ORIGINAL ARTICLE

Comparison of Nebulized Glycopyrronium with a Combination of Salbutamol and Ipratropium on Ventilatory Parameters in Critically Ill Mechanically Ventilated Patients of Chronic Obstructive Pulmonary Disease: An Observational Study

Preeti Priya[1], Soumya S Nath[2], Virendra Kumar[3], Suraj Kumar[4]

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Abstract

Background: The present study examined the duration of bronchodilation induced by nebulized glycopyrronium bromide (GB) and compared its effectiveness and incidence of any side effects with the combination of salbutamol and ipratropium bromide (SI) in critically ill mechanically ventilated chronic obstructive pulmonary disease (COPD) patients.

Patients and methods: This prospective, observational study was conducted in mechanically ventilated adult patients of COPD (18–75 years). Data of two groups of patients were collected for 12 hours each for three consecutive days after the nebulization – Group I: those who received 25 μg of GB, and Group II: those who received 1.25 mg of levo-salbutamol and 500 μg of ipratropium by nebulization.

Results: A significantly higher number of patients in group II had copious secretions. The mean static compliance was comparable at all time intervals, whereas the mean airway pressure was significantly lower in group II from 15 minutes to 4 hours post-nebulization. In group I, the onset of bronchodilation was 30 minutes on days 1 and 3, and 60 minutes on day 2, whereas, in group II, it was 60 minutes on days 1 and 2 and 30 minutes on day 3. In group I, bronchodilation was 10 hours on day 1 and 12 hours each on days 2 and 3, whereas in group II, bronchodilation was 4 hours on day 1 and 6 hours each on day 2 and 3.

Conclusion: Compared with SI, GB nebulization resulted in lesser respiratory secretions, a longer duration of action in terms of lowered airway resistance, and no adverse effects like hypertension, tachycardia, or desiccation of respiratory secretions.

Keywords: Glycopyrronium, Ipratropium bromide, Nebulization, Salbutamol.

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Highlights

Nebulized glycopyrronium to mechanically ventilated chronic obstructive pulmonary disease (COPD) patients with respiratory failure leads to lesser respiratory secretions, fewer tracheal suctions, and longer duration of action in terms of lowered airway resistance compared with the combination of salbutamol and ipratropium. Glycopyrronium was not associated with any adverse effects like hypertension, tachycardia, and desiccation of respiratory secretions.

Introduction

Chronic obstructive pulmonary disease is a significant worldwide health issue leading to considerable suffering and mortality. Its incidence is increasing because of several factors, the most important being smoking and air pollution. The COPD is distinguished from other illnesses by persistent airway inflammation of lung parenchyma. The hallmark pathophysiology is deteriorating level of restriction of expiratory airflow as a result of raised resistance of the airway and reduced elastic recoil. Further, dynamic hyperinflation leads to increased work of breathing.[1]

Patients with COPD often seek admission to the ICU because of acute exacerbation. Acute exacerbation of COPD (AECOPD) is defined as acute deterioration of the clinical status of COPD patients.[2] The AECOPD may be severe and lead to acute respiratory failure (ARF). Analysis of the arterial blood gas (ABG) reveals declining gas exchange, which in turn, leads to hypercapnia and/or hypoxemia.[3] As a result, many patients with AECOPD require non-invasive or invasive mechanical ventilation, and AECOPD is linked to high mortality, to the tune of 11–32%.[4,5]

[1–4]Department of Anaesthesiology and Critical Care Medicine, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Corresponding Author: Soumya S Nath, Department of Anaesthesiology and Critical Care, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, Phone: +91 9648935430, e-mail: soumyanath@rediffmail.com

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The mainstay of management of AECOPD is steroids (oral/parenteral and inhaled), bronchodilators, anti-muscarinic agents, antibiotics, and ventilatory support. Non-invasive ventilatory (NIV) support is the first line of ventilatory support for patients of AECOPD.[6] According to the GOLD guide, NIV should be considered in cases of respiratory acidosis, weakness of muscles of breathing, severe breathlessness, raised work of breathing, employing accessory muscles of breathing, intercostal retraction, paradoxical breathing, and persistent hypoxemia, despite oxygen supplementation.[7] However, there are several patients in whom one has to institute invasive mechanical ventilation if they develop respiratory arrest, loss of consciousness, do not tolerate NIV, hemodynamic instability, psychomotor agitation requiring sedation, bradycardia or gasping, tachypnea (>35 mins/min), pH <7.25 or hypoxemia.[8]

