J MEDICINE 2026; 27: 62-66

Original Article

Role of Nebulized Magnesium Sulfate in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

Background: *Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) is a common cause of hospitalization leading to rises in mortality and morbidity in low and middle-income countries (LMICs) including Bangladesh. Therapeutic benefits have been seen in acute Asthma patients nebulized with magnesium sulfate. So the aim of this study was to investigate the role of nebulized magnesium sulfate as an adjuvant treatment in AECOPD.*

Objectives: *To evaluate the role of nebulized magnesium sulfate in the management of AECOPD.*

Methods: *It was a randomized controlled trial where 324 subjects were enrolled and allotted into two groups with 162 in each group. Then each group received either 2.5 mg salbutamol mixed with 2.5 ml magnesium sulfate or 2.5 mg salbutamol mixed with 2.5 ml isotonic normal saline on three occasions at 30 minutes intervals via nebulizer. The role of magnesium sulfate was investigated by measuring PEFR (Peak Expiratory Flow Rate) as primary outcome parameter at 30, 60 and 90 minutes after nebulization. The secondary outcome measure was to assess Intensive Care Unit (ICU) admission for ventilator support, mortality, changes in respiratory rate and oxygen saturation.*

Results: *The mean PEFR in the magnesium sulfate group at 30, 60 and 90 minutes were 91.36±16.66, 129.44±33.13 and 163.78 ±66.30. Also mean PEFR in normal saline group at 30, 60 and 90 minutes were 72.16±16.66, 85.49±24.80 and 97.81±33.66. PEFR was higher in magnesium group then normal saline group and p-value was <0.001 which was statistically significant. A total of 15.4% patients were admitted to the ICU and 4.9% died among patients nebulized with magnesium sulfate. But 27.2% were admitted to the ICU and 13% died among patients nebulized with normal saline. There p-value was 0.0146 which was statistically significant.*

Conclusions: *Nebulized magnesium as an adjuvant to bronchodilators in the setting of AECOPD resulted in significant improvement of PEFR.*

Keywords: *AECOPD, Magnesium Sulfate, Peak Expiratory Flow Rate.*

DOI: *https://doi.org/10.3329/jom.v27i2.92251*

Received: *01.02.2026;* ***Accepted:*** *06.05.2026*

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is defined as a preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases.[1] Bangladesh is one of the country where the burden of non-communicable diseases (NCDs) like COPD is increasing and the prevalence of COPD among Bangladeshi adults is 12.5% approximately.[2] Acute exacerbation of COPD is one of the most common conditions and also one of the leading causes of hospitalization and increased consumption of medical expenses. These patients may experience an acute worsening of respiratory symptoms that require hospitalization with additional therapy due to an increased risk of mortality and other negative outcomes, such as

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endotracheal intubation or intensive care admission. Therefore, effective treatment is necessary to minimize the negative impact of exacerbation and prevent hospital readmissions.[3] The current guidelines recommendation for treating COPD exacerbation are oxygen therapy, short-acting beta-2 agonists, muscarinic antagonists, corticosteroids, antibiotics, and non-invasive ventilation.[4] But in spite of all measures many patients die due to respiratory failure. So, new pharmacotherapy is needed for treatment strategies to reduce death due to exacerbation of COPD.[5] Magnesium acts as a bronchodilator by causing calcium channel antagonism of the sarcoplasmic reticulum of smooth muscle. It depresses muscle fibers' excitability by preventing acetylcholine release from cholinergic nerve endings. It also has an anti-inflammatory effect by stabilizing T cells.[3] Many meta-analyses of randomized controlled trials have confirmed the efficacy of magnesium therapy in acute severe asthma.[6] According to GINA 2018 guidelines, a single dose of intravenous magnesium sulfate can be considered for severe life-threatening asthma exacerbations who fail to respond to first-line treatment with persistent hypoxemia and fail to achieve 60% predicted Forced Expiratory Volume in 1 second (FEV1) after one hour of care. The recommended dose is 1.2 gm to 2 gm, delivered by infusion over 20 minutes.[7] Also a good correlation between forced expiratory volume in 1 second (FEV1) and peak expiratory flow rate (PEFR) has been reported in COPD.[8] But fewer data are found regarding use of magnesium sulfate in acute exacerbation of COPD in both intravenous and nebulized form. All previous studies showed improvement in PEFR when nebulized with magnesium sulfate but did not show any significant reduction in hospital admission and mortality rate. No such research was conducted in Bangladesh on the role of nebulized magnesium in the acute exacerbation of COPD in the past. In our study, we used PEFR as a follow-up measure of airway obstruction due to its ease of use, easy instruction to the patient, and good correlation between PEFR and FEV1. This study primarily aimed to evaluate the role of nebulized magnesium sulfate in acute exacerbations of COPD.

