ORIGINAL PAPER

doi: 10.5455/medarh.2019.73.72-25
MED ARCH. 2019 APR; 73(2): 72-75
RECEIVED: JAN 12, 2019 | ACCEPTED: FEB 10, 2019

Beta-blocker Use in Moderate and Severe Chronic Obstructive Pulmonary Disease

Faris Zvizdic[1], Edin Begic[2,3], Aida Mujakovic[4,5], Enisa Hodzic[6], Besim Prnjavorac[4,7], Omer Bedak[7], Faruk Custovic[3], Haris Bradaric[8], Azra Durak-Nalbantic[1]

[1]Department for Cardiology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[2]Department of Pharmacology, Sarajevo Medical School, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina

[3]Department of Cardiology, General Hospital "Prim. Dr. Abdulah Nakas", Sarajevo, Bosnia and Herzegovina

[4]Department of Pathophysiology, Sarajevo Medical School, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina

[5]Department of Pulmonary Diseases, General Hospital "Prim. Dr. Abdulah Nakas", Sarajevo, Bosnia and Herzegovina

[6]Intensive Care Unit, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[7]Department of Internal Medicine, General Hospital, Tesanj, Bosnia and Herzegovina

[8]Health Care Centre Maglaj, Maglaj, Bosnia and Herzegovina

Corresponding author: Faris Zvizdic, MD, MSc, Clinical Center University of Sarajevo, Bolnicka 25, 71000 Sarajevo, Bosnia and Hercegovina. E-mail: fariszvizdic@gmail.com. ORCID ID: http://www.orcid.org: 0000-0001- 7647-2723.

ABSTRACT

Introduction: The most appropriate choice of pharmacological treatment of heart rhythm disorders occurring in patients with chronic obstructive pulmonary disease (COPD) and cardiovascular comorbidity is often a topic of debate between pulmonologists and cardiologists in clinical practice, although numerous studies and clinical trials have demonstrated evidence to support the use of selective beta-blockers (BBs) in these patients. Aim: To examine the difference in the number of exacerbations in patients treated with a combination of verapamil and digoxin or BB alone in patients with different COPD stages. Patients and methods: The study included 68 patients (n = 68) diagnosed with COPD who were followed-up during a 12-month period, and the number of exacerbations were analyzed. The patients were divided into two groups according to the stage of COPD: 1) GOLD II (moderate), and GOLD III (severe), and in each group a subdivision was established in relation to the use of either a combination of verapamil and digoxin or the use of BBs alone in pharmacological treatment. The inclusion criteria for patients were defined as following: a) established diagnosis of COPD according to present or deteriorated relevant clinical symptoms and signs, b) the ejection fraction (EF) of a left ventricle (LV) >35%, and c) spirometric cut-points classified as GOLD II (FEV1 / FVC <0.7, FEV1 predicted 50-80%), or GOLD III (FEV1 / FVC <0.7, FEV1 predicted 30-50%) stage of the COPD. The exclusion criteria were EF of LV <35% and a lethal outcome during a follow-up period (2 patients were encountered). Exacerbation was defined as functional deterioration of the COPD symptoms verified by spirometric functional testing, frequency of hospitalizations according to GOLD stage assignment or verified clinical symptoms deterioration. Results: Regardless the pharmacological treatment, there is a statistically significant increase in the number of COPD exacerbations, in a 12-month period follow-up, in the GOLD III group (severe) compared to the GOLD II group (moderate) (1. In the group of patients taking verapamil and digoxin, a two-tailed t-test was used to analyze the results between the GOLD II and GOLD III stage groups, p = 0.01, and 2. In the group of patients taking BBs, a two-tailed t-test was also used to analyze the results between the GOLD II and GOLD III stage groups, p = 0.003). Within the COPD GOLD II stage group, there appears to be no statistically significant difference in the number of exacerbations between the patients taking verapamil and digoxin (n = 24) and the patients taking BBs alone (n = 15), although, in patients taking BBs alone, there appears to be a trend towards a decrease in the exacerbations compared to the number of exacerbations in patients taking verapamil and digoxin (p = 0.007). Within the COPD GOLD III stage group, there is no difference in the number of exacerbations between the patients taking verapamil and digoxin (n = 20), and the patients taking BBs alone (n = 9), as analyzed by a two-tailed t-test, p = 0.577. Conclusion: Use of selective BBs in the treatment of cardiovascular comorbidity in patients with COPD represents a far better choice of pharmacological approach in the treatment of patients diagnosed with COPD GOLD II (moderate) stage.