Short-acting β_2 agonists (SABA) are advocated as standalone strategy or combined with short-acting anticholinergic agents for early bronchodilation in AECOPD, but there is lack of quality scientific evidence supporting the role of SABA is such situations.[9] Moreover, SABA are needed to be repeated three or four times a day to maintain optimal bronchodilation coverage when short-acting muscarinic antagonists (SAMA) and SABA are administered. As a result, long-acting molecules that would reduce daily posology and a shorter delivery time would be desirable.[10] In such settings, long-acting muscarinic antagonists (LAMA) could have a role, but there is a lack of quality data on using LAMA during severe AECOPD.[11]

Compared with ipratropium bromide and tiotropium bromide, glycopyrronium is more effective as the lesser concentration of the latter prevents the contraction of bronchial smooth muscles by about half.[12]

There is no data on the action of glycopyrronium, a LAMA, in patients of AECOPD who are mechanically ventilated. Therefore, the present study was designed with the primary objective to assess the duration of bronchodilation caused by nebulized glycopyrronium in mechanically ventilated patients of AECOPD. The secondary objectives were to compare the effectiveness and any side effects of nebulized glycopyrronium with the combination of salbutamol (short-acting β_2 agonist) and ipratropium bromide (short-acting muscarinic antagonist) in critically ill mechanically ventilated patients of COPD.

Patients and Methods

This prospective, observational, open-label study involved adult patients of COPD (18–75 years) admitted to the intensive care unit of a tertiary care hospital and who were mechanically ventilated because of ARF.

Patients with heart diseases like coronary artery disease-confirmed or suspected, valvular disease, pneumonia, pulmonary edema, refractory hypoxemia, pneumothorax, hemodynamic instability or tachyarrhythmia, who had pre-existing thick or inspissated sputum, or receiving any heart rate (HR) controlling drug, like beta-blockers, calcium channel blockers, amiodarone or ivabradine, or those who have known sensitivity to glycopyrrolate, salbutamol, or ipratropium were excluded.

Nebulized glycopyrronium and a combination of salbutamol and ipratropium are routinely used in our ICU, at the discretion of the treating intensivist. We recruited 30 patients each who were nebulized with glycopyrronium (group I) and those who were nebulized with salbutamol and ipratropium (group II). All nebulizations were performed by the inbuilt ultrasonic vibrating mesh nebulizer available in our ventilators (550 Series, Nihon Kohden, Japan).

