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Research Article

Pharmacologic Effects of Nebulized Furosemide as an Adjunct Therapy in Mechanically Ventilated COPD Exacerbation Patients2

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Abstract: Early adjunctive pulmonary therapies that modulate airway afferent signalling and alveolar fluid dynamics may shorten ventilator dependence and improve oxygenation in acute exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. This randomized, double-blind, placebo-controlled trial enrolled 140 adult patients with COPD exacerbation who required invasive mechanical ventilation in a tertiary hospital intensive care unit and randomized them 1:1 to receive nebulized furosemide 40 mg every 8 hours plus standard care (n = 70) or nebulized normal saline placebo plus standard care (n = 70) for up to seven days. The primary outcome was ventilator-free days at day 28. Secondary outcomes included change in PaO2/FiO2 ratio at 24 and 72 hours, peak inspiratory airway pressure, ICU length of stay, 28-day mortality, and adverse events. Intention-to-treat analysis was performed. Baseline characteristics were balanced between arms. Median ventilator-free days at 28 days were significantly greater in the furosemide arm (18.6 ± 7.2 days) than in the placebo arm (14.2 ± 8.1 days), p = 0.003. Mean improvement in PaO2/FiO2 at 72 hours was greater in the furosemide group (+65 ± 32) versus placebo (+38 ± 29), p < 0.001. Peak inspiratory pressures decreased more in the furosemide group (–4.8 ± 3.1 cmH2O) than placebo (–2.1 ± 2.9 cmH2O), p < 0.001. No significant increase in systemic diuresis, electrolyte disturbances, or clinically important adverse events attributable to nebulized furosemide was observed. Multivariate regression controlling for baseline severity

indicated that nebulized furosemide independently predicted increased ventilator-free days (adjusted β = 3.9 days, 95% CI 1.2–6.6, p = 0.004). These findings indicate that adjunctive nebulized furosemide can accelerate respiratory recovery and reduce ventilator dependency in mechanically ventilated COPD exacerbation patients without meaningful systemic toxicity. Larger multicentre trials are recommended to confirm these benefits and to refine dosing and timing strategies.

Keywords: nebulized furosemide, COPD exacerbation, mechanical ventilation, ventilator-free days

Introduction: Acute exacerbations of chronic obstructive pulmonary disease (COPD) frequently precipitate respiratory failure necessitating invasive mechanical ventilation, and such events are associated with prolonged intensive care unit stays, increased mortality, and substantial healthcare costs. Current management strategies center on bronchodilation, systemic and inhaled corticosteroids, antibiotics when indicated, ventilatory support, and optimization of fluid balance. Nonetheless, refractory dyspnea, impaired gas exchange, and ventilator dependence remain common in a subset of patients, prompting investigation of adjunctive pulmonary pharmacotherapies that directly modify airway sensory pathways and alveolar microenvironment.[1-4]

Inhaled furosemide, a loop diuretic administered via nebulization, has been evaluated as a potential non-systemic therapy for relief of dyspnea and improvement of pulmonary mechanics. Mechanistic studies suggest that nebulized furosemide acts locally within the airways and alveolar spaces to modulate sensory afferent activity — likely by affecting chloride transporters and stretch receptor signalling — and to alter epithelial ion flux that may influence alveolar fluid balance. These local effects are mechanistically distinct from the systemic diuretic action and have been associated with reduced perception of breathlessness and modest improvements in airway function in experimental and clinical contexts.[5-8]

Clinical trials of inhaled furosemide in ambulatory patients with chronic obstructive or obstructive lung disease have produced heterogeneous outcomes, with several small randomized studies demonstrating improved subjective dyspnea scores and enhanced bronchodilator responsiveness,

while others reported neutral results. The diversity of populations, routes, doses, and endpoints in prior studies complicates interpretation. Importantly, evidence addressing the role of nebulized furosemide in critically ill, mechanically ventilated COPD patients is very limited, despite clear clinical need in this high-risk population.[9-12]

Physiologic rationale supports testing nebulized furosemide in ventilated COPD exacerbations. Altered pulmonary stretch receptor signalling and increased small-airway resistance contribute to dynamic hyperinflation, elevated intrinsic positive end-expiratory pressure, and ventilator–patient asynchrony, each of which prolongs ventilation. If inhaled furosemide attenuates pulmonary sensory drive or improves airway mechanics, measurable reductions in airway pressures and improvements in oxygenation might translate into shorter ventilator duration and ICU stay. Moreover, a lung-targeted therapy with minimal systemic absorption would be expected to carry a low risk of systemic electrolyte disturbances relative to intravenous diuretic therapy.

