Original Investigation

Eurasian J Pulmonol 2015; 17: 142-8

The Effects of Budesonid that Added to Tiotropium Therapy on Health Related Quality of Life, Exercise Capacity and Pulmonary Functions in COPD Patients

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Abstract

Objective: The aim of this study was to evaluate the effects of adding inhaled budesonide to the tiotropium treatment on the pulmonary function tests, health-related quality of life and exercise capacity of patients with chronic obstructive pulmonary disease (COPD).

Methods: Forty study subjects with COPD were randomized to two groups. The patients in the first group was treated with 1x1 18 mcg of Tiotropium and the patients in the second group was treated with the combination of tiotropium (18 mcg 1x1) and budesonide (400 mcg 2x1) for three months. Pulmonary function tests, six minute walk test, body mass index and Saint George Respiratory Questionnaire (SGRQ) scores were recorded both at the beginning and 3 months later and the results at the begining and third month were compared with each other. There were no statistically significant difference in all basline parameters between the two groups.

Results: At the end of the study, no statistically significant differences were obtained between two groups in terms of pulmonary function tests ($p>0.05$). Significant improvements were observed on the parameters of walking distance ($p=0.023$) and SGRQ scores (symptom score: $p<0.001$, activity score: $p=0.001$, impact score: $p=0.003$ and total score: $p<0.001$) in Group 2 when compared with Group 1.

Conclusion: These results show that, in patients with COPD, tiotropium/budesonide combination is more effective than alone tiotropium inhalation in quality of life and exercise performance. But this combination is not more effective in improving lung functions.

Keywords: Budesonide, chronic obstructive pulmonary disease, exercise capacity, quality of life questionnaire, tiotropium

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disorder that does not demonstrate complete reversibility and that is characterized by limited air flow. It mainly presents with a chronic inflammatory response given by the lungs to harmful particles and gases. Chronic inflammation causes "remodeling" and obstruction in the airways. Inflammation and its outcomes can be seen in all tissues of the lungs, and it also demonstrates systemic features (1, 2).

It has been found that in patients with COPD, regular treatment with inhaled corticosteroids does not change forced expiratory volume in 1 second (FEV_1) loss; however, it decreases the frequency of attacks and leads to improvement in the health condition of COPD patients with low FEV_1 and recurrent exacerbations. On the other hand, long-acting bronchodilators are recommended to all patients at Stage 2 (1). Previous studies revealed that tiotropium, a long-acting bronchodilator, affected FEV_1 values more positively than a placebo or ipratropium and decreased the number of attacks (3-6). Recently, the number of large studies conducted with long-acting β_2 agonist+inhaled corticosteroid combinations has increased. However, there are a few studies on the effects of long-acting anticholinergic+inhaled corticosteroid combinations on the pulmonary functions, exercise capacity, and quality of life of this patient group.

In our study, the efficiency of inhaled budesonide that was added to long-acting anticholinergic therapy used in COPD patients was evaluated through a quality of life questionnaire and exercise

Received Date: 14.11.2014
Accepted Date: 24.06.2015
Available Online Date: 09.11.2015

DOI: 10.5152/ejp.2015.21939

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• Available online at www.eurasianjpulmonol.com

capacity examinations in addition to spirometric examinations. The most detailed and standardized questionnaire used for COPD is St. George's Respiratory Questionnaire (SGRQ). This questionnaire is also used to determine the effects of many drugs on the quality of life (7). One of the exercise tests, which is easy to use, is the 6-min walk test (6MWT). There is a significant correlation between walking distance and survival rate. The 6-min walk test is commonly used, particularly for evaluating the effects of pulmonary rehabilitation (8).

In this study, we aimed to investigate the effects of inhaled budesonide therapy in addition to tiotropium, which is a long-acting bronchodilator used in COPD patients, on the quality of life, exercise capacity, and respiratory function of patients.