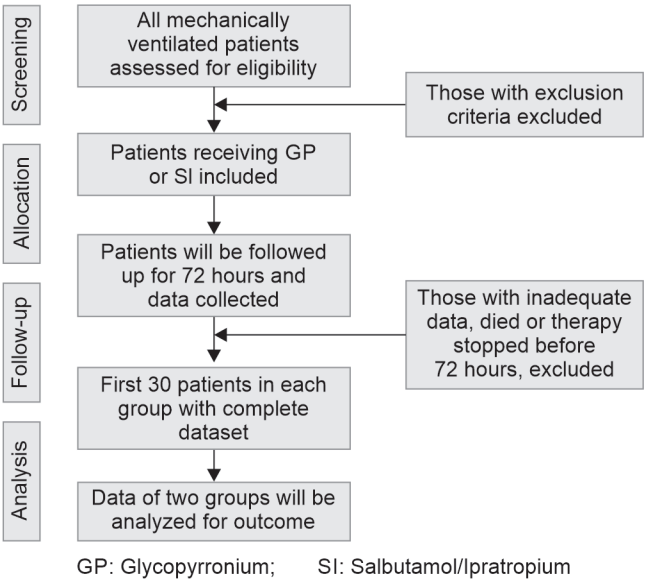

Fig. 1: Flowchart showing the workflow of the study

All the patients were studied for 12 hours each for three consecutive days after commencing mechanical ventilation and nebulization with glycopyrronium or salbutamol and ipratropium. All patients were orotracheally intubated (low-pressure cuffed endotracheal tube, internal diameter of 8.0 mm for males and 7.0 mm for females, and fixed to the face at tube length of 28 ± 1 mm at incisors) and adequately sedated (infusion of fentanyl and midazolam titrated to Richmond Agitation Sedation Scale of –4, i.e., deep sedation). Patients were ventilated on volume-controlled mode using settings that minimize dynamic hyperinflation [tidal volume of 7–8 mL/kg, square wave flow-time profile, no end-inspiratory pause, and external positive end-expiratory pressure (PEEPe) of 5 cm H_2O] and a fractional concentration of inspired oxygen (FiO_2) that achieved 89–94% of arterial oxygen saturation (SaO_2). Minute ventilation was regulated in each patient to preserve arterial pH within normal range and kept stable during data collection.

For making valid measurements of airway resistance, it is essential that the patient's respiratory efforts are being suppressed while mechanically ventilated. The lack of respiratory muscle activity was confirmed if these conditions were fulfilled—negative deflection of airway pressure (Paw) was absent, stable Paw waveform, peak inspiratory pressure remained constant from breath to breath, and exponential fall of expiratory flow.

Patients of group I received 25 µg of nebulized glycopyrronium, and group II received 1.25 mg of levosalbutamol and 500 µg of ipratropium. Patients did not receive any other bronchodilator other than specified for their group. Glycopyrronium and salbutamol/ipratropium were nebulized every 12 hours, to observe the duration of action (bronchodilation). The attending physician was free to advise salbutamol/ipratropium at 6–8 hours if they deemed the need. In that case, the patient was excluded from the study. Figure 1 shows the flowchart showing the workflow of the study.

All patients received corticosteroid 1 mg/kg of body weight, intravenous prednisolone, or an equivalent dose of methyl-prednisolone daily. All other aspects of medical management

(fluid, antimicrobial therapy, nutrition, prophylaxis against deep venous thrombosis, and stress ulcer) were as per existing protocols. Figure 1 shows the study workflow.

SaO_2 and HR were noted continuously using a pulse oximeter (Drager Infinity C700 monitor with Infinity Kappa System, manufactured by Drager Medical Systems Inc, USA).

The following data were recorded:

- Demographic data like age, gender, height, and ideal body weight.
- Duration of COPD, history of smoking or cooking with wood or coal.
- Occupation-past and present.
- Regularity of medical therapy.
- Comorbidities like diabetes, hypertension, and coronary artery disease.
- Nature of sputum before starting nebulization and twice daily, and number of suctions needed daily.
- Respiratory system mechanics, HR, and blood pressure (BP) were recorded before (baseline) and at 15, 30, and 60 minutes as well as at 2, 3, 4, 6, 8, 10, and 12 hours after each nebulization. End-inspiratory static compliance of the respiratory system (C_{STAT}) as well as minimum (R_{INT}) and maximum (R_{RS}) resistance of the respiratory system were computed according to standard formulae. The duration of the resulting bronchodilation is defined as the period after the test drug (glycopyrronium or salbutamol and ipratropium) nebulization that R_{INT} stayed below 85% of its baseline value. The duration of the bronchodilation was recorded for all patients.
- Mean airway pressure.

Sample Size Calculation

To date, there is no report that studied the effectiveness of any long-acting muscarinic antagonist on bronchodilation in mechanically ventilated critically ill patients of COPD. So, we opted for a sample size of convenience and decided to include 30 patients in each group—the glycopyrronium nebulization group (group I) and those who were nebulized with salbutamol and ipratropium (group II).

Data Analysis

Data concerning the overall effects of glycopyrronium, ipratropium, and salbutamol on respiratory system mechanics and hemodynamic parameters was inputted in a Microsoft Excel sheet. The confidentiality of each study participant was ensured during the study. We utilized the Statistical Package for Social Sciences for Windows version 21.0 (SPSS Inc., Chicago, IL, USA) to analyze the collected data. The study results were presented with a descriptive summary using percentages, graphs, mean, and standard deviation. Probability (p) was calculated to test statistical significance at the 5% significance level. The Chi-square test was used to compare categorical variables, whereas the independent *t*-test was utilized for comparing continuous variables between the two groups. The results are presented as mean ± standard deviation. Two means are deemed to be statistically significant if the *p*-value is less than 0.05.