Keywords: Chronic Obstructive Pulmonary Diseases, Safety, Treatment, Beta blockers.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVDs) frequently coexist, and the therapeutic modality of certain pathology is directly dependent on pathology of another (1). CVDs are the most important comorbidities in patients diagnosed with COPD (1). COPD shares risk factors (age, smoking, genetic base, systemic inflammation) with a number of disease processes related to cardiovascular system and they are also associated with cardiac arrhythmias, coronary heart disease, hypertension, right and/or left ventricular failure, hypokalemia and

hypomagnesaemia (2,3,4). Pharmacological approach to patients with COPD is reflected in prisms of cardiovascular status, taking into account the effects of angiotensin-converting-enzyme inhibitors, blockers of angiotensin receptors, beta blockers (BB), calcium channel blockers and diuretics, and their effect on the respiratory system as well as their interactions with drugs that are used primary in COPD treatment. On the other hand, the influence of bronchodilator on the cardiovascular system is often unfavorable. Theophylline has numerous well-defined cardiac effects, including a dose-dependent increase in heart rate, enhancement of atrial automaticity, and acceleration of intracardiac conduction (2). Theophylline is associated with following rhythm disorders (sinus tachycardia, premature atrial beats, supraventricular tachycardia, atrial fibrillation, unifocal and multifocal atrial tachycardia, and ventricular arrhythmias) (3). BBs may have negative effect on lung function in patients with COPD, but if not used they may contribute to increased cardiovascular events, especially in high-risk patients (2). Even though there is a clear evidence of BBs efficiency, there is a general hesitation of their use in patients with COPD, because of contraindications and fear of inducing adverse reactions and bronchospasm (4). BBs are basically divided into selective and non-selective in relation to the mechanism of action and site of action. Also they are divided into three generations, the first one as non-selective, (the β1 and β2 receptor blockers), the second one as cardio selective beta-blockers that block the β1 receptors, but also β2 receptors in higher doses, and third generation which has an effect on vasodilatation. BBs may have β2-intrinsic sympathomimetic activity, as well as alpha-adrenergic blockade. Treatment of heart rhythm disturbances and correction of hypertensive status in patients diagnosed with COPD are corrected by calcium channel blockers (verapamil) with addition of inotrope (digoxin) at low or high doses depending on cardiac status of the patient (presence of heart failure (HF)). Given that beta blockers have great benefit on the heart rate, heart function, electric stability as well as on survival and mortality associated with cardiovascular status, taking into account increased pulmonary arterial pressure, and tricuspid valve status, therapeutic modality in patients diagnosed with COPD and associated CVD is of great significance, and is often dubious in relation to a pulmonologist and cardiologist (or specialist of internal medicine). Due to the high cardiovascular comorbidity in COPD, BBs have been proposed as a therapeutic option (because of cardio protective effects in addition to reducing heart rate and improving systolic and diastolic dysfunction)(5,6). It has been shown that the use of selective blockers in standard doses is effective and safe for use in patients diagnosed with COPD, thus at high doses should be used with caution (depending on which BB is used), while non-selective BBs should be avoided (6, 7, 8, 9,10).

2. AIM

To examine the difference in the number of exacerbations in patients treated with a combination of verapamil and digoxin or a beta-blocker alone in different COPD patient stages and to emphasize focus on the safety of BB use in patients diagnosed with COPD.

3. PATIENTS AND METHODS

The study included 68 patients (n = 68) diagnosed with COPD who were followed-up during a 12-month period, and the numbers of exacerbations were analyzed. Patients were examined in Health Care Center Maglaj, General Hospital Tesanj and Clinical Center University of Sarajevo (through whole health care system in Bosnia and Herzegovina). The patients were divided according to the stage of COPD into two groups: 1) GOLD II (moderate), and 2) GOLD III (severe), with a subdivision created in each group in relation to the use of either a combination of verapamil and digoxin or the use of beta-blockers alone in their pharmacological treatment. The inclusion criteria were the following ones: a) a diagnosis of COPD, b) the ejection fraction (EF) of a left ventricle (LV) >35%, and c) GOLD II (FEV1 / FVC <0.7, FEV1 predicted 50-80%), or GOLD III (FEV1 / FVC <0.7, FEV1 predicted) stage of the COPD. The exclusion criteria were EFLV <35% and a lethal outcome during a follow-up period (2 patients). Exacerbation was defined as functional deterioration of the COPD symptoms verified by spirometric functional testing, frequency of hospitalizations according to GOLD stage assignment or verified clinical symptoms deterioration.