METHODS

Patient Selection

Forty patients who were followed up for Stage 3-4 COPD, diagnosed according to the GOLD guideline, at Fırat University Medical Faculty, Department of Thoracic Diseases, who were in a stable state for the previous 6 weeks, and who did not have respiratory tract infections or acute COPD attacks during this period, were included in the study. On the other hand, patients who had a history of asthma diagnosis, atopy, and peripheral blood eosinophilia (≥600/mm^3), recent myocardial infarction (MI), heart failure, known symptomatic prostatic hypertrophy, and narrow-angle glaucoma and who developed an additional disease apart from COPD during the study were excluded from the study.

At the beginning, the drugs that the patients had previously used were noted. Theophylline, inhaled anticholinergics and/or long-acting β agonists were discontinued 48 h before the study, short-acting inhaled β_2 agonists were stopped 12 h before, and inhaled steroids were stopped 2 weeks before.

Patients who did not tolerate a discontinuance of inhaled drugs were excluded from the study. During the study period, patients were permitted to use rescue drugs. Patients complying with the study requirements were divided into two groups with a simple randomization method. Each patient was included in Group 1 or Group 2 according to the application sequence. The first group (Group 1) was administered tiotropium inhaler capsule 18 mcg (Spiriva Inhaler Capsule; Boehringer Ingelheim, Ingelheim, Germany) once a day. The second group (Group 2) was administered budesonide inhaler capsule 400 mcg (Miflonide 400 mcg inhaler capsule; Novartis, Basel, Switzerland) in the morning and evening, in addition to tiotropium inhaler capsule 18 mcg once a day. Each patient in the study was followed up for 3 months.

For all cases, detailed pulmonary function tests (PFT) and maximum inspiratory and maximum expiratory pressures (MIP and MEP) were measured at the beginning and at the end of the third month. Pulmonary function tests was initially performed at least 24 h after the use of a long-acting bronchodilator and at least 6 h after the use of short-acting bronchodilators between 8:00 a.m. and 10:00 a.m. At the end of the third month, PFT was performed 24 h after the previous dose of tiotropium and at least 6 h after using short-term bronchodilators if the patient had used a rescue drug. Moreover, a quality of life questionnaire was applied and exercising capacities were evaluated.

Measurement of Pulmonary Function Tests

Pulmonary function tests was conducted with a pulmonary function test device (Medgraphics Ultima series CPX 790705-209; MGC Diagnostics Corporation, Saint Paul, MN, USA) in our clinic using nose clips at room temperature and in the sitting position. Of the routine tests, FEV_1, forced vital capacity (FVC) values, and FEV_1/FVC ratio were measured and recorded. At least three measurements were made and the best results were evaluated. The data were interpreted in accordance with the estimated values of the European Respiratory Society (9).

Lung volumes were measured by body plethysmograph (Medgraphics, Elite SeriesTm Plethysmograph; MGC Diagnostics Corporation, Saint Paul, MN, USA). The residual volume (RV), resistance of airway (RAW), and MIP and MEP values were recorded. The MIP value was measured at least five times at the level of RV and the best three values were recorded (10-12).

Table 1. Study groups' demographic features, baseline spirometry, quality of life, exercise capacity, and FFM values

	Group 1	Group 2
Number of patients	16	20
Age of patient (years)	62.62±7.05	63.75±10.13
Gender (M/F)	14/2	16/4
Duration of COPD (years)	4.8	5.1
Present/past smoking history	4/12	6/14
Cigarettes (packs.year)	25.64±6.54	26.55±5.94
FEV_1 (L)	1.40±0.23	1.21±0.30
FEV_1 (%)	43.18±4.83	41.90±7.52
FVC (%)	68.75±7.83	61.70±13.62
FEV_1/FVC	55.87±8.13	54.10±8.33
RV (%)	197.56±49.75	226.00±58.26
TLC (%)	119.06±16.92	128.10±25.67
Raw (%)	188.81±102.21	224.25±113.92
MIP (cmH_2O)	−60.43±20.60	−62.90±17.80
MEP (cmH_2O)	71.56±20.18	67.65±19.95
SGRQ		
Symptom score	52.31±16.20	59.75±17.27
Activity score	59.64±18.62	71.46±19.39
Impact score	40.95±9.78	50.43±19.64
Total score	48.92±9.00	58.27±17.29
6MWT (m)	411.68±79.92	406.35±86.61
FFM (kg)	56.18±5.69	53.19±7.57