Results

Table 1 displays the distribution of study participants in both groups based on their demographic profile. Patients in both groups were comparable in mean age, gender, duration of COPD, proportion of smokers, and comorbidities suffered. Males outnumber females in both groups.

Table 2 compares the nature of sputum and the number of suctions between the two groups on 3 days. On days 2 and 3, a significantly higher number of patients in group II had copious secretions. Group II patients required more frequent endotracheal suction on day 2 than group I.

Table 1: Distribution of study participants in both groups based on their demographic profile

Variables	*Group I (n = 30)*	*Group II (n = 30)*	*p-value*
Age (years)	54.63 ± 6.43	54.87 ± 8.39	0.904
Gender			
Male	23 (76.7%)	22 (73.3%)	0.766
Female	7 (23.36%)	8 (26.7%)	
Duration of COPD (years)			
<5	5 (16.7%)	7 (23.3%)	0.132
6–10	16 (53.3%)	13 (43.3%)	
11–15	6 (20%)	6 (20%)	
>15	3 (10%)	4 (13.3%)	
Smoking (*n* = 37)			
Yes	20 (66.7%)	17 (56.7%)	0.426
Comorbidity (*n* = 38)			
Diabetes	1 (3.3%)	0 (0.0%)	0.445
Hypertension	11 (36.7%)	9 (30.0%)	
Hypothyroidism	1 (3.3%)	1 (3.3%)	
Diabetes and hypothyroidism	1 (3.3%)	1 (3.3%)	
Hypertension and diabetes	7 (23.3%)	6 (20.0%)	

Table 2: Comparison of the nature of sputum and suction number between the two groups

Nature of sputum	*Group I (n = 30)*	*Group II (n = 30)*	*p-value*
Day 1			
Copious	30 (100.0%)	27 (90.0%)	0.076
Non-copious	0 (0.0%)	3 (10.0%)	
Day 2			
Copious	17 (56.7%)	26 (86.7%)	0.01*
Non-copious	13 (43.3%)	4 (13.3%)	
Day 3			
Copious	0 (0.0%)	20 (66.7%)	0.001*
Non-copious	30 (100.0%)	10 (33.3%)	
Number of endotracheal suctions			
Day 1 (*n* = 60)			
1–2	0 (0.0%)	2 (6.7%)	0.337
3–4	19 (63.3%)	18 (60%)	
>4	11 (36.7%)	10 (33.3%)	
Day 2 (*n* = 60)			
1–2	3 (10.0%)	3 (10.0%)	0.001*
3–4	27 (90%)	20 (66.7%)	
>4	0 (0.0%)	7 (23.3%)	
Day 3 (*n* = 60)			
1–2	11 (36.7%)	3 (10.0%)	0.474
3–4	19 (63.3%)	25 (83.3%)	
>4	0 (0.0%)	2 (6.7%)	

*Significant

Table 3: Comparison of heart rate (HR) and mean blood pressure (MBP) at various follow-ups between the two groups

	HR (beats/min)			*MBP (mm Hg)*		
Variables	*Group I (n = 30)*	*Group II (n = 30)*	*p-value*	*Group I (n = 30)*	*Group II (n = 30)*	*p-value*
Baseline	82.83 ± 10.40	82.90 ± 12.45	0.982	28.97 ± 6.48	30.43 ± 9.05	0.474
Mean of three days						
15 minutes	81.97 ± 8.86	80.33 ± 10.26	0.512	31.20 ± 6.58	33.61 ± 8.58	0.227
30 minutes	81.60 ± 7.65	80.77 ± 9.48	0.709	33.93 ± 6.88	37.37 ± 9.41	0.112
60 minutes	80.53 ± 9.48	80.77 ± 7.93	0.917	36.74 ± 7.18	39.93 ± 0.44	0.147
2 hours	81.17 ± 8.32	80.47 ± 9.18	0.758	39.86 ± 7.02	41.68 ± 9.98	0.419
3 hours	83.17 ± 9.45	80.83 ± 9.42	0.342	42.53 ± 6.92	41.68 ± 10.24	0.707
4 hours	81.33 ± 8.30	81.07 ± 9.70	0.909	42.13 ± 6.39	40.18 ± 10.41	0.385
6 hours	81.80 ± 9.09	82.70 ± 10.10	0.718	39.96 ± 5.99	36.98 ± 9.71	0.157
8 hours	81.30 ± 8.74	82.47 ± 8.75	0.608	37.16 ± 5.97	33.72 ± 9.03	0.086
10 hours	82.07 ± 8.49	82.47 ± 10.61	0.873	35.51 ± 5.97	32.43 ± 8.00	0.097
12 hours	80.50 ± 7.37	82.63 ± 10.42	0.364	33.80 ± 5.80	31.38 ± 7.58	0.172

