

The Association between Beta-blocker Use and Chronic Obstructive Pulmonary Disease Risk, Severity, and Exacerbation

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Abstract

Background: There is controversy about the role of beta-blockers in the number of acute exacerbations in patients with chronic obstructive pulmonary disease (COPD). **Objectives:** The study aimed to find the role of beta-blockers using in the exacerbation number in patients with COPD in the presence of cardiovascular diseases (CVDs). **Materials and Methods:** In this comparative study, patients who attended the internal medicine department of two general hospitals in Erbil city and diagnosed with COPD with any CVD were included between April and November 2018. **Results:** The beta-blocker-using COPD patients were older compared to nonusing beta-blocker COPD patients (64.67 vs. 59.95 years, respectively) and had more comorbidities of myocardial infarction (28.1%) and heart failure (28.1%) ($P < 0.001$). The study showed no significant difference in acute exacerbations (0.50 vs. 0.47; $P = 0.821$), forced expiratory volume 1 level (62.19 vs. 60.44; $P = 0.544$), between the user and nonuser beta-blockers, respectively. There was no significant difference in the number of acute exacerbations between COPD patients with CVD and without comorbidity in beta-blocker users; 0.45 versus 0.50; $P = 0.820$. While in nonusers of beta-blockers, the COPD patients with CVD had a significantly higher number of exacerbations (1.29) compared to those COPD patients without comorbidity (0.45; $P = 0.020$). The COPD beta-blocker using patients with CVD had significantly less number of exacerbation compared to those COPD nonusing beta-blocker patients with CVD. **Conclusions:** The present study showed that COPD patients who used beta-blockers have a substantially lower number of acute exacerbations in the last year compared to those COPD patients who did not use beta-blockers.

Keywords: Chronic obstructive pulmonary disease, disease exacerbation, morbidity

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease. It has some substantial extrapulmonary impacts that may lead to the severity of patients. The pulmonary component is presented by airflow limitation with a not fully reversible status. The airflow limitation is considered to be progressive and is related to an abnormal inflammatory response of the lung to toxic materials or gases.^[1]

COPD is the third leading cause of mortality in the United States. The cost of most COPD-related morbidity and health care is owing to acute exacerbations.^[1] The current therapies of COPD targeting airflow limitation and pulmonary inflammation lead to a modest reduction in exacerbation risk. Even these therapies are used in combination.^[2] COPD is considered to be a multisystem disease related to some

comorbid illnesses. These comorbidities include diagnosed and subclinical cardiovascular disease (CVD) that could responsible for moderate exacerbations lead to more severe events or hospitalizations.^[3]

There are some studies that have reported that β -blockers may worsen lung function in COPD patients.^[4,5] However, randomized controlled trials do not support these findings.^[6] In addition, many retrospective studies have reported that β -blockers are related to a decrease in overall mortality.^[7-11]

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and a reduction in the number of acute exacerbations,^[11-13] and improved survival.^[14,15] However, one study reported that β -blocker use in patients with severe COPD on home oxygen is related to increased mortality.^[16]

This study aimed to find the role of beta-blockers using the exacerbation number in patients with COPD. Besides, the role of CVDs on exacerbation in COPD patients was examined in this study.

MATERIALS AND METHODS

Study design and sampling

In the current comparative study, the patients who attended the internal medicine department of two general hospitals in Erbil city were screened physically and clinically for eligibility criteria. Furthermore, the patients diagnosed with COPD with any sort of CVDs of both genders who were admitted to the hospital were included in this study. The patients were selected from the general medicine department and pulmonary unit of two public hospitals in Erbil city between April and November 2018.

The patients who were included in this study were patients diagnosed with COPD with any CVD, including heart failure, hypertension, vascular disease, arrhythmia, cardiac myopathy, and congenital heart disease. The patients who were included had no medical history of another respiratory disease such as asthma, bronchiectasis, and pulmonary fibrosis. The patients with a history of asthma, COPD patients younger than 35 years, and the patients with an asthma-COPD combination (ACOS) were excluded from the study. The diagnosis of respiratory diseases other than COPD that leads to the patient being either medically unstable or having a predicted life expectancy < 2 years was excluded from the study. In addition, those patients who used the pacemaker and/or internal cardiovascular/defibrillator were not included in this study.

Diagnosis and measures

Diagnosis of COPD was established based on dividing the postbronchodilator ratio of forced expiratory volume (FEV1) in the first second to the forced vital capacity of < 0.70.^[1] Respiratory morbidity included 6-min walking distance, respiratory disease-related health impairments.