For all parameters p>0.05

Values are presented as mean ± SD.

COPD: Chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in1 s; FFM: fat free body mass; FVC: forced vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; Raw: resistance of airway; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire; TLC: total lung capacity; 6MWT: 6-min walk test

Measurement of Fat-Free Mass

Fat-free mass (FFM) was measured via a single-frequency (50 kHz) bioelectrical impedance analyzer (Tanita Body Composition Analyzer, model TBF 300; Tanita Corporation, Tokyo, Japan).

Evaluation of the Quality of Life

The quality of life was evaluated with the Turkish version of SGRQ. The questionnaire, consisting of 76 questions, was applied by means of an interview and the symptom, impact, activity, and total scores were calculated through the formulas in the explanation of the test (13).

Measurement of Exercise Capacity

Exercise capacity was evaluated with 6MWT, which was performed by evaluating dyspnea and leg fatigue according to the BORG scale and heart rate per minute on a 30 m long indoor flat surface (by marking each 3 meters). At the end of 6 meters, the total distance that was walked was recorded in meters. The criteria of the American Thoracic Society were taken into consideration for testing (14).

All cases were informed about the inhalation techniques, and their written informed consent was obtained. Ethical approval for the study was received from the Ethics Committee of Fırat University.

Statistical Analysis

The obtained data were statistically analyzed using the Statistical Package for Social Sciences (SPSS) ver. 15.0 (SPSS Inc.; Chicago, IL, USA) software. The Mann–Whitney U test was used for statistical comparison of the groups, and the Wilcoxon test was used for comparing intra-group baseline values and the values obtained at the end of the third month. Moreover, the chi-square test was employed for comparing data such as gender and history of smoking between groups. The data obtained were presented as mean±standard deviation. A value of $p<0.05$ was accepted to be statistically significant.

Table 2. Spirometry, quality of life, exercise capacity, and FFM values of study groups at the end of the 3rd month

	Group 1	Group 2
FEV_1 (L)	1.49±0.31	1.32±0.37
FEV_1 (%)	48.43±8.89	47.20±13.14
FVC (%)	67.12±13.18	61.35±15.19
FEV_1/FVC	58.75±7.97	56.00±6.96
RV (%)	191.81±47.08	219.65±40.86
TLC (%)	118.06±19.29	121.95±19.25
Raw (%)	137.75±70.74	178.65±97.46
MIP (cmH_2O)	−58.31±19.56	−55.50±18.79
MEP (cmH_2O)	69.93±20.06	64.45±19.11
SGRQ		
Symptom score	56.24±18.24	54.46±17.25
Activity score	63.10±18.77	64.36±18.59
Impact score	45.09±10.49	42.89±15.77
Total score	48.92±9.00	58.27±17.29
6MWT (m)	403.18±69.73	429.45±83.97
FFM (kg)	55.98±6.00	53.53±5.68

For all parameters p>0.05

Values are presented as mean±SD.

COPD: Chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FFM: fat free body mass; FVC: forced vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; Raw: resistance of airway; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire; TLC: total lung capacity; 6MWT: 6-min walk test

RESULTS

A total of 40 patients from both groups were included in the study. Some patients in Group 1 were excluded from the study (one for having an attack in the control period and three for not coming for the control period). The demographic features, baseline spirometry, respiratory muscle strength, quality of life, exercising capacity, and FFM values of the patients that completed the study are presented in Table 1. No statistically significant difference was found between the baseline values of both groups in terms of all parameters.