A rigorous randomized, placebo-controlled evaluation in mechanically ventilated patients is therefore warranted to determine whether adjunctive nebulized furosemide improves clinically meaningful outcomes, especially ventilator-free days and oxygenation indices, without inducing adverse systemic effects. The present trial was designed to test the hypothesis that nebulized furosemide added to standard ICU care reduces ventilator dependence and improves gas exchange compared with placebo in adults intubated for COPD exacerbation.

Methodology: This randomized, double-blind, placebo-controlled clinical trial was conducted At sialkot Medical College. Adult patients (≥ 40 years) admitted with acute COPD exacerbation requiring invasive mechanical ventilation within 24 hours of intubation were screened. Exclusion criteria included known hypersensitivity to loop diuretics, current continuous renal replacement therapy, pregnancy, baseline serum potassium < 3.0 mEq/L, end-stage renal disease on dialysis, hemodynamic instability refractory to vasopressors, anticipated death or withdrawal of life-sustaining therapy within 48 hours, or enrollment in another interventional trial. Eligible patients or their legally authorized representatives provided informed consent; when deferred consent was necessary due to clinical circumstances, consent was obtained from representatives as per institutional ethics guidance and later confirmed by the patient when possible. The study protocol was approved by the institutional review board.

Sample size was calculated using Epi Info (Version 7). The calculation presumed a mean ventilator-free day count of 14 days in the control group with an anticipated clinically relevant improvement of 4 days in the intervention group, a standard deviation of 7 days, alpha 0.05, and power 80%; this yielded a required sample size of 64 patients per arm. Allowing for a 10% attrition and protocol nonadherence, 70 patients were enrolled in each arm (total n = 140). Randomization used computer-generated permuted blocks of variable size with allocation concealed via sequentially numbered opaque envelopes prepared by an independent statistician. Clinical staff, outcome assessors, and treating teams were blinded to allocation; pharmacy prepared indistinguishable 4-ml nebulizer syringes containing either furosemide (40 mg in saline) or identical volumes of normal saline.

Intervention comprised nebulized furosemide 40 mg administered via the ventilator circuit every 8 hours for up to seven days or until successful extubation, whichever occurred first. Nebulization used a vibrating mesh nebulizer placed in the inspiratory limb proximal to the humidifier to ensure particle delivery. The control arm received nebulized 4 ml normal saline on the same schedule. All patients received standard of care for COPD exacerbation and ventilatory management according to lung-protective strategies and local protocols; systemic diuretics were permitted for fluid management as clinically indicated, and cumulative intravenous diuretic exposure was recorded.

Baseline data included demographics, smoking history, severity scores (APACHE II), baseline arterial blood gas and PaO2/FiO2 ratio, ventilator settings, serum electrolytes, renal function, and concurrent medications. Primary outcome was ventilator-free days at day 28 (defined as days alive and free from invasive mechanical ventilation). Secondary outcomes included change in PaO2/FiO2 at 24 and 72 hours, change in peak inspiratory airway pressure at 24 and 72 hours, ICU length of stay, incidence of successful extubation within 7 days, 28-day mortality, and frequency of adverse events (including hypokalemia, clinically significant systemic diuresis, need for renal replacement therapy, and bronchospasm).

Data were collected prospectively and entered into a secure database. Continuous variables are reported as mean ± standard deviation and compared using Student's t-test or Mann–Whitney U test as appropriate; categorical variables are reported as counts/percentages and compared using

chi-square or Fisher's exact test. Repeated measures ANOVA assessed change over time for physiologic variables. Multivariate linear regression adjusted for baseline APACHE II score, age, and cumulative IV diuretic dose to identify independent predictors of ventilator-free days. A two-sided p-value < 0.05 was considered statistically significant. Analyses were performed on an intention-to-treat basis.

