Evaluation of Bronchodilator Use During Chronic Obstructive Pulmonary Disease Exacerbation Inpatient Admissions

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Abstract

Background: It is unknown whether the timing of initiation of a long-acting bronchodilator (LABD) during a chronic obstructive pulmonary disease (COPD) exacerbation or the method of short-acting bronchodilator (SABD) delivery may aid in improving patient outcomes. **Objective:** The goal of this study was to determine the impact of bronchodilator management in the hospital setting on clinical outcomes in patients with COPD exacerbation. **Methods:** This retrospective, single-center study evaluated patients admitted to the non-intensive care unit setting with a COPD exacerbation as defined by the *International Classification of Diseases, Ninth Revision* codes. The primary outcome was difference in 30-day readmission rates for early LABD therapy (≤ 24 hours from hospital admission) versus late/no LABD therapy (> 24 hours from hospital admission or not during hospitalization). Secondary objectives included length of stay (LOS) for this group, and 30-day readmission rates and LOS for the SABD via inhaler versus nebulizer groups. **Results:** Two hundred twenty patients were included. There was no difference in 30-day readmission rate (15.2% vs 18.2%, $P = .6$) and LOS (median 4 [interquartile range, IQR 3–6] days for both groups, $P = .34$) between early versus late/no LABD therapy initiation, respectively. No difference was observed in 30-day readmission rate (16.7% vs 16.6%) and LOS (median 2.5 [IQR 1.1–3.9] days vs median 4 [IQR 2–6] days) between inhaler and nebulizer SABD therapy groups. **Conclusions:** No difference was observed in 30-day readmission rates or LOS when utilizing early LABD compared with late/no LABD therapy or comparing inhaler and nebulizer SABD delivery methods during COPD exacerbation.

Keywords

respiratory, disease management, outcomes research

Introduction

Chronic obstructive pulmonary disease (COPD) is a significant health care burden.¹ It is the third-leading cause of death in the United States and previously projected to cost 30 billion dollars in direct health care expenditures annually. A significant contributor to the high cost of COPD is hospital expenditures related to exacerbations. Several interventions can reduce exacerbation risk, including bronchodilator therapy.² The efficacy of maintenance bronchodilator therapy for improvement in morbidity is well established; however, the optimal role of long-acting bronchodilators (LABD) in exacerbation management is not well characterized.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines do not provide a strong recommendation on the optimal bronchodilator regimen for COPD exacerbation management.² Current guidelines recommend administration of short-acting β_2 -agonists (SABA), with or without short-acting muscarinic antagonists (SAMA) around the clock. However, there are no recommendations regarding the preferred method of short-acting bronchodilator (SABD)

delivery as there are limited data comparing nebulizers with inhalers during exacerbation. Use of either delivery method is considered to have similar outcomes, provided appropriate technique is utilized.³ A previous meta-analysis found no difference in pulmonary function tests during an acute episode when comparing the 2 delivery methods.⁴ This meta-analysis was conducted prior to the market introduction of LABD therapy.

The current GOLD guidelines recommend to continue LABDs during an exacerbation or to initiate them as soon as possible.² However, there is a paucity of data on the role of long-acting agents in hospitalized patients during an exacerbation. A previous study found improved 30-day readmission rates for patients prescribed a long-acting β_2 -agonist

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(LABA) compared with a SABA during hospitalization for COPD exacerbation management.⁵ Other studies have evaluated the impact of LABD addition during hospitalization, but the optimal timing of initiation has not been evaluated.⁶⁻⁹ Investigating the optimal time to initiate LABD during COPD exacerbation and the preferred SABD delivery method may aid in improving patient outcomes and minimizing health care expenditures. The goal of this study was to determine the impact of bronchodilator management in the hospital setting on clinical outcomes in patients with COPD exacerbation.