Both groups included in the study were re-evaluated with respect to pulmonary functions and other parameters after being followed up for 3 months; no statistically significant difference was observed between the two groups in terms of all parameters (Table 2).

When each group was evaluated in itself with respect to the values obtained at the beginning and at the end of the study, it was detected that the FEV_1 (as both liter and expected value percentage)

Table 3. Spirometry, quality of life, exercise capacity, and FFM values obtained at the beginning and at the end of the study in Group 1

	Baseline	3rd month	p
FEV_1 (L)	1.40±0.23	1.49±0.31	0.010
FEV_1 (%)	43.18±4.83	48.43±8.89	0.006
FVC (%)	68.75±7.83	67.12±13.18	>0.05
FEV_1/FVC	55.87±8.13	58.75±7.97	0.024
RV (%)	197.56±49.75	191.81±47.08	>0.05
TLC (%)	119.06±16.92	118.06±19.29	>0.05
Raw (%)	188.81±102.21	137.75±70.74	>0.05
MIP (cmH_2O)	−60.43±20.60	−58.31±19.56	>0.05
MEP (cmH_2O)	71.56±20.18	69.93±20.06	>0.05
SGRQ			
Symptom score	52.31±16.20	56.24±18.24 5	>0.0
Activity score	59.64±18.62	63.10±18.77	>0.05
Impact score	40.95±9.78	45.09±10.49	>0.05
Total score	48.92±9.00	51.90±11.04	>0.05
6MWT (m)	411.68±79.92	403.18±69.73	>0.05
FFM (kg)	56.18±5.69	55.98±6.00	>0.05

For all parameters p>0.05

Values are presented as mean±SD.

COPD: Chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FFM: fat free body mass; FVC: forced vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; Raw: resistance of airway; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire; TLC: total lung capacity; 6MWT: 6-min walk test

Table 4. Spirometry, quality of life, exercise capacity, and FFM values obtained at the beginning and at the end of the study in Group 2

	Baseline	3rd month	p
FEV_1 (L)	1.21±0.30	1.32±0.37	0.040
FEV_1 (%)	41.90±7.52	47.20±13.14	0.015
FVC (%)	61.70±13.62	61.35±15.19	>0.05
FEV_1/FVC	54.10±8.33	56.00±6.96	>0.05
RV (%)	226.00±58.26	219.65±40.86	>0.05
TLC (%)	128.10±25.67	121.95±19.25	>0.05
Raw (%)	224.25±113.92	178.65±97.46	>0.05
MIP (cmH_2O)	−62.90±17.80	−55.50±18.79	>0.05
MEP (cmH_2O)	67.65±19.95	64.45±19.11	>0.05
SGRQ			
Symptom score	59.75±17.27	54.46±17.25	0.009
Activity score	71.46±19.39	64.36±18.59	0.002
Impact score	50.43±19.64	42.89±15.77	0.001
Total score	58.27±17.29	52.02±15.59	0.001
6MWT (m)	406.35±86.61	429.45±83.97	0.005
FFM (kg)	53.19±7.57	53.53±5.68	>0.05

For all parameters p>0.05

Values are presented as mean±SD.

COPD: Chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FFM: fat free body mass; FVC: forced vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; Raw: resistance of airway; RV: residual volume; SGRQ: St. George's Respiratory Questionnaire; TLC: total lung capacity; 6MWT: 6-min walk test

and FEV_1/FVC values in Group 1 were higher at the end of the third month than the baseline values (p=0.010, p=0.006, and p=0.024, respectively). On the other hand, no statistically significant difference was found for the other parameters (Table 3).