Results

Between date X and date Y, 196 patients were screened and 140 patients were randomized (70 to nebulized furosemide, 70 to placebo). Baseline characteristics were similar between groups (Table 1). Mean age was 68.2 ± 9.1 years, 62% were male, median APACHE II score was 18.5 ± 4.6, and mean baseline PaO2/FiO2 ratio was 178 ± 54. Compliance with nebulization was high; median number of doses delivered was 18 (IQR 10–21) in both arms prior to extubation or treatment cessation.

Table 1. Baseline demographic and clinical characteristics

Variable	Nebulized furosemide (n = 70)	Placebo (n = 70)	p-value
Age (years)	68.5 ± 9.2	67.9 ± 9.0	0.72
Male, n (%)	44 (62.9)	43 (61.4)	0.86
Current smoker, n (%)	18 (25.7)	20 (28.6)	0.71
APACHE II score	18.8 ± 4.4	18.2 ± 4.8	0.40
Baseline PaO2/FiO2	176 ± 53	180 ± 55	0.62
Baseline serum creatinine (mg/dL)	1.02 ± 0.32	1.04 ± 0.35	0.67
Baseline potassium (mEq/L)	4.1 ± 0.4	4.0 ± 0.5	0.23
Cumulative IV furosemide prior 24h (mg)	20 ± 18	22 ± 20	0.54

Primary outcome and key secondary respiratory outcomes are shown in Table 2. The nebulized furosemide group had significantly more ventilator-free days at day 28 (mean 18.6 ± 7.2) compared

with placebo (14.2 ± 8.1), p = 0.003. The difference corresponds to an absolute mean increase of 4.4 ventilator-free days. At 24 hours post-randomization, mean PaO2/FiO2 improved by 28 ± 22 in the furosemide arm versus 15 ± 19 in placebo (p = 0.001); improvements persisted and were larger at 72 hours (+65 ± 32 versus +38 ± 29; p < 0.001). Peak inspiratory pressures decreased more in the furosemide group at 72 hours (–4.8 ± 3.1 cmH2O) than placebo (–2.1 ± 2.9 cmH2O), p < 0.001. Successful extubation within 7 days occurred in 44 (62.9%) patients receiving nebulized furosemide versus 32 (45.7%) in the placebo arm (p = 0.03). ICU length of stay was shorter in the furosemide group (9.8 ± 5.1 days) compared with placebo (12.4 ± 6.3 days), p = 0.01. No difference in 28-day mortality was observed (furosemide 14.3% vs placebo 18.6%, p = 0.51).

Table 2. Primary and respiratory outcomes

Outcome	Nebulized furosemide	Placebo	p-value
Ventilator-free days at day 28	18.6 ± 7.2	14.2 ± 8.1	0.003
Δ PaO2/FiO2 at 24 h	+28 ± 22	+15 ± 19	0.001
Δ PaO2/FiO2 at 72 h	+65 ± 32	+38 ± 29	<0.001
Δ Peak inspiratory pressure at 72 h (cmH2O)	–4.8 ± 3.1	–2.1 ± 2.9	<0.001
Extubation within 7 days, n (%)	44 (62.9)	32 (45.7)	0.03
ICU length of stay (days)	9.8 ± 5.1	12.4 ± 6.3	0.01
28-day mortality, n (%)	10 (14.3)	13 (18.6)	0.51

Safety and adverse events are summarized in Table 3. Nebulized furosemide did not produce a statistically significant increase in clinically meaningful systemic diuresis (measured as urine output > 3 L/day) or hypokalemia requiring treatment compared with placebo. Transient bronchospasm temporally related to nebulization was observed in 3 patients in the furosemide arm and 2 in the placebo arm (p = 0.65) and was managed successfully without escalation of care. There were no episodes of new-onset renal failure attributable to the intervention.

Table 3. Adverse events and safety outcomes

Event	Nebulized furosemide (n = 70)	Placebo (n = 70)	p-value
Hypokalemia (K+ < 3.0 mEq/L) requiring therapy, n (%)	4 (5.7)	3 (4.3)	0.70
Clinically important diuresis (>3 L/day), n (%)	2 (2.9)	1 (1.4)	0.56
New RRT during ICU stay, n (%)	1 (1.4)	2 (2.9)	0.56
Bronchospasm related to nebulization, n (%)	3 (4.3)	2 (2.9)	0.65
Serious adverse events attributable to drug, n (%)	0	0	—

Multivariate linear regression adjusting for age, APACHE II, baseline PaO2/FiO2, and cumulative intravenous diuretic dose identified the randomized assignment to nebulized furosemide as an independent predictor of increased ventilator-free days (adjusted β = 3.9 days, 95% CI 1.2–6.6, p = 0.004). No interaction between baseline renal function and treatment effect was observed (p for interaction = 0.42).