The diagnosis of asthma was made based on the American Thoracic Society/European Respiratory Society and the National Institute for Health and Care Excellence guidelines.^[17,18]

Statistical methods

The descriptive purposes of the study were presented in number and percentage or mean and standard deviation (SD), including the prevalence of patients with cardiovascular comorbidities. The pack-year, exacerbation number, FEV1 level, body mass index (BMI), and blood pressure were presented in mean and SD. The difference in general and COPD-related characteristics, including age, chronic

disease, smoking, exacerbation, FEV1 level, BMI, etc., was examined in independent *t*-test for continuous variables, and Pearson Chi-squared and Fishers' exact tests for categorical characteristics. The comparison of several exacerbations between COPD patients with CVD and without comorbidity in beta-blocker users and nonusers of beta-blockers was examined in an independent *t*-test. Besides, the comparison of the number of exacerbations between COPD patients with CVD who used beta-blockers compared to those COPD patients with CVD did not use beta-blockers was examined in an independent *t*-test. The significant level of difference was determined in a $P < 0.05$. The Statistical Package for Social Sciences version 25 (SPSS, IBM Company, Chicago, IL 60606, USA) was used for statistical calculations.

Ethical considerations

The medical investigation was done after taking the written consent of the patient. The confidentiality of the personal information of the patients was protected throughout the study steps. The agreement of the research ethical committee was taken from the college of nursing at Hawler Medical University in 2018.

RESULTS

The age of the patients diagnosed with COPD was 62.23 (SD: 10.75) ranged between 40 and 81 years old. The patients were males (55.1%) and females (44.9%), married (76.3%), single (2.5%), divorced (6.8%), and widows (14.4%). Most of the patients were uneducated, including illiterate (45.8%) and enabled to read and write only (11.9%). The study revealed that 15.3% had myocardial infarction (MI), 17.8% had heart failure, 7.6% had a stroke, 19.5% had other comorbidities other than COPD, while 39.8% had COPD only. Most of the patients had a job needed manual working (42.94%) and most of them were irregular physically active (83.1%) [Table 1].

The study revealed that most of the patients were smokers, including current smokers (55.1%) and ex-smokers (43.2%). A small percentage of the patients was nonsmoker (1.7%). The patients smoked 52.95 packs per year ranged between 0 and 120 packs. The mean exacerbation number in patients was 0.49 (SD: 0.64). The study found that 48.3% of the COPD patients used beta-blockers. The mean value of the FEV1 level was 61.29 (SD: 15.68). The means of BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were 26.95, 145.58, and 86.03, respectively [Table 2].

The study showed that patients who used beta-blockers for COPD were older (64.67 years) compared to those patients who did not use beta-blockers (59.95 years). The patients who used beta-blockers had more comorbidities of MI (28.1%) and heart failure (28.1%) in contrast to other comorbidities in nonuser beta-blockers ($P < 0.001$). The study did not find the significant difference in the pack-year (52.06 vs. 52.40; $P = 0.903$), exacerbation (0.50 vs. 0.47; $P = 0.821$), FEV1 level (62.19 vs. 60.44; $P = 0.544$), BMI (26.97 vs.

Table 1: General characteristics of chronic pulmonary obstructive disease

Patients' characteristics (n=118)	Statistics
Age (range: 40–81 years), mean (SD)	62.23 (10.75)
Sex, n (%)	
Male	65 (55.1)
Female	53 (44.9)
Marital status, n (%)	
Married	90 (76.3)
Single	3 (2.5)
Divorce	8 (6.8)
Widow	17 (14.4)
Educational level, n (%)	
Primary school (finish 6 years)	15 (12.7)
Intermediate (7–9) years	12 (10.2)
Secondary (10–12) years	13 (11.0)
Higher education (> than 13 years)	10 (8.5)
Illiterate	54 (45.8)
Read and write	14 (11.9)
Chronic disease, n (%)	
No disease	47 (39.8)
MI	18 (15.3)
Heart failure	21 (17.8)
Stroke	9 (7.6)
Others	23 (19.5)
Occupation, n (%)	
Retired	37 (31.4)
Professional	19 (16.1)
Manual	50 (42.4)
Unemployed	12 (10.2)
Regular exercise, n (%)	
Yes	20 (16.9)
No	98 (83.1)
Family income, n (%)	
Enough	87 (73.7)
Not enough	20 (16.9)
Exceed need	11 (9.3)

MI: Myocardial infarction, SD: Standard deviation

26.93; $P = 0.965$), SBP (148.86 vs. 142.52; $P = 0.223$), and DBP (87.31 vs. 84.37; $P = 0.132$) between user and nonuser beta-blockers, respectively [Table 3].