4. RESULTS

In the GOLD II group, 24 patients who were on verapamil and digoxin therapy and 15 patients were on selective beta-blocker therapy (8 patients were on metoprolol, 6 patients were on bisoprolol and 1 patient was on nebivolol) were monitored. In the GOLD III group, 20 patients who were on verapamil and digoxin therapy and 9 patients who were on selective beta-blocker therapy (3 patients were on metoprolol, 6 patients were on bisoprolol) were monitored. Regardless of the pharmacological treatment, there is a statistically significant increase in the number of exacerbations in patients diagnosed with the COPD, during a 12-month period follow-up, in the GOLD III group (severe) compared to the GOLD II group (moderate) (1. for the patients taking verapamil and digoxin, a two-tailed t-test was used to analyze the results between the GOLD II and GOLD III groups, p = 0.01, and 2. for the patients taking beta-blockers, a two-tailed t-test was also used to analyze the results between the GOLD II and GOLD III groups, p = 0.003. (Table 1).

Within the GOLD II group of patients diagnosed with COPD, there appears to be no statistically significant difference in the number of exacerbations between the patients taking verapamil and digoxin (n = 24) and the patients taking beta-blockers alone (n = 15), although, in patients taking beta-blockers, there appears to be a trend towards a decrease in the exacerbations when compared to the exacerbations in patients taking verapamil and digoxin (p = 0.007).

Within the GOLD III group of patients diagnosed with COPD, there is no difference in the number of exacerba-

Pharmacological therapy	Number of exacerbations during 12 months		Two-tailed T test
	GOLD II (AVE ± STDEV)	GOLD III (AVE ± STDEV)	
Group I: verapamil and digoxin (AVE ± STDEV)	1.333 ± 0.963 (N=24)	2.100 ± 0.912 (N=20)	0.010*
Group II: beta-blockers (AVE ± STDEV)	0.600 ± 0.632 (N=15)	1.889 ± 0.928 (N=9)	0.003*

Table 1. COPD exacerbations are increased the GOLD III stage. (The number of exacerbations are increased in the GOLD III stage for COPD patients receiving either verapamil and digoxin or beta-blocker therapy. "AVE": average or mean number of exacerbations; "STDEV":standard deviation; *p<0.05.)

Pharmacological therapy	Number of exacerbations during 12 months		Two-tailed T test
	verapamil and digoxin (AVE ± STDEV)	beta-blockers (AVE ± STDEV)	
GOLD II	1.333 ± 0.963 (N=24)	0.600 ± 0.632 (N=15)	0.007*
GOLD III	2.100 ± 0.912 (N=20)	1.889 ± 0.928 (N=9)	0.577

Table 2. COPD exacerbations are decreased during a 12-month treatment with beta-blockers. (The number of exacerbations are decreased in the GOLD II category for the COPD patients receiving beta-blockers. "AVE": average or mean number of exacerbations; "STDEV": standard deviation; *p<0.05.)

tions between the patients taking verapamil and digoxin (n = 20), and the patients taking beta-blockers (n = 9), as analyzed by a two-tailed t-test, p = 0.577 (Table 2)

5. DISCUSSION

Research has prospective character and included 68 patients, of whom 64.7% were on antiarrhythmic therapy with verapamil and digoxin, and the use of this combination was more applied to patients in GOLD III stage COPD group. In clinical studies, the use of beta-blockers reduced morbidity and mortality in patients with coronary heart disease or HF (11,12). The results of our research showed that in the moderate, GOLD II stage COPD group, BB use reduces the number of exacerbations over a 12-month period. In GOLD III, a severe COPD stage, the number of exacerbations does not depend on therapy even with a combination of verapamil and digoxin or BBs alone. Lim and associates showed that BBs are underprescribed in COPD patients even though there are clear indications for their therapeutic application, but further research is required to determine real benefit or contraindications of their use in COPD patients (13). Bhat et al. confirmed benefit of BBs use in COPD patients (14). Meta-analysis of Du et al. concluded that BB use in patients with COPD not only decreases the risk of overall mortality but also reduce the risk of exacerbation of COPD and also they confirmed that BBs are underprescribed in COPD patients. (15) Au et al. showed that BBs use in patients with COPD is associated with a significant reduction in COPD exacerbations and COPD mortality (16).