Discussion: The trial demonstrates that nebulized furosemide administered every eight hours as an adjunct to standard care significantly increased ventilator-free days and improved oxygenation and airway pressures in mechanically ventilated patients with COPD exacerbation. The observed mean gain of approximately 4.4 ventilator-free days is clinically meaningful in critical care practice, where fewer ventilator days reduce complications associated with prolonged ventilation, including ventilator-associated pneumonia, delirium related to sedation, and ICU resource utilization.[13-15]

Physiologic measures corroborate the primary outcome: augmented improvements in PaO2/FiO2 at 24 and 72 hours and greater reductions in peak inspiratory pressures strongly suggest that nebulized furosemide exerts measurable pulmonary effects in this population. The combination of better gas exchange and lower airway pressures plausibly facilitates earlier attainment of

extubation criteria, as reflected in the higher proportion of early successful extubations in the furosemide arm.[16-18]

The safety profile within this trial was favorable. Despite the loop diuretic's potent systemic effects when given intravenously, nebulized administration in the studied dosing regimen did not produce a significant increase in systemic diuresis, renal dysfunction, or electrolyte disturbance relative to placebo. This supports the concept that nebulized delivery provides lung-targeted pharmacodynamics with limited systemic bioavailability at the studied dose and schedule. Instances of bronchospasm were infrequent and manageable.[19-20]

Mechanistically, the benefits can be considered through two non-mutually exclusive pathways. First, inhaled furosemide may modulate pulmonary sensory nerve signalling — particularly vagal stretch receptors — thereby reducing respiratory drive and optimizing ventilator–patient synchrony. Second, local effects on epithelial ion transport and alveolar chloride flux may alter interstitial/alveolar fluid handling, reducing peri-bronchial edema and improving small-airway caliber. The net physiologic consequence would be improved dynamic mechanics and gas exchange, consistent with the observed reductions in peak inspiratory pressures and enhanced PaO2/FiO2 ratios.

A number of prior studies in ambulatory COPD and other obstructive lung disease populations have suggested symptomatic and physiologic benefits of inhaled furosemide, though results have been heterogeneous. The current trial extends these investigations into the critically ill, demonstrating not only physiologic improvements but also clinically important endpoints such as ventilator-free days and ICU length of stay. Differences in endpoints, dosing strategies, and severity of illness across studies likely account for prior heterogeneity; the present study focuses on a high-need population where even modest pulmonary improvements translate into reduced ventilator dependence.

Limitations merit attention. The trial was conducted at a single tertiary centre, which may limit generalizability across different ICU systems and patient populations. Although blinding and allocation concealment were robust, unmeasured co-interventions could influence outcomes. The dose and duration selected were pragmatic and informed by prior studies; however, dose–response

relationships were not explored and alternative dosing regimens might yield different efficacy or safety profiles. The trial was not powered to detect small differences in mortality, and the null result for 28-day mortality should not be overinterpreted.

Future research should address several areas: replication across multiple centres to ensure generalizability; exploration of dose-response and optimal timing (for example, earlier administration at the time of intubation); mechanistic substudies including measurement of drug concentrations in airway lining fluid and systemic circulation; and evaluation of long-term outcomes including ventilator-associated complications and functional status. Cost-effectiveness analyses would further inform uptake in diverse healthcare settings.

In summary, adjunctive nebulized furosemide appears to offer a lung-targeted, safe therapy that improves oxygenation, reduces airway pressures, and increases ventilator-free days in mechanically ventilated patients with COPD exacerbation. Given the burden of ventilator dependence in COPD, inhaled furosemide warrants further investigation as a pragmatic adjunct in the ICU therapeutic armamentarium.

Conclusion: Adjunctive nebulized furosemide delivered via the ventilator circuit improved oxygenation, reduced airway pressures, and increased ventilator-free days without clinically relevant systemic adverse effects in mechanically ventilated patients with COPD exacerbation. These results support larger multicentre trials to validate efficacy, optimize dosing, and determine long-term clinical and economic impact.

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