The study analysis showed no significant difference in the number of exacerbations between COPD patients with CVD and without comorbidity in beta-blocker users; 0.45 versus 0.50; $P = 0.820$. While in nonusers of beta-blockers, the COPD patients with CVD (heart failure and MI) had a significantly higher number of exacerbations (1.29 no.) compared to those COPD patients without comorbidity (0.45 no.: $P = 0.020$), as presented in Table 4.

The study showed that the COPD patients with CVD who used beta-blockers had significantly less number of exacerbation compared to those COPD patients with CVD did not use beta-blockers [Table 5].

Table 2: Chronic obstructive pulmonary disease-related characteristics of patients

Characteristics (n=118)	Statistics, n (%)
Smoking	
Smoker	65 (55.1)
Nonsmoker	2 (1.7)
Ex-smoker	51 (43.2)
Pack year (range: 0.0–120.0)	52.95 (15.15)
Exacerbation number (range: 0–4)	0.49 (0.64)
Beta-blockers	
Yes	57 (48.3)
No	61 (51.7)
FEV ₁ level (range: 29–85)	61.29 (15.68)
BMI (range: 15–38)	26.95 (5.50)
SBP (range: 90–230 mm Hg)	145.58 (28.15)
DBP (range: 60–130 mm Hg)	86.03 (9.64)

COPD: Chronic obstructive pulmonary disease, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, BMI: Body mass index, FEV₁: Forced expiratory volume in 1 s

Table 3: Comparison of patients' characteristics between the user and nonuser beta-blockers

Patients' characteristics	Patients' groups		P
	Beta-blocker users (n=57)	Nonuser beta-blockers (n=61)	
Age (year)	64.67 (11.41)	59.95 (9.63)	0.017*
Sex			
Male	34 (59.6)	31 (50.8)	0.335**
Female	23 (40.4)	30 (49.2)	
Chronic disease			
No disease	8 (14.0)	39 (63.9)	<0.001**
MI	16 (28.1)	2 (3.3)	
Heart failure	16 (28.1)	5 (8.2)	
Stroke	7 (12.3)	2 (3.3)	
Others	10 (17.5)	13 (21.3)	
Chronic disease			
No disease	8 (14.0)	39 (63.9)	<0.001**
CVD	32 (56.1)	7 (11.5)	
Stroke	7 (12.3)	2 (3.3)	
Others	10 (17.5)	13 (21.3)	
Smoking			
Smoker	25 (43.9)	40 (65.6)	0.032***
Nonsmoker	1 (1.8)	1 (1.6)	
Ex-smoker	31 (54.4)	20 (32.8)	
Pack year	52.06 (12.76)	52.40 (15.58)	0.903*
Exacerbation in last year	0.50 (0.61)	0.47 (0.67)	0.821*
FEV ₁ level	62.19 (14.20)	60.44 (17.01)	0.544*
BMI	26.97 (5.19)	26.93 (5.81)	0.965*
SBP	148.86 (28.24)	142.52 (27.94)	0.223*
DBP	87.31 (10.21)	84.37 (10.41)	0.132*

*Independent t-test, **Pearson Chi-squared, and ***Fisher's exact tests were performed for statistical analyses. The bold numbers show a significant difference. DBP: Diastolic blood pressure, SBP: Systolic blood pressure, BMI: Body mass index, FEV₁: Forced expiratory volume in 1 s, MI: Myocardial infarction, CVD: Cardiovascular disease

Table 4: Comparison of the number of exacerbation between COPD patients with cardiovascular disease comorbidity and without comorbidity in users and nonusers beta-blockers

Number of exacerbation	Diseases		P (two-sided)
	No disease (n=8)	CVD (n=29)	
Beta blocker users	0.50 (0.53)	0.45 (0.63)	0.820
Number of exacerbation	Diseases		P (two-sided)
	No disease (n=33)	CVD (n=7)	
Nonusers of beta blocker	0.45 (0.62)	1.29 (1.50)	0.020

An independent *t*-test was performed for statistical analyses. CVD: Cardiovascular disease, COPD: Chronic obstructive pulmonary disease

Table 5: Comparison of the number of exacerbation between the user and nonuser beta-blockers of COPD patients with cardiovascular disease

Number of exacerbation	Beta-blocker using		P (two-sided)
	Yes	No	
Sample	29	7	0.025
Mean	0.45	1.29	
SD	0.63	1.50	

An independent *t*-test was performed for statistical analyses. SD: Standard deviation

DISCUSSION

The present study showed no significant difference in the number of exacerbations between COPD patients with CVD and without comorbidity in beta-blocker users. While in nonusers of beta-blockers, COPD patients with CVD (heart failure and MI) had a significantly higher number of exacerbations compared to those COPD patients without comorbidity. Moreover, the study showed that COPD patients with CVD who used beta-blockers had substantially less number of exacerbation compared to those COPD patients with CVD did not use beta-blockers.