In retrospective and observational analyses, both cardioselective and noncardioselective BBs decrease mortality in COPD patients with and without CVD, including patients with hypertension, HF, and atherosclerosis, as well as those undergoing major vascular surgery (17,18,19). It has been shown that even BB blockers can have protective effect on patients with COPD (reduction of patient symptoms, reduction in the incidence and severity of noninfectious COPD exacerbations and enhancing exercise capacity) (20,21). In our study selective BB were used (most commonly metoprolol and bisoprolol). To determine whether cardioselectivity affects lungs or vascular function in patients with HF, carvedilol, metoprolol succinate, and bisoprolol were compared in a randomized, open-label, triple-crossover study. The BB switches were well-tolerated in patients with COPD, although there were changes in airway function, with FEV1 being lowest with carvedilol and highest with bisoprolol. BB use did not decrease the effectiveness of β2-agonists (22). Verapamil is a negative inotropic and chronotropic agent that relaxes smooth muscles (23). Digoxin is a positive inotropic agent and is used especially in patients with systolic HF (24). Verapamil causes prolongation of the conduction time through the atrioventricular (AV) node and the best effect of verapamil on AV nodal conduction time and heart rate decrease happens during the attack of tachycardia with decrease of effect in normal heart rate (25). Verapamil should not be a drug of choice for patients who have diastolic HF or HF with preserved ejection fraction (HFpEF), in patients after myocardial infarction and who have high risk of myocardial infarction. It should be noted that verapamil should not have an effect on stabilization of the left ventricular ejection fraction, and can lead to exacerbation of HF (especially in patients with COPD, primarily in severe stages with a right ventricular hypertrophy) with a rather difficult dose profile and digoxin interaction, in which case it increases digoxin concentration (26,27,28). Although the sample of the research is small, the study shows that the use of BBs in patients diagnosed with moderate COPD should be therapeutic option of choice in terms of respiratory pathology but BBs also have an effect on myocardial and cardiovascular status alone. Although in this study, patients with ejection fraction under 35% were not taken into consideration, BBs in such patients are drugs of better choice due to the BB effect on left ventricle. Regardless of the fear of prescribing BBs in severe COPD stages, BBs are in the same position as the combination of verapamil and digoxin. Nevertheless, each patient needs to be approached individually in the therapeutic mode itself, and other comorbidities have an effect as well as the echocardiographic finding itself.

In addition, BBs prescribed to such patients are often subdosed, which should be avoided, as the effect of BB on the cardiovascular system is best demonstrated at recommended doses (fear of bronchospasm has an effect on subdosing when BBs do not meet therapeutic effect). Avoiding triggers, with adequate patient monitoring and optimal mode of therapy, is the imperative of everyday work in patients with COPD.

6. CONCLUSION

The use of selective beta-blockers in the treatment of cardiovascular comorbidity in patients with COPD represents far better choice of pharmacological therapeutic approach in treatment of patients within the GOLD II (moderate) stage of COPD.

Author's contribution: F.Z., E.B., A.M., H.B., B.P. and O.B. gave substantial contribution to the conception and design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

- Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms.
- Conflicts of interest: There are no conflicts of interest. Part of research (preliminary results), in smaller sample, was presented on 8th Pulmology days in Tesanj, Bosnia and Herzegovina.
- Financial support and sponsorship: None.