Table 4: Comparison of mean static compliance (C_{STAT}) and mean airway pressure (MAP) between the two groups

	C_{STAT} (mL/cm H_2O)			*MAP (cm H_2O)*		
Variables	*Group I (n = 30)*	*Group II (n = 30)*	*p-value*	*Group I (n = 30)*	*Group II (n = 30)*	*p-value*
Baseline	28.97 ± 6.48	30.43 ± 9.05	0.474	18.17 ± 4.26	16.58 ± 3.21	0.108
Mean of 3 days						
15 minutes	31.20 ± 6.58	33.61 ± 8.58	0.227	17.30 ± 4.34	14.75 ± 2.93	0.010*
30 minutes	33.93 ± 6.88	37.37 ± 9.41	0.112	16.83 ± 4.33	13.84 ± 2.87	0.003*
60 minutes	36.74 ± 7.18	39.93 ± 9.44	0.147	16.20 ± 4.36	13.19 ± 2.68	0.002*
2 hours	39.86 ± 7.02	41.68 ± 9.98	0.419	15.74 ± 5.01	13.23 ± 2.51	0.007*
3 hours	42.53 ± 6.92	41.68 ± 10.24	0.707	15.82 ± 4.17	13.30 ± 2.29	0.005*
4 hours	42.13 ± 6.39	40.18 ± 10.41	0.385	15.60 ± 4.13	13.63 ± 2.56	0.030
6 hours	39.96 ± 5.99	36.98 ± 9.71	0.157	15.54 ± 4.19	14.48 ± 2.34	0.229
8 hours	37.16 ± 5.97	33.72 ± 9.03	0.086	15.61 ± 4.07	15.32 ± 2.56	0.742
10 hours	33.51 ± 5.97	32.43 ± 8.00	0.097	15.93 ± 4.12	15.81 ± 2.57	0.887
12 hours	33.80 ± 5.80	31.38 ± 7.58	0.172	16.33 ± 4.19	15.99 ± 2.81	0.708

*Significant

Table 3 compares the means of HR and mean arterial pressure (MAP) for 3 days at various follow-ups between the two groups. The HR and MAP were comparable in both groups at all time intervals studied.

Table 4 compares mean static compliance (C_{STAT}) and mean airway pressure between the two groups. The mean C_{STAT} was comparable at all time intervals, whereas the mean airway pressure was significantly lower in group II from 15 minutes to 3 hours post-nebulization.

Table 5 compares the mean of maximum inspiratory resistance (R_{RS}) and minimum inspiratory resistance (R_{INT}) between the study groups. The R_{RS} was significantly different between the two groups at 6, 8, 10, and 12 hours after nebulization, and R_{INT} at 6, 8, and 10 hours after nebulization.

Table 6 shows the comparison of the onset and duration of bronchodilation between the two groups. Per our study protocol, the duration of bronchodilation resulting from nebulizing glycopyrronium or salbutamol-ipratropium was the period when R_{INT} stayed below 85% of its baseline value. We found that in group I, the onset of bronchodilation was 30 minutes on day 1 and day 3 and 60 minutes on day 2, whereas, in group II, the onset of bronchodilation was 60 minutes on day 1 and 2 and 30 minutes on day 3. In group I, bronchodilation was 10 hours on day 1 and 12 hours each on day 2 and day 3, whereas in group II, bronchodilation was 4 hours on day 1 and 6 hours each on day 2 and day 3.

Figures 2 and 3 show the comparison of the mean of differences of R_{INT} from baseline at various follow-ups in groups I and II, respectively. In group I, the differences from the baseline were highest at the third hour; all the differences were higher from that at 15 minutes and remained so till 12 hours. In group II, the difference from the baseline was highest at the second hour, but after 6 hours, the difference from the baseline was lower than that at 15 minutes.