Materials and Methods

This randomized controlled trial was conducted on patients admitted with acute exacerbation of COPD in the medicine department of Sylhet MAG Osmani Medical College & Hospital, Sylhet, from 1st July 2022 to 30th June, 2024. The study population fulfilling the eligibility criteria within the given period was enrolled as a sample. Sample size was calculated by using the formula for clinical trial with 80% statistical power and 5.0% significance level and was found to be 162 in each group with adjustment of 10% attrition. Convenient sampling was used for sampling.

At first, all patients admitted to the department of Medicine with a diagnosis of an acute exacerbation of COPD were clinically assessed and given standard treatment with 2.5 mg salbutamol plus 500 µg ipratropium bromide by nebulization, intravenous steroid (100 mg hydrocortisone) and intravenous antibiotics. Oxygen (2 l/min by nasal prongs) was given if oxygen saturations on room air were <90%. Only subjects with a PEFR<300 l/min measured 20 min after the salbutamol plus ipratropium nebulization were enrolled in the trial. A total of 324 patients were selected based on eligibility criteria. Then, informed written consent was obtained and a brief questionnaire was administered, obtaining information about demographic characteristics, the duration and severity of symptoms, medication used and smoking status. Routine blood tests (serum creatinine, sodium, potassium, complete blood count) were done.

Patients were divided into Group A (magnesium group) and Group B (saline group). Block randomization was used to allocate every case to either Group A or Group B. The block size was 4 (2×2). A total of 162 patients were allocated to each group. After randomization, Group A patients received nebulization with 2.5 mg salbutamol mixed with 2.5 ml magnesium sulfate. Group B patients received 2.5 mg salbutamol mixed with 2.5 ml isotonic saline on three occasions at 30-minute intervals. We recorded PEFR before the first study nebulizer, before each subsequent nebulization, and then 30 min after the last nebulization. Three measurements were made at each time point, and the highest record was used for analysis. Respiratory rate, blood pressure, and oxygen saturation by pulse oximetry was recorded as clinical observations**.** The patients were followed up for one week after being admitted and the outcome was noted regarding the requirement of ventilator support and mortality. So our outcome variables were: 1) Peak expiratory flow rate (PEFR), 2) Respiratory rate, 3) Oxygen saturation 4) ICU requirement for invasive or non-invasive ventilator support, 5) Hospital mortality rate.

Data were collected in a predesigned data collection sheet containing the variables of interest.

Ethical clearance was taken from the ethical review committee of Sylhet MAG Osmani Medical College before the commencement of the study. Informed written consent was taken from the patient, and study-related information was explained in the local language to the patient. The purpose and method of the study, the risks and benefits of participating in the survey, respondent's right to participate voluntarily, and right to withdraw at any point were explained in the local language. All information were collected with complete respect to the patient's wish and without force or pressure.