In Group 2, although a significant increase was found only in liter and expected % values of FEV_1 (p=0.040 and p=0.015, respectively), no change was detected in the other measurements (Table 4). Furthermore, different from Group 1, significant changes were observed in the 6MWT distances (p=0.005) and SGRQ scores in Group 2 (p=0.009 for symptom score, p=0.001 for impact score, p=0.002 for activity score, and p=0.001 for total score).

Considering the differences between the values obtained at the beginning and at the end of the study, it was detected that although the quality of life questionnaire scores decreased in Group 2, they increased in Group 1, and the difference between them was statistically significant (p=0.009 for symptom score and p=0.001 for activity, impact, and total scores). In Group 1, there was a decrease of 5.37 m on average in the 6MWT, but in Group 2, there was an increase of 23.1 m on average. The difference between these data was statistically significant (p=0.018) (Figures 1, 2). Although an increase was detected in the FEV_1 values as liter and expected percentage in both groups, there was no statistically significant difference between the groups in terms of the mean increase (p>0.05).

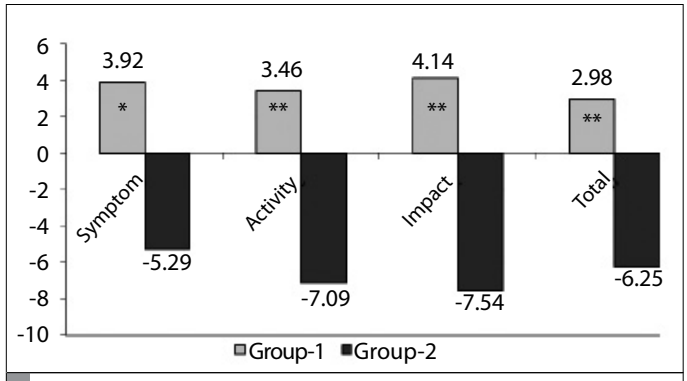

Figure 1. Changes in St. George's Respiratory Questionnaire (SGRQ) in both study groups (*: p=0.009, **: p=0.001, data labels reflect the mean changes)

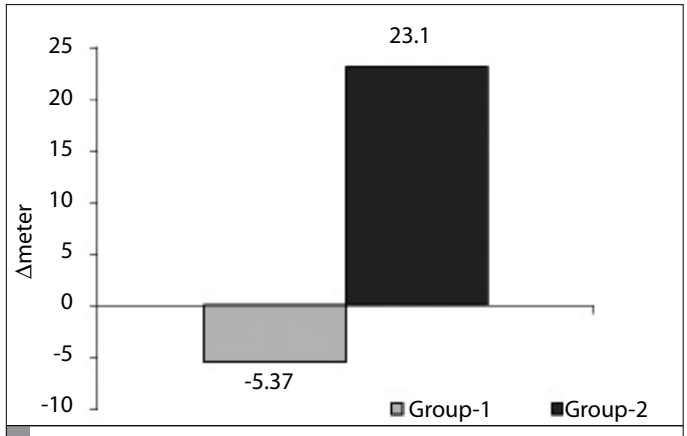

Figure 2. Changes in the values of walking distance obtained as a result of the 6-min walk test (6MWT) in both study groups (Δmeter) (p=0.018, data labels reflect the mean changes)

DISCUSSION

It is known that airway inflammation plays a role in the pathogenesis of chronic obstructive pulmonary disease. Therefore, it is aimed to treat this early inflammation in the airways via anti-inflammatory agents and to prevent the progression of disease. Recently, researchers have tried to shed light on this issue through studies conducted regarding the role of inhaled steroids in COPD treatment. In the study we performed for this purpose, it was observed that the addition of inhaled steroids to routine bronchodilator treatment did not affect pulmonary functions, but had positive effects on exercise capacity, and the quality of life.

It has been revealed in many studies that inhaled tiotropium is effective in improving lung functions and the quality of life in patients with COPD compared with a placebo (15). Moreover, according to the results of many studies, tiotropium shows an equivalent effect with long-acting β_2 agonists in many parameters, such as the rates of hospitalization and pulmonary functions and the improvement of symptoms in COPD treatment (16).