REFERENCES

1. AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice?. Ther Adv Respir Dis. 2018;12:1753465817750524.
2. Chatila WM, Thomashow BM, Minai OA, Criner GJ, Make BJ. Comorbidities in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5(4):549-55.
3. Sessler CN, Cohen MD. Cardiac arrhythmias during theophylline toxicity. A prospective continuous electrocardiographic study. Chest. 1990 Sep;98(3):672-8.
4. Albouaini K, Andron M, Alahmar A, Egred M. Beta-blockers use in patients with chronic obstructive pulmonary disease and concomitant cardiovascular conditions. Int J Chron Obstruct Pulmon Dis. 2007;2(4):535-40.
5. Heindl S, Lehnert M, Criee CP, et al Marked sympathetic activation in patients with chronic respiratory . ailure. Am J Respir Crit Care Med 2001; 164: 597–601.
6. Huang YL, Lai CC, Wang YH, et al. Impact of selective and nonselective beta-blockers on the risk of severe exacerbations in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2017;12:2987-2996.
7. Chang CL, Mills GD, McLachlan JD, et al. Cardio-selective and non-selective beta-blockers in chronic obstructive pulmonary disease: effects on bronchodilator response and exercise. Intern Med J. 2010 Mar;40(3):193-200.
8. Liao KM, Lin TY, Huang YB, Kuo CC, Chen CY. The evaluation of β-adrenoceptor blocking agents in patients with COPD and congestive heart failure: a nationwide study. Int J Chron Obstruct Pulmon Dis. 2017;12:2573-2581
9. Duffy S, Marron R, Voelker H, et al. Effect of beta-blockers on exacerbation rate and lung function in chronic obstructive pulmonary disease (COPD). Respir Res. 2017;18(1):124.
10. Begic E, Mujakovic A, Hodzic E, et al. The safety of beta-blocker use in chronic obstructive pulmonary disease. Abstract book, 8th Pulmology days, Tesanj, Bosnia and Herzegovina. 37-39.
11. Smith SC, Allen J, Blair SN, et al. . AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update Endorsed by the National Heart, Lung, and Blood Institute. Journal of the American College of Cardiology, 2006; 47(10): 2130–2139
12. Abraham WT, Chin FMH, Feldman AM, et al. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. Journal of the American College of Cardiology, 2009; 53(15): e1–90.
13. Lim KP, Loughrey S, Musk M, et al. Beta-blocker under-use in COPD patients. Int J Chron Obstruct Pulmon Dis. 2017;12:3041-3046.
14. Bhatt SP, Wells JM, Kinney GL, et al. β-Blockers are associated with a reduction in COPD exacerbations. Thorax. 2015;71(1):8-14.
15. Du Q, Sun Y, Ding N, et al. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. PLoS One. 2014;9(11):e113048
16. Au DH, Bryson CL, Fan VS, Udris EM, Curtis JR, et al. (2004) Beta-blockers as single-agent therapy for hypertension and the risk of mortality among patients with chronic obstructive pulmonary disease. Am J Med 117:925–931.
17. Schnell K, Weiss CO, Lee T, et al. The prevalence of clinically-relevant comorbid conditions in patients with physician-diagnosed COPD: a cross-sectional study using data from NHANES 1999–2008. BMC Pulm Med. 2012;12:26–34.
18. Angeloni E, Melina G, Roscitano A, et al. β-blockers improve survival of patients with chronic obstructive pulmonary disease after coronary artery bypass grafting. Ann Thorac Surg. 2013;95:525–531.
19. van Gestel YR, Hoeks SE, Sin DD, et al. Impact of cardioselective β-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. Am J Respir Crit Care Med.2008;178:695–700.
20. Rutten FH, Zuithoff PA, Hak E, et al. β-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. Arch Intern Med. 2010;170:880–887.
21. Farland MZ, Peters CJ, Williams JD, et al. Beta-blocker use and incidence of chronic obstructive pulmonary disease exacerbations. Ann Pharmacother.2013;47:651–656.
22. Minor DS, Meyer AM, Long RC, et al. β-Blockers and Chronic Obstructive Pulmonary Disease: Inappropriate Avoidance?. J Clin Hypertens (Greenwich). 2013;15:925–930.
23. Dargie H, Rowland E, Krikler D. Role of calcium antagonists in cardiovascular therapy. Br Heart J 1981;46:8–16.
24. Jordaens L, Trouerbach J, Calle P, et al. Conversion of atrial fibrillation to sinus rhythm and rate control by digoxin in comparison to placebo. Eur Heart J. 1997;18:643–8.
25. Roberts SA, Diaz C, Nolan PE, et al. Effectiveness and costs of digoxin treatment for atrial fibrillation and flutter. Am J Cardiol. 1993;72:567–73.
26. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the acc/aha 2005 guidelines for the diagnosis and management of heart failure in adults: A report of the American college of cardiology foundation/American heart association task force on practice guidelines: Developed in collaboration with the international society for heart and lung transplantation. Circulation. 2009;119:e391–e479.
27. Patel K, Fonarow GC, Ahmed M, et al. Calcium channel blockers and outcomes in older patients with heart failure and preserved ejection fraction. Circ Heart Fail. 2014;7(6):945-52.
28. Ledwitch KV, Barnes RW, Roberts AG. Unraveling the complex drug–drug interactions of the cardiovascular drugs, verapamil and digoxin, with P-glycoprotein. Bioscience Reports Apr 2016, 36(2): e00309.