Methods

This was a noninterventive, retrospective, single-center study that included patients admitted to an internal medicine service at a 320-bed academic medical center between January 2014 and December 2015 with COPD exacerbation. The institutional review board approved this study. Patients with COPD exacerbation were identified from *International Classification of Diseases, Ninth Revision (ICD-9)* codes. Patients less than 18 years of age or who were initially admitted to the intensive care unit (ICU), due to possible inability to administer LABD therapy, were excluded. In an effort to evaluate a solely COPD population and minimize confounders, patients with a documented history of asthma or asthma exacerbation were also excluded.

The identified patient population was analyzed in 2 different cohorts: (1) patients were categorized into 2 groups based on timing of LABD prescribing (LABD cohort) and (2) patients were categorized according to receipt of inhaler or nebulizer predominant SABD therapy (SABD cohort). For the LABD cohort, early LABD was defined as therapies prescribed within 24 hours of hospital admission. Patients prescribed LABD therapy greater than 24 hours after hospital admission or who did not receive LABD therapy during hospitalization were classified as late/no LABD. In the SABD therapy cohort, predominant therapy was defined as administration, verified with our institution's medication administration record, of greater than 50% of SABD doses via one delivery method (inhaler or nebulizer) during the hospitalization.

The primary study objective was to determine whether any difference existed in 30-day readmission rates for patients in the early versus late/no LABD groups. Secondary objectives included determining whether any difference existed in (1) hospital length of stay (LOS) for the LABD cohort, (2) 30-day readmission rates for the SABD cohort, and (3) hospital LOS for the SABD cohort.

Data collected from each patient's electronic medical record included demographic data, in-hospital and home COPD medications prescribed, hospital LOS, rates of ICU transfers and daily vital signs (heart rate [HR], systolic blood pressure [SBP]) to assess for clinical stability.

Collected data also included a pulmonary function test performed any time prior to or during hospitalization, if available, for each patient, to confirm COPD diagnosis.²

Immunization status was determined by documented receipt of the vaccination according to the Centers for Disease Control and Prevention guidelines.¹⁰ Prespecified baseline characteristics were collected to determine overall health status. Specifically, home oxygen therapy was chosen as the primary marker of disease severity in this COPD patient population. *ICD-9* codes established hypertension and diabetes diagnoses. These 2 diagnoses were recorded at baseline to account for potential confounding factors for increased hospital LOS from systemic corticosteroid administration. ICU admission was at the discretion of the attending physician. The dose, duration, and choice of systemic corticosteroids and antibiotic therapy were also at the discretion of the attending physician.

Statistical Analysis

Nominal data were analyzed using either chi-squared or Fisher exact test and continuous data were evaluated using the Mann-Whitney *U* test. The Mann-Whitney *U* test was chosen for continuous data because the results of the Shapiro-Wilk test indicated the continuous data were not normally distributed. A multivariable logistic regression was performed to assess for factors associated with 30-day readmission. Variables were chosen based on biological plausibility for effect on the outcome or statistical significance ($P < .05$) on univariable analysis. Statistical significance was chosen for inclusion in the multivariable analysis to minimize the risk of collinearity between variables. Due to the exploratory nature of this study, determining an appropriate baseline 30-day readmission rate to calculate the needed sample size was challenging. The national average 30-day all-cause COPD readmission rate of 19% was utilized to determine needed sample size. A difference of 10% between the 2 treatment groups with 80% power and 5% alpha would require 203 patients in each group.¹¹ All statistical analyses were performed using IBM SPSS Statistics Version 23 (Armonk, New York). All tests of significance were 2-tailed with $P < .05$ considered statistically significant.

Results

During the 2-year period, 347 patient encounters were identified. One hundred twenty-seven patients were excluded: 74 for initial ICU admission, 49 for admission to non-internal medicine services at our institution and 4 for documentation of asthma. A total of 220 patients were eligible for study inclusion. As stated previously, this patient population was analyzed in 2 different cohorts, LABD and SABD.

LABD Cohort

There were 165 and 55 patient encounters included in the early LABD group and late/no LABD group, respectively. Baseline characteristics were similar between groups, with a

Table 1. Baseline Characteristics for LABD Cohort.