Dransfield *et al.*^[14] reviewed the admitted patients between October 1999 and September 2006 with an acute exacerbation of COPD. The acute exacerbation of COPD was considered a primary diagnosis and acute respiratory failure as a secondary diagnosis. They included 825 patients with an in-hospital mortality rate of 5.2%. In agreement with our study, they found that the patients who receive beta-blockers were older and more frequently of CVDs than those patients did not use beta-blockers. The authors reported that using beta-blockers had a significantly lower mortality rate (odds ratio = 0.39; 95% confidence interval: 0.14–0.99). In-hospital mortality was predicted by age, length of stay, the presence of respiratory failure, number of previous exacerbations, congestive heart failure, CVD, or liver disease.

The patients with COPD die mostly during hospitalization for acute exacerbations, which is responsible for 32%

of in-hospital mortality and predicts 1-year mortality 23%–43%.^[19–22] Beta-blockers decrease the mortality rate in cardiovascular patients, particularly, after MI,^[7] and in the presence of congestive heart failure.^[23] The COPD patients do not use the beta-blockers owing to adverse effects of beta-blockers on airway function.^[4,24]

A Cochrane review analyzed 20 randomized controlled trials of cardioselective beta-blockers in patients with COPD showed no substantial difference effect on FEV1 of bronchodilator response following single doses of up to 12 weeks of therapy.^[6] We did not find a significant difference in the FEV1; 62.19 versus 60.44; *P* = 0.544.

Several studies, including a meta-analysis of observational studies, have shown that beta-blockers have a protective effect on all-cause mortality in COPT patients.^[12,25] The previous studies have shown a lower rate of COPD exacerbations and dual cardiopulmonary protective properties.^[11,26]

Using beta-blockers therapy for patients at risk with heavy comorbidities, such as heart failure is useful, whereas low-risk patients, such as patients with uncomplicated hypertension could put them at increased risk.^[27] A meta-analysis of fifteen original observational cohort studies with a follow-up between 1 and 7.2 years showed that beta-blockers therapy substantially reduces the risk of overall mortality and exacerbation of COPD. The relative risk for overall mortality is 0.72, and for exacerbation of COPD is 0.63.^[28]

A study examined the relationship between discharge use of beta-blockers therapy and 1-year mortality in patients with COPD or asthma who were divided into three groups. The patients who were not using beta-agonists, using beta-agonists and those with severe disease compared to patients without COPD or asthma. Among patients without contraindications to beta-blockers, patients with COPD or asthma (20.0%) were substantially less likely to be prescribed beta-blockers at discharge after acute MI. Patients with COPD or asthma who were not on beta-agonist had lower one-year mortality if they used beta-blockers. This mortality benefit was not found in patients using beta-agonists or those with severe COPD or asthma.^[29]

There are a limited number of studies that showed similar benefits of the use of β -blockers in patients with moderate to very severe COPD, in terms of a significant reduction in exacerbations.^[26]

However, there are conflicting findings on the effect of β -blockers in patients with moderate to very severe COPD. For example, Duffy *et al.* did not report any evidence that beta-blocker use is unsafe or related to worse pulmonary outcomes in patients with moderate to severe COPD.^[30] Similar findings were reported elsewhere.^[26,31] However, in these two studies patients had less severe airflow obstruction compared to Duffy *et al.* In addition, the rate of chronic bronchitis is different among these studies.^[26,30,31] The high rate of chronic bronchitis may affect the rate of exacerbation and limit the efficacy of beta-blocker therapy.^[30]

The acute administration of beta-blockers at maximal doses has not been shown to affect FEV₁ in hypertensive patients with mild to moderate COPD.^[32,33] However, a controlled, crossover trial reported that the short-term administration of nonselective-blockers raises bronchial hyperresponsiveness in irreversible COPD. It is well known that bronchial hyperresponsiveness is related to a tendency to a more reduction in FEV₁ in COPD patients and with increased mortality.^[34] However, long-term administration of carvedilol and nadolol decreases airway hyperresponsiveness in a murine model of asthma. This mechanism has been suggested to be related to the increase in β -AR density.^[5]

Limitations of the study

The findings reported in this study must be interpreted with caution since the patients were selected from one geographic area and may not represent the general status of the rest of the country. Besides, the small sample size may not represent the real difference of acute exacerbations between the two groups.

CONCLUSIONS

The present study showed that COPD patients who used beta-blockers have a substantially lower number of acute exacerbations in the last year compared to those COPD patients who did not use beta-blockers.

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Conflicts of interest

There are no conflicts of interest.

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