Result

The highest number of patients, about 41.98%, were between 60 and 69 years of age. A paired t-test was done and there was no statistically significant difference in age between the two treatment groups. Male predominance was observed in both groups and Chi-Square test showed no significant in between group difference. Majority of patients in both groups were current smoker with no significant difference in between groups (Table-1). Intra group difference of PEFR30 and PEFR60 and PEFR90 showed significant improvement in both side (Table-2). Also the boxplot compares the Peak Expiratory Flow Rate at 90 minutes (PEFR90) of two treatment groups which showed PEFR90 values are higher in Group A compared to Group B that was confirmed by ANOVA (Figure). Requirement of ventilator support in ICU, in hospital mortality and death rate are shown in Table-3 and Table-4.

Relative Risk (RR) was 0.38. Absolute Risk Reduction (ARR) was 0.08. So NNT (number of patients needed to treat) was =1/ARR=1/0.08=12.

Table 1. Comparison of age, sex and current smoking status

Parameter	Group-A	Group-B	P value
Mean age	63.41	64.69	0.182
Male	91.36%	85.80%	0.1623
Female	8.64%	14.20%	
Current smoker	70.98%	71.60%	0.909

Table 2: Change of PEFR at 30, 60, and 90 minutes in group A and group B

Time	PEFR in group A	PEFR in group B	P- value
0 minutes	60	60	
30 minutes	91.36 ± 16.66	72.16±16.66	< 0.001
60 minutes	129.44 ± 33.13	85.49±24.80	< 0.001
90 minutes	163.78±66.30	97.81±33.66	< 0.001

Table 3: Requirement of ventilator support in the ICU in both groups

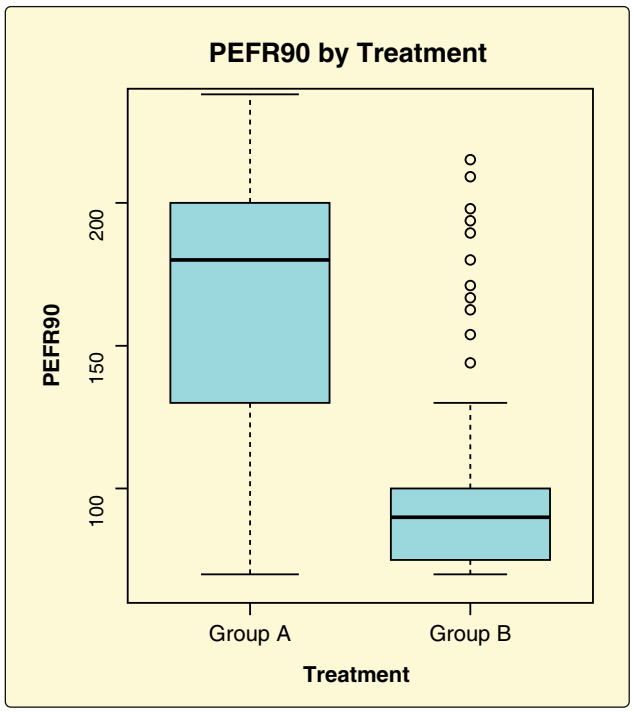
	Patient at ICU			p-
Treatment	Yes	No	Total	value
Group A	25 (15.4%)	137 (84.6%)	162 (100.0%)	
Group B	44 (27.2%)	118 (72.8%)	162 (100.0%)	0.0146
Total	69 (21.3%)	255 (78.7%)	324 (100.0%)	

Table 4: In hospital mortality with treatment in both groups

	Hospital Mortality			p-
Treatment	Yes	No	Total	value
Group A	8(4.9%)	154(95.1%)	162(100.0%)	
Group B	21(13.0%)	141(87.0%)	162(100.0%)	0.0195
Total	29(9.0%)	295(91.0%)	324(100.0%)	

Table 5: Change of Respiratory Rate and O2 saturation at 0 and 90 minutes

Parameter	Group	0 minute	90 minute	p-value
Respiratory	Group-A	25.80± 5.47	21.29± 4.51	<0.001
rate	Group-B	26.16± 5.01	23.81±2.35	<0.001
O2	Group-A	87.65±5.47	90.30±14.50	<0.001
saturation	Group-B	86.44±5.48	88.01±8.58	<0.001