Discussion

Patients of group II had a higher incidence of copious sputum on day 2 and 3 of the study. As a result, more patients in group II needed more than four endotracheal suctions on day 2 and day 3 (Table 2). The present study is the first to demonstrate that glycopyrronium nebulization reduced mucus production and obviates the need

Table 5: Comparison of maximum inspiratory resistance (R_{RS}) and minimum inspiratory resistance (R_{INT}) between the two groups

	R_{RS} (cm H_2O/L/sec)			*R_{INT} (cm H_2O/L/sec)*		
Variables	*Group I (n = 30)*	*Group II (n = 30)*	*p-value*	*Group I (n = 30)*	*Group II (n = 30)*	*p-value*
Baseline	24.73 ± 4.63	25.90 ± 5.71	0.354	22.68 ± 4.64	23.12 ± 5.89	0.746
Mean of 3 days						
15 minutes	23.37 ± 4.32	23.30 ± 5.75	0.960	21.22 ± 4.39	20.85 ± 5.64	0.780
30 minutes	21.67 ± 4.43	21.76 ± 5.75	0.942	19.69 ± 4.43	18.98 ± 5.60	0.587
60 minutes	20.44 ± 4.41	20.88 ± 5.64	0.740	18.42 ± 4.36	18.20 ± 5.36	0.860
2 hours	19.34 ± 4.04	20.28 ± 5.64	0.460	17.57 ± 4.00	17.65 ± 5.45	0.949
3 hours	19.12 ± 3.99	20.64 ± 5.70	0.237	17.01 ± 3.99	18.05 ± 5.45	0.403
4 hours	19.27 ± 3.68	21.04 ± 5.20	0.134	17.13 ± 3.75	18.68 ± 5.06	0.182
6 hours	19.62 ± 3.96	22.72 ± 5.87	0.020*	17.51 ± 3.96	20.05 ± 5.52	0.045*
8 hours	20.31 ± 4.25	24.28 ± 6.16	0.005*	18.07 ± 4.07	21.36 ± 6.21	0.018*
10 hours	20.94 ± 4.56	25.26 ± 5.83	0.002*	18.85 ± 4.54	22.31 ± 5.93	0.014*
12 hours	21.62 ± 4.96	25.55 ± 5.41	0.005*	19.63 ± 4.87	22.81 ± 5.80	0.25

*Significant

Table 6: Comparison of onset and duration of bronchodilation (when minimum inspiratory resistance, R_{INT}) was less than 85% from baseline between the two groups

	Group I (GP) (n = 30)		*Group II (SI) (n = 30)*	
Follow-up	*Onset*	*Duration (R_{INT} value is 85% of baseline)*	*Onset*	*Duration (R_{INT} value is 85% of baseline)*
Day 1	30 minutes	10 hours	60 minutes	4 hours
Day 2	60 minutes	12 hours	60 minutes	6 hours
Day 3	30 minutes	12 hours	30 minutes	6 hours

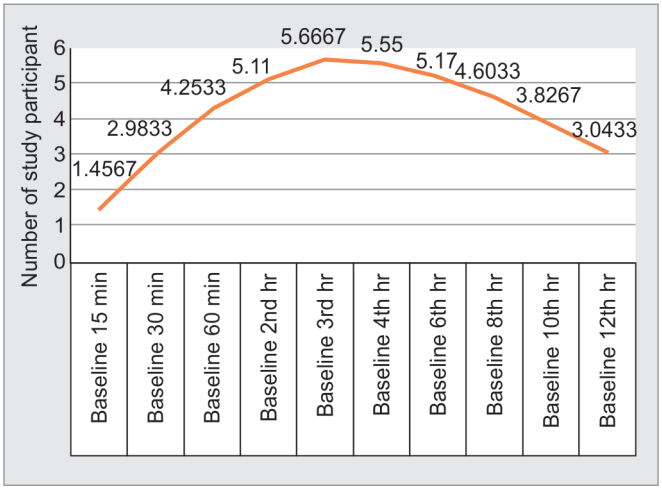

Fig. 2: Comparison of the mean of differences of R_{INT} from baseline at various follow-ups in group I