Characteristic	Early LABD (n = 165)	Late LABD (n = 55)	P value
Age (years)	65.1 (58.7-74.2)	70.1 (64.7-82)	.008
Gender (female)	100 (60.6%)	31 (56.4%)	.58
Pulmonary function test	39 (23.7%)	6 (10.9%)	.04
Influenza vaccination	36 (21.8%)	9 (16.4%)	.39
23-valent pneumococcal vaccination	63 (38.2%)	17 (30.9%)	.33
Hypertension	124 (75.2%)	40 (72.7%)	.72
Diabetes	51 (30.9%)	14 (25.5%)	.44
Admission oxygen saturation (%)	96 (94-98)	96 (93.5-99)	1
Home oxygen therapy	70 (42.4%)	10 (18.2%)	.001
Day 1 heart rate	101 (89-113)	100 (87-113)	.26
Day 1 systolic blood pressure	152 (135-169)	148 (131-165)	.85
Home medications			
SABD	160 (97%)	54 (98.1%)	1
SABA	159 (96.4%)	53 (96.4%)	1
Albuterol	156 (94.5%)	52 (94.5%)	
Scheduled	26 (15.8%)	26 (47.3%)	
As needed	130 (78.8%)	26 (47.3%)	
Levalbuterol	3 (1.8%)	1 (1.8%)	
Scheduled	0	0	
As needed	3 (1.8%)	1 (1.8%)	
SAMA	138 (83.6%)	51 (92.7%)	.093
Ipratropium	138 (83.6%)	51 (92.7%)	
Scheduled	107 (64.8%)	46 (83.6%)	
As needed	31 (18.8%)	5 (9.1%)	
LABD	165 (100%)	11 (20%)	<.001
LABA	141 (85.5%)	11 (20%)	<.001
Salmeterol	67 (40.6%)	7 (12.7%)	
21 µg twice daily	4 (2.4%)	0	
42 µg twice daily	7 (4.2%)	2 (3.6%)	
50 µg twice daily	40 (24.2%)	5 (9.1%)	
100 µg twice daily	16 (9.7%)	0	
Formoterol	73 (44.2%)	4 (7.3%)	
4.5 µg twice daily	7 (4.2%)	0	
5 µg twice daily	5 (3%)	0	
9 µg twice daily	59 (35.8%)	4 (7.3%)	
12 µg twice daily	2 (1.2%)	0	
Arformoterol 15 µg twice daily	2 (1.2%)	0	
LAMA	100 (60.1%)	8 (14.5%)	<.001
Tiotropium 18 µg daily	99 (60%)	8 (14.5%)	
Aclidinium 400 µg twice daily	1 (0.6%)	0	
ICS	138 (83.6%)	11 (20%)	<.001
Fluticasone	69 (41.8%)	7 (12.7%)	
88 µg twice daily	1 (0.6%)	0	
100 µg twice daily	1 (0.6%)	1 (1.8%)	
115 µg twice daily	3 (1.8%)	0	
230 µg twice daily	3 (1.8%)	3 (5.5%)	
250 µg twice daily	27 (16.4%)	3 (5.5%)	
460 µg twice daily	6 (3.6%)	0	
500 µg twice daily	28 (17%)	1 (1.8%)	
Budesonide	65 (39.4%)	4 (7.3%)	
80 µg twice daily	2 (1.2%)	0	
160 µg twice daily	18 (10.9%)	1 (1.8%)	
320 µg twice daily	45 (27.3%)	3 (5.5%)	
Mometasone	6 (3.6%)	0	
100 µg twice daily	5 (3%)	0	
200 µg twice daily	1 (0.6%)	0	
220 µg twice daily	1 (0.6%)	0	

Note. Results are presented as n (%) or median (interquartile range). LABD = long-acting bronchodilator; SABD = short-acting bronchodilator; SABA = short-acting beta₂-agonist; SAMA = short-acting muscarinic antagonist; LABA = long-acting beta₂-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

few notable exceptions (Table 1). Patients in the early LABD group were significantly younger than patients in the late/no LABD treatment group (65.1 [58.7-74.2] vs 70.1 [64.7-82] years; $P = .008$). Pulmonary function tests confirming COPD diagnosis were previously obtained in a higher number of patients in the early LABD group than the late/no LABD group (23.7% vs 10.9%; $P = .04$). In addition, the requirement of home oxygen therapy was significantly higher in patients prescribed early LABD therapy (42.4% vs 18.2%; $P = .001$). Home SABD use was similar between patient groups; however, more patients in the early LABD cohort received LABA, long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS) therapy prior to admission.