Figures: *Boxplot*

Discussion

Age and sex are critical demographic factors that can significantly influence the clinical outcomes of patients experiencing acute exacerbations of COPD. The mean age of patients were 63.41 years in group A and 64.69 years in group B of our study. Nouira et al, also noticed in their study that most of the patients were between the ages of 61 to 70 years that was similar to our study.[9] According to existing literature review, studies have consistently showed that

COPD is more prevalent in males which is attributed to historical factors such as higher smoking rates and occupational exposures. Claxton et al. reported that men represented approximately 75-80% of COPD cases in similar acute settings.[10] However, in our study, male predominance was over 85%, which is significantly higher and may reflect regional or demographic factors influencing disease patterns. But no significant group difference was found regarding age and sex distribution.

In our study, we observed that the current smoking status was similar across both groups (Group A: 70.98% and Group B: 71.60%). The high prevalence of current smokers in both groups highlights the ongoing challenge of managing COPD in populations with significant tobacco use.

We selected patients with a PEFR<300 L/min (measured 20 min after nebulization with salbutamol and ipratropium) to see the effect of nebulized magnesium in severe COPD. PEFR was chosen as the primary outcome variable and repeatable measure of bronchodilator response in acute exacerbation of chronic obstructive pulmonary disease. A good correlation between forced expiratory volume in 1 second (FEV1) and PEFR has been reported in COPD.[8]

In our study, the treatment group receiving nebulized magnesium sulfate showed a significant improvement in PEFR compared to the control group. This difference of response in two groups at 90 minutes was statistically significant (p-value <0.001). It indicates that magnesium sulfate may enhance bronchodilation in acute exacerbations of COPD. When we compared our result with other studies like Bajracharya et al. who reported a statistically significant increase in PEFR from initiation to 30, 60, and 90 minutes after nebulization with magnesium sulfate.[11] This supported our study that nebulized magnesium sulfate had therapeutic benefits on PEFR in acute exacerbation of COPD.

In our study, we evaluated the impact of nebulized magnesium sulfate on respiratory rate (RR) and oxygen saturation in patients experiencing acute exacerbations of COPD. Both groups exhibited higher respiratory rates and lower oxygen saturation levels at baseline, indicating a comparable degree of respiratory distress. Pair t-test analysis of response at 90 minutes of intervention showed significant response in both groups. This reduction in respiratory rate and improvement in oxygen saturation suggested a potential alleviation of bronchospasm associated with the exacerbation.

In evaluating the role of nebulized magnesium sulfate in acute exacerbations of COPD, we assessed its impact on ICU admission and hospital mortality rates. About 15.4 % required ICU admission among patients who were nebulized with magnesium sulfate and 4.9% died. On the other hand, in patients nebulized with normal saline ICU admission was required in 27.2% and 13% patients died. Statistical analysis showed significant reduction of ICU admission rate and death in magnesium sulfate group. But a study in Pakistan showed no statistically significant difference in ICU admission and mortality in between magnesium sulfate group and normal saline group.[12]

Also in our study, relative risk and absolute risk reduction both were positive. So, magnesium showed better efficacy. Patient nebulized with magnesium sulfate did not developed any side effect like headache, nausea, vomiting, low blood pressure and decreased patella reflex. This was the benefit of using nebulized route instead of intravenous route. So, nebulized magnesium sulfate appeared to have significant benefits in acute exacerbation of COPD.

Conclusion

This randomized control trial showed better bronchodilator effect of nebulized magnesium sulfate with salbutamol than nebulized salbutamol alone.

Limitations

1. We used a small sample size.
2. It was a single center study.
3. It was a non-blinded or open-label trial.
4. Long term follow up was not done.

Recommendations

RCT involving multicenter and large sample with blinding and long term follow up is needed to fully understand the benefit of nebulized magnesium sulfate in acute exacerbation of COPD.

Conflict of Interest

The authors have no conflicts of interest to declare.

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