Many studies investigating the effects of inhaled corticosteroids on airway obstruction in these patients have been conducted. The results obtained from these studies are contradictory. Although some studies revealed positive effects of inhaled corticosteroids on pulmo-

nary functions, some revealed them to be ineffective. However, it was suggested in some studies that the inclusion of COPD patients with asthmatic features such as airway reversibility and allergies could contribute to this early response (17-22).

Studies including large series have recently been conducted on short- and long-term uses of inhaled steroids in stable COPD treatment. Although it was observed in EUROSCOP and Copenhagen studies that inhaled steroids did not affect FEV_1 loss, the EUROSCOP study revealed a significant superiority of the budesonide group in the evaluation of the quality of life. However, no statistically significant difference was found between the two groups with respect to exacerbations (23, 24). Moreover, the effects of inhaled fluticasone propionate on the pulmonary functions, exacerbation, and quality of life were investigated in moderate-severe COPD in an ISOLDE study; compared with the placebo group, it was demonstrated that the decrease in FEV_1 was lower by a rate of 32% and was higher in the first 3 months. In more severe cases, there was a decrease in exacerbations at the rate of 25%, which was particularly more apparent in the first year, the number of hospitalizations also decreased, and an increase in the quality of life was observed (25).

In another large-scale study, TORCH, it was shown that the use of fluticasone propionate alone or in combination with salmeterol decreased annual FEV_1 loss (26). In our study, the addition of inhaled steroids to bronchodilator treatment provided no additional benefit to respiratory functions. As stated above, in the results of previous studies examining the effects of inhaled steroids on the pulmonary functions of COPD patients, there are some contradictions. This might have resulted from dissimilarities between the patient groups. Moreover, in our study, the follow up periods of the patients were limited to 3 months.

In the literature, no studies examining the direct effects of inhaled steroids on RV and total lung capacity (TLC) in COPD patients can be found. However, in the 12-week double-blind study of John et al. (27), it was demonstrated that beclomethasone did not affect FEV_1 level in COPD patients, but decreased the RV/TLC percentage, which is an indicator of hyperinflation, from 144% to 131%. On the other hand, in our study, it was found that the use of inhaled steroids did not have significant effects on RV and TLC.

Rochester and Braun (28) found lower PImax (MIP) and PEmax (MEP) values in COPD patients than in normal patients. The decreases in PImax and in PEmax were attributed to hyperinflation and diffuse muscle weakness (low body mass index, hypokalemia, systemic steroid use, hypoxemia), respectively. In patients with COPD, the effect of inhaled corticosteroids on respiratory muscle strength is unclear. However, in a study by Jardim et al. (29), it was detected that the use of inhaled flunisolide in healthy individuals did not have an acute or clinical effect on peripheral or respiratory muscle strength. Similarly, the use of inhaled steroids was found to have no positive or negative effect on respiratory muscle strength in our study.

In patients with COPD, RAW increases because of various reasons. In a literature review, we found no study investigating the effect of inhaled steroids on RAW in COPD patients. However, in a long-term study, it was reported that a significant decrease was observed in bronchial hyperactivity and RAW values in asthma patients using low-dose (200 µg) budesonide for 3 years, GAW values increased, and thus, the occurrence of an acute attack was prevented through improved pulmonary functions (30). Our study showed that the addition of inhaled steroids to bronchodilator treatment had no significant effect on airway resistance in COPD patients. To obtain an effect, it may be necessary to lengthen the study period.