The primary outcome of 30-day readmission rates occurred at a similar frequency between the early LABD (15.2%) and late/no LABD (18.2%) groups ($P = .6$). The rate of COPD-related readmissions was similar between groups (7.3% vs 7.3%; $P = 1$). Hospital LOS was similar between the 2 treatment groups (4 [3-6] days in both) ($P = .34$). ICU admission was required for 2 (1.2%) patients in the early LABD group and no patients in the late/no LABD group ($P = 1$).

Nearly all patients in the study were prescribed inpatient SABD therapy (Table 2). For the 2 LABD groups, there were no significant differences in prescribing of SABD in general or in around the clock SABD in the first 24 hours of admission specifically. The total number of SABD doses required during hospitalization was similar between LABD groups. The most common LABD prescribed while inpatient was LABA therapy. LAMA therapy was utilized less frequently than LABA or ICS therapy. All included patients were prescribed systemic corticosteroids.

At baseline, vital parameters (HR and SBP) were similar. HR was significantly higher for patients in the late/no LABD group (89 [79-98.8] vs 95 [82.5-104.5]; $P = .02$) at day 3. Day 3 SBP was similar in both treatment groups (141 [127-150] vs 143 [131.5-156]; $P = .86$). Requirement of oxygen at discharge was higher in the early LABD patient group (47.3% vs 27.3%; $P = .009$). Due to potential confounders and underlying baseline differences between treatment groups, a multivariable logistic regression for 30-day readmission rates was performed to assess for factors significantly associated with the outcome (Table 3). This analysis included record of pulmonary function test, age, home LABD therapy and home oxygen therapy prior to admission. No factors included in the model were significantly associated with 30-day readmission rates.

SABD Cohort

Of the 220 patients eligible for study inclusion, 214 patients were prescribed SABD. Three patients did not receive any doses while in the hospital and were excluded from this analysis. Therefore, 211 patients were included in the SABD cohort analysis. The majority of patients received nebulizer predominant therapy ($n = 199$). Baseline characteristics were similar between

groups (Table 4). The total number of bronchodilator doses received was similar between patients prescribed inhalers (12 [8.5-20.5]) versus patients prescribed nebulizers (15 [8-24]).

Thirty day readmission rates were similar between the inhaler and nebulizer groups (16.7% vs 16.6%, respectively). Hospital LOS was numerically shorter in patients prescribed inhalers (2.5 days [1.1-3.9] vs 4 days [2-6]).

Discussion

At the time of manuscript submission, no studies were identified evaluating the use and timing of LABD in COPD exacerbation management in a non-ICU patient population. We found no differences in the 30-day readmission rates between patients with early LABD initiation and patients with late/no LABD initiation.

The majority of included patients were prescribed their home LABD upon hospital admission. At baseline, the early LABD group had a higher percentage of patients with confirmed COPD via pulmonary function tests. In addition, a higher severity of illness may have been present in this group based on home oxygen requirements. However, all included patients in this study were classified as either GOLD Grade Group C or Group D COPD, given they required hospitalization for a COPD exacerbation, and therefore required chronic LABD therapy.² During the study time period, the available GOLD guidelines recommended using airflow limitation on pulmonary function tests to determine appropriate maintenance COPD therapy, in addition to exacerbation history and presence of symptoms.² In 2017, the GOLD guidelines revised treatment determination to include only exacerbation history and presence of symptoms as these outcomes better predict mortality and hospitalizations.^{2,12,13} This further illustrates the appropriateness of LABD therapy initiation for all hospitalized patients with COPD exacerbation.