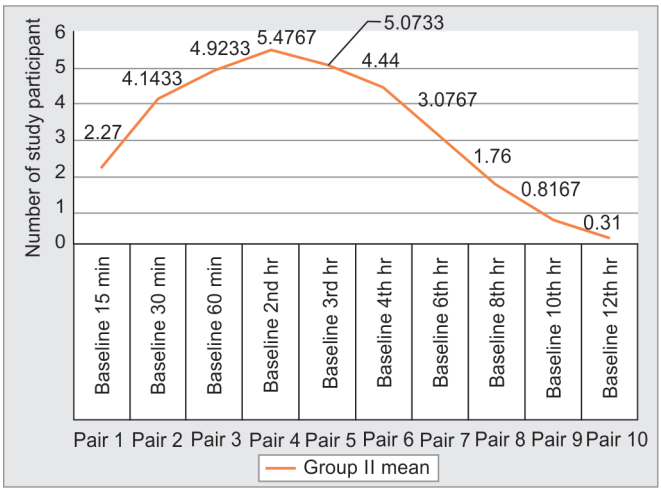

Fig. 3: Comparison of the mean of differences of R_{INT} from baseline at various follow-ups in group II

for multiple sections of the respiratory tract. This effect may be because of the blocking of muscarinic M_3 receptors responsible for mucus secretion.[13]

No patient in either group had any hypertensive response or tachycardia. Both the groups exhibited comparable mean BP and HR (Table 3). In a study involving patients suffering from COPD fulfilling grade II or III of GOLD criteria (moderate or severe), with the patients receiving nebulized glycopyrronium, the authors did not observe any significant variations in HR, BP (systolic or diastolic), or ECG parameters, like QTc, when administered in doses ranging from 12.5 to 400 µg.[13]

The C_{STAT} was comparable between the two groups at all times during the study. In group I, the C_{STAT} was higher than the baseline at all time points, and the highest was between 2 and 8 hours (Table 4). Similar results were obtained in patients of group II, but that was with three doses of nebulization. The mean airway pressure was lower than the baseline at all time points in group I patients. The airway pressures were comparable in both groups, but were significantly reduced in group II compared with group I, from 15 minutes to three hours. We did not come across any study that compared glycopyrronium and a combination of salbutamol and ipratropium nebulization in patients of COPD who were being mechanically ventilated because of respiratory failure, nor were any trials comparing the two preparations in non-ventilated patients of COPD. Most studies involving aerosolized agents in patients with COPD were done in ambulatory patients. Among studies that examined nebulized glycopyrronium individually was the one by

Leaker et al., who showed that when patients were nebulized with glycopyrronium at doses of 100 and 200 µg, there were clinically meaningful improvements of more than 100 mL in forced expiratory volume in one second (FEV1), which stayed so for 24 hours after the nebulization.[13]

We measured the airway resistance (maximum inspiratory resistance or R_{RS} and the minimum airway resistance or R_{INT}) at different time points for 12 hours for 3 days. Table 5 showed that the mean R_{RS} was lower than the baseline at all time points in both the groups, but during the later hours, i.e., 6–12 hours, group I patients had significantly reduced mean R_{RS} compared with that of group II. Similarly, R_{INT} was lower than the baseline at all time points in both the groups, but during the later hours, i.e., 6–10 hours, group I patients showed significantly decreased R_{INT} contrasted to group II. This suggests that glycopyrronium continued to exert its action even 6–10 hours after the drug was administered by nebulization in the mechanically ventilated patients of COPD when the effect of nebulized salbutamol and ipratropium started to wane. We did not find any study that measured the R_{RS} and R_{INT} after administering nebulized LAMA, like glycopyrronium.

Acetylcholine (Ach) promotes bronchoconstriction primarily by stimulating M_3 muscarinic receptors on the smooth muscle cells of the airways. M_1 receptors stimulate cholinergic reflexes. On the contrary, M_2 receptors, on the cholinergic nerve endings, when stimulated, impede Ach release. Glycopyrronium can selectively block the M_1 and M_3 receptors through competitive muscarinic receptor antagonism, unlike non-selective agents like atropine and ipratropium.[13] Moreover, glycopyrronium detaches very slowly from the M_1 and M_3 receptors, which explains its long duration of action of about 24 hours.[13,14] Further, glycopyrronium is also more potent than other antimuscarinic agents like ipratropium, as the concentration of glycopyrronium that is needed to inhibit the contractility of bronchial smooth muscles is half that of ipratropium.[14]