In our literature review, no study on the effects of inhaled steroids on FFM in COPD patients was encountered. However, in a study conducted on female patients diagnosed with asthmatic bronchiole and receiving steroid therapy, it was observed that systemic steroid treatment caused FFM loss, particularly in the lower extremities; however, inhaled steroids led to no change (31). In another study conducted with 64 patients with COPD, FFM loss in COPD patients was found to be associated with impaired lung functions, continuance of smoking, and frequent exacerbations; a decrease in FFM was observed in patients continuing to use systemic steroids (32). On the other hand, in our study, no statistically significant difference was observed in terms of FFM in patients using inhaled steroids for 3 months compared with the control group. Despite the short study period, it can be concluded that inhaled steroids did not have any negative effect on FFM because their systemic absorptions were low according to the results, contrary to systemic steroids.

In cases with COPD, the quality of life is impaired in time. The effects of regular treatment with inhaled corticosteroids on the quality of life are controversial. In a randomized controlled study conducted by Bourbeau et al. (33), patients were randomly divided into two groups after having received oral prednisolone therapy for 2 weeks. One group was administered a placebo for 6 months, and the other group was administered 1600 µg budesonide a day. No significant difference was observed with respect to the quality of life. In addition, Lung Health Study II demonstrated that inhaled corticosteroids did not have any effect on the quality of life measurements (34).

Contrary to these studies, it was reported in many studies that the addition of inhaled steroids to a long-acting bronchodilator agent improved the quality of life much more than the separate use of these drugs (35-39). In long-term studies conducted with large series, which are mentioned above, it was revealed that the use of inhaled steroids affected the quality of life positively in patients with COPD (26, 27). Similarly, our study showed that the addition of inhaled steroids to long-acting bronchodilator therapy affected the quality of life questionnaire scores in a positive way. The occurrence of an improvement in the quality of life without any recovery in pulmonary functions shows that the respiration survey reflects some other features besides airway obstruction.

The evaluation of exercise capacity, in COPD patients is very important. In the literature, there are contradictory results related to the effect of inhaled steroids on 6MWT. No statistically significant difference was found between the use of inhaled steroids and a placebo and 6MWT results in a group of patients with severe irreversible airway obstruction (40). In another study conducted by Yıldırım (41), a group of COPD patients receiving long-acting bronchodilator therapy was compared to another group of COPD patients receiving inhaled steroids+long-acting bronchodilator therapy. The increase in walking distance at the end of 6 weeks was found to be significantly higher in the group using inhaled steroids. In a similar study

by Paggiaro et al. (22), the walking distance was reported to be longer in patients administered fluticasone propionate than in patients administered a placebo. As in the last two studies mentioned above, a statistically significant increase in walking distance was observed in the patient group using budesonide+tiotropium compared with those using only tiotropium in our study; it was thought that this might be associated with the reduction in the patients' daily symptoms and subjective complaints.

A meta-analysis conducted recently revealed that the combination of inhaled corticosteroids and long-acting β_2 agonists improved pulmonary functions and the quality of life scores much more than a single long-acting β_2 agonist agent (42). However, there are a few studies comparing the efficiencies of inhaled corticosteroids/long-acting anticholinergic combination and a single long-acting anticholinergic agent in patients with COPD. In one of these literature studies, it was reported that an improvement was observed in the quality of life and exercise capacity, of the patients after 6 weeks of treatment, and changes in the FEV_1 values were found to be insignificant compared with the group using single tiotropium. Moreover, it was suggested in this study that the efficiency of budesonide+tiotropium could be increased when used at a low dose (39).

CONCLUSION

Our study revealed that the addition of inhaled steroids to tiotropium, which is a long-acting inhaled anticholinergic, did not cause significant effects on pulmonary functions, but positively affected the quality of life and exercise capacity. This study is important because it is one of only a few studies using tiotropium and an inhaled steroid agent in the literature. However, we must accept that it has some limitations. Because our study was conducted on a small patient group in a single center, our findings cannot be generalized for the whole population. Moreover, the study period is shorter than many comprehensive studies. Therefore, it should be supported by further multi-centered and long-time studies.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Fırat University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: All authors contributed equally during the preparation of this manuscript.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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