Pilot studies demonstrated the efficacy and safety of LABD during COPD exacerbation.⁷ The introduction of tiotropium into a respiratory therapy protocol at a single center decreased overall hospital LOS by 1 day and reduced health care costs.⁶ However, timing of tiotropium initiation was not assessed in this study. Similar cost findings were observed in a mixed cohort of asthma and COPD patients with the introduction of formoterol at a single center.⁸ The largest study evaluating LABD in COPD exacerbation was a retrospective cohort study in 421 hospitals that found no difference in clinical outcomes between patients prescribed LABD and patients who were not.⁹ The concomitant use of LABD and SABD in COPD exacerbation may not be necessary, and standardization of bronchodilator use at an institution can result in cost savings.¹⁴ In addition, continuation of a home LABD therapy improves overall continuity of care and allows for reinforcement of inhaler technique during hospital admission. Following hospital discharge, receipt of inhaler therapy is associated with variable outcomes. Blee and colleagues evaluated providing patients the remainder of their

Table 2. COPD Inhaled Medications Prescribed During Hospitalization in LABD Cohort.

Outcomes	Early LABD (n = 165)	Late LABD (n = 55)	P value
SABD	160 (97%)	54 (98.1%)	1
SABA (albuterol)	159 (96.4%)	53 (96.4%)	1
Scheduled	149 (90.3%)	52 (94.5%)	
As needed	10 (6.1%)	1 (1.8%)	
SAMA (ipratropium)	138 (83.6%)	51 (92.7%)	.093
Scheduled	137 (83%)	45 (81.8%)	
As needed	1 (0.6%)	6 (10.9%)	
Around the clock SABD in first 24 hours	100 (60.6%)	35 (63.6%)	.69
SABD doses received	15.5 (9-24)	19 (10-29.5)	.13
LABD	165 (100%)	11 (20%)	<.001
LABA	156 (94.5%)	7 (12.7%)	<.001
Salmeterol 42 µg twice daily	37 (22.4%)	1 (1.8%)	
Formoterol	119 (72.1%)	6 (10.9%)	
4.5 µg twice daily	4 (2.4%)	0	
9 µg twice daily	115 (70%)	6 (10.9%)	
LAMA	72 (43.6%)	6 (10.9%)	<.001
Tiotropium 18 µg once daily	72 (43.6%)	6 (10.9%)	
ICS	156 (94.5%)	7 (12.7%)	<.001
Fluticasone	36 (21.8%)	5 (5.5%)	
110 µg twice daily	0	1 (1.8%)	
220 µg twice daily	0	3 (5.5%)	
230 µg twice daily	18 (10.9%)	0	
460 µg twice daily	18 (10.9%)	1 (1.8%)	
Budesonide	120 (72.7%)	6 (10.9%)	
160 µg twice daily	21 (12.7%)	1 (1.8%)	
320 µg twice daily	99 (60%)	5 (9.1%)	

Note. Results are presented as n (%). COPD = chronic obstructive pulmonary disease; LABD = long-acting bronchodilator; SABD = short-acting bronchodilator; SABA = short-acting beta₂-agonist; SAMA = short-acting muscarinic antagonist; LABA = long-acting beta₂-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

Table 3. Multivariable Logistic Regression.

Outcome	Odds ratio	95% confidence interval	P value
Pulmonary function test	0.46	0.2-1.06	.07
Age	1.01	0.98-1.04	.53
Home LABD	1.27	0.52-3.07	.6
Home oxygen	0.84	0.38-1.83	.66

Note. LABD = long-acting bronchodilator

Table 4. Baseline Characteristics for SABD Cohort.

Characteristic	Inhaler (n = 12)	Nebulizer (n = 199)
Age (years)	62.3 (54.7-67.7)	67.1 (59.5-78.1)
Gender (male)	4 (33.3%)	81 (40.7%)
Pulmonary function test	3 (25%)	42 (21.1%)
Influenza vaccination	1 (8.3%)	42 (21.1%)
23-valent pneumococcal vaccination	2 (16.7%)	73 (36.7%)
Hypertension	6 (50%)	150 (75.4%)
Diabetes	2 (16.7%)	60 (30.2%)
Home oxygen therapy	3 (25%)	74 (37.2%)

Note. Results are presented as n (%) or median (interquartile range). SABD = short-acting bronchodilator.

multidose inhaler at hospital discharge and demonstrated a reduction in 30-day readmission rates compared with a historical cohort.¹⁵ Conversely, Bishwakarma and colleagues evaluated Medicare prescription records for LABD with or without ICS users compared with nonusers and found no difference in 30-day readmissions.¹⁶ Further investigation is needed to determine the appropriate method to ensure COPD medication adherence to prevent hospital readmissions.