Per our study protocol, the duration of bronchodilation resulting from nebulizing glycopyrronium or salbutamol-ipratropium was when R_{INT} values continued to be less than 85% of its value before start of nebulization. We found that in group I, the onset of bronchodilation was 30–60 minutes and lasted till 10–12 hours, whereas, for group II, the onset of bronchodilation was 30–60 minutes, lasting till 4–6 hours (Table 6 and Fig. 2). Also, the effect of glycopyrronium nebulization continued for at least 12 hours (the endpoint of the study period), as the R_{RS} and R_{INT} continued to be lower than the baseline value and were significantly lower than the patients of group II. Santus et al. compared two LAMAs, aclidinium (400 µg) and glycopyrronium (50 µg), in terms of alterations in residual volume (RV) and intra-thoracic gas volume (ITGV) in patients of severe or very severe COPD. They observed that aclidinium showed increase in RV within 5 minutes whereas it took 60 minutes with glycopyrronium for any rise.[14] In contrast, Tashkin and Gross reported that inhaled glycopyrronium, based on various trials, starts acting in 5 minutes. However, they cautioned that this might not be true for patients who are on long-term treatment with glycopyrronium.[15]

The Food and Drug Administration advised glycopyrronium nebulization as a single treatment and as a component of a fixed drug combination for COPD to be administered twice-a-day. European Medicines Agency approved glycopyrronium for nebulization as a once-a-day regime for treating patients with COPD.[14] Leaker et al. also reported that the effect of nebulized glycopyrronium lasts for at least 24 hours, as was evidenced by the clinically significant improvement in FEV1.[13] In the present study, patients of group I received glycopyrronium nebulization twice daily, as it has not been unanimously proven that its action lasts for 24 hours. Moreover, unlike our study population, the recommendations and previous trials were on non-ventilated ambulatory patients. Further, it was reported that the duration of bronchodilation caused by glycopyrronium nebulization was shorter in mechanically ventilated patients than in non-ventilated patients of COPD.[16]

Limitations of the Study

The present study has the following limitations:

- The endpoint of the study was 12 hours each day.
- We did not study the alterations in the arterial oxygen and carbon dioxide partial pressure or spirometry parameters that would reflect changes in airway resistance, like plateau pressure (Pplat), intrinsic PEEP (iPEEP), and trapped gas volume above passive FRC at the end of expiration (Vtrap), and outcome parameters like survival, duration of ICU and hospital stay.

Conclusion

The study results show that 25 µg of nebulized glycopyrronium to mechanically ventilated COPD patients with respiratory failure has several advantages over the two-drug combination of salbutamol and ipratropium, like lesser respiratory secretions, fewer tracheal suctions, and a longer duration of action in terms of lowered airway resistance. It was not associated with any adverse effects like hypertension, tachycardia, or desiccation of respiratory secretions. Monotherapy minimizes the risk of polypharmacy and drug interactions, particularly in the critically ill.

The onset of action of glycopyrronium nebulization, recorded in our study and measured by bronchodilation, was longer than what was recorded in previous studies. Moreover, the duration of action of glycopyrronium was also recorded to be shorter than in previous studies, partly because our study protocol limited the collection of data to 12 hours and partly because in mechanically ventilated patients, the effects last shorter, as reported in previous studies. This needs to be explored in future more extensive studies.

Author Contributions

Dr Preeti Priya: Data collection, tabulation, and analysis; Dr Soumya S Nath: Conceptualization, design of the study, and writing the draft; Dr Virendra Kumar: Writing the draft and final approval; Dr Suraj Kumar: Data acquisition, reading the draft, and final approval of the draft.

Ethical Approval

The study protocol was approved by the institute ethical committee (IEC 132/22 dated 24/09/22) and registered in the clinical trials registry of India (CTRI/2022/11/047216 dated 11/11/22).

Orcid

Preeti Priya https://orcid.org/0009-0005-6197-7661
Soumya S Nath https://orcid.org/0000-0002-5981-5437
Virendra Kumar https://orcid.org/0000-0002-3359-1738
Suraj Kumar https://orcid.org/0000-0002-6303-1600

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