerbation.

STATEMENT OF ETHICS

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and national guidelines for human research. The study protocol was approved by the Research Ethics Committee of the School of Medicine, Shahid Beheshti University of Medical Sciences (Approval No. IR.SBMU.MSP.REC.1402.364).

FUNDING

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

This article contains all data created and examined throughout this investigation. The corresponding author will provide datasets used or analysed during the current work upon reasonable request.

AI ASSISTANCE DISCLOSURE

The authors hereby declare that OpenAI's ChatGPT-5 was used solely for grammar and language refinement during the preparation of this manuscript. No content generation or substantive editing was performed by the AI. All intellectual content and scientific contributions are the original work of the authors.

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