A COPD inhaler discharge counseling program was not in place during the study period; however, health care providers may have observed patients use prescribed inhalers and demonstrate appropriate technique. Counseling on appropriate inhaler technique has previously led to improved patient outcomes in a small study.¹⁷ Overall safety outcomes in the current study were similar between the 2 groups, with the exception of a higher HR at day 3 for patients in the late/no LABD group. Based on the available research, it may be reasonable to continue or initiate LABD therapy at hospital admission and provide SABD only as needed, rather than a scheduled basis.

The predominant SABD delivery method in this patient population was nebulizer (94%). Patients prescribed inhaler predominant therapy were numerically younger than patients prescribed nebulizer predominant therapy. However, no significant differences were observed between treatment groups at baseline. Hospital LOS was numerically shorter in the patients receiving inhaler predominant therapy. A previous crossover study comparing these administration methods in 20 patients found no difference in pulmonary function tests between nebulizers and inhalers delivered via a spacer.¹⁸ Historic cost-benefit analyses demonstrate health-system cost savings with inhaler therapy in non-ICU patients.^{19,20} Provider preference and concern for proper inhaler technique is likely the reason for high nebulizer utilization in the current study. Patients in the nebulizer predominant group were numerically older and this may be reflective of age-related concerns with inhaler technique.²¹ Use of spacers at our institution by respiratory therapy is variable and may have contributed to high nebulizer prescribing rates. Further research is needed on the appropriate route of SABD delivery in COPD exacerbation and the role provider preference has in therapy selection.

Limitations in the current study include the timing of LABD initiation chosen for group allocation. There is no guidance regarding the optimal time of LABD initiation during hospitalization for COPD exacerbation. Twenty-four hours was chosen to allow for complete patient assessment by the attending physician following hospital admission. The exact time of initiation for LABD therapy was not recorded. The majority of patients in the late/no LABD group were not initiated on a LABD during hospitalization. Due to the retrospective nature of the study, reasons for lack of LABD prescribing could not be assessed. Also, the timing of symptom onset prior to hospitalization was not available to be assessed, potentially impacting the patient outcomes in our study cohort. Due to limitations of

our electronic medical record, other characteristics that may impact patient outcomes, such as ethnicity and smoking status, were unable to be determined. Medication adherence following hospital discharge was also unable to be assessed. A power analysis was calculated using national data, but the sample size needed was not met in this study population. However, the readmission rate observed in both treatment groups was numerically lower than nationally reported data.

Imbalances were present between groups, notably the requirement of home oxygen therapy and history of obtaining pulmonary function tests. All patients included in the study qualified for LABD therapy based on their exacerbation history, but we were unable to determine exact GOLD categorization due to the retrospective study design. In addition, a multivariable logistic regression was performed to account for imbalances between patient groups, and no included factor was significantly associated with 30-day readmission rates. Overall use of SABD administered via inhaler was low in this study population. Therefore, it is difficult to determine any meaningful differences between the 2 treatment groups.

Conclusion

This study did not detect a difference in 30-day readmission rates when utilizing early LABD compared with late/no LABD therapy in patients with COPD exacerbation admitted to the non-ICU setting. No differences in patient outcomes were observed between SABD delivery methods. Future studies need to be conducted in larger patient populations to determine the appropriate timing of LABD initiation and ensure appropriate inhaler technique. Until further evidence is available, the GOLD guideline recommendations for early initiation of LABD therapy should be followed for hospitalized patients admitted to the non-ICU setting.

Declaration of Conflicting Interests

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