

Cost-Effectiveness Analysis of Budesonide/Formoterol and Fluticasone/Salmeterol for Stable Chronic Obstructive Lung Disease

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Cost-Effectiveness Analysis of Budesonide/Formoterol and Fluticasone/Salmeterol for Stable Chronic Obstructive Lung Disease

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is one of the four largest types of non-communicable diseases in the world, requiring long-term and routine treatment. Treatment with the inhalation route is in the form of a Dry-Powder Inhaler (DPI) which is easy to use and carry. Combination of corticosteroid and Long-acting Beta-2 Agonist (LABA) in the form of DPI available in Indonesia are budesonide/formoterol and salmeterol/fluticasone. The purpose was to identify therapy was more cost-effective between budesonide/formoterol than fluticasone/salmeterol in clinical symptoms using the CAT value and lung function in FEV1/FVC (Forced Expiratory Volume in First Seconds/ Forced Vital Capacity) ratio.

Methods: This research study was pre-post design with cost-effectiveness analysis, in outpatient COPD patients in a hospital in Gresik Regency, from October 2019 to January 2020. There were two outcomes of respondents in this study, namely lung function seen from the value of FEV1, and clinical symptoms seen from the value of CAT. The study used hospital perspective.

Results: There were 38 respondents involved. Fluticasone/salmeterol therapy was more effective than the budesonide/formoterol group in improving FEV1/FVC ratio, while budesonide/formoterol was more effective than the fluticasone/salmeterol group in improving clinical symptoms by CAT assessment. The ACER value of lung function between the fluticasone/salmeterol group (IDR.176.465/Liter) was lower than that of budesonide/formoterol (IDR.296.832/Liter). And the ACER clinical symptoms value between the fluticasone/salmeterol group (IDR.16,283/score) was smaller than that of budesonide/formoterol (IDR.17,340/score).

Conclusion: Fluticasone/salmeterol was more cost-effective than budesonide/formoterol in improving lung function. Meanwhile, for clinical symptoms, fluticasone/salmeterol was trade-off with budesonide/formoterol.

Keywords: COPD; FEV1/FVC ratio; inhaled corticosteroid; Long-acting Beta-2 Agonist

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an inflammatory response due to noxious substances or gases. COPD is one of the respiratory system diseases that is the cause of high morbidity and mortality in the world.¹ COPD comorbidities will result in cardiovascular disease, bronchial cancer,

lung infections, thromboembolic disorders, the presence of asthma, hypertension, osteoporosis, joint pain, depression and anxiety.²

Respiratory diseases such as asthma and COPD require long-term and regular treatment. The route of drug administration is generally by inhalation because the effect is directly on the target organ in the lungs and causes side effects that tend to be smaller than other routes, because the drug works topically so it does not require larger doses as in



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systemic administration. One of the maintenance treatments for COPD is a combination of LABA (long-acting beta-2 agonist) and corticosteroid in one package.^{3,4}

Inhalers were an important drug delivery device in COPD because they enter the respiratory system directly and have fewer side effects.⁵ The DPI type inhaler was relatively easier than MDI because it does not require coordination between the cooler and the cooler. Dry-powder inhaler (DPI) is in the form of a fine powder that acts directly on the respiratory tract of the bronchioles so that the effect of the drug can be faster and side effects that often appear in systemic treatment.^{6,7} The combination of ICS and LABA in the form of DPI in Indonesia was combination of budesonide/formoterol and salmeterol/fluticasone.

The total direct cost of COPD diagnosis-treatment for each year from 2012 to 2016 in Turkey. The direct costs of the patients who were admitted to step 1, step 2, and step 3 health care centers between 2012 and 2016 increased by 41%; the increase was 60% and 24%, for inpatient and outpatient groups respectively. In the year 2016, the direct total cost was 1003TL (\$332) per patient. For the inpatient group, the mean number of hospitalizations per patient, mean number of hospitalization days, and the mean cost per hospitalization were 0.4, 6.5, and 1926TL (\$637), respectively.⁸ In Indonesia, a previous study on COPD inpatients at Sukoharjo General Hospital,⁹ showed that the average cost of COPD for severe severity was IDR.1,349,671 for the three types of financing, for the very severe level, the types of general financing, JAMKESMAS (*Jaminan Kesehatan Masyarakat*/ Community Health insurance) and JAMKESDA (*Program Jaminan Kesehatan Masyarakat Daerah*/ Regional Public Health Insurance Program) were IDR.1,051,955.5, ID.1,815,859 and IDR. 1,589,706.5. The results showed that the average real cost of COPD treatment was lower and significantly different from the cost of the INA-CBG package. While the cost of outpatient treatment had not been found.

Based on the results of the above study, it was

more directed to the cost of therapy in COPD patients, but not many studies had examined the effectiveness compared to the costs incurred by patients with COPD and family.^{10,11} The implementation of these studies can give clinicians confidence in providing therapy rationally (effectively and efficiently) and reduce costs incurred by patients or their families.^{12,13} This method of cost-effectiveness analysis was the simplest, easiest and most applicable method in its application. The most appropriate pharmacoeconomic method for analysis was CEA (cost-effectiveness analysis) because of comparing therapeutic outcomes that can be measured in the same unit and costs are measured in currency.¹⁴ CEA was most often used for economic analysis of health economics and is often used in drug therapy.^{15,16} Outcomes of therapy in CEA can be investigated with the COPD Assessment Test (CAT) and spirometry.^{17,18,19,20}

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends a multidimensional assessment called the Combined COPD assessment that combines the degree of obstruction or a history of acute exacerbations and an assessment of the patient's symptoms/impacts.²¹ The spirometry classification assessment alone often does not represent the impact of COPD on the patient's quality of life.^{22,23} The quantitative assessment of symptoms, represented by the CAT, was aimed at evaluating the health impact on sufferers. This instrument has been validated in several European countries as well as the United States and has a good correlation with the more complex St George Respiratory Questionnaire (SGRQ). The CAT which has been translated into 61 languages and in Asia has been validated together, including in Indonesia. This test contains 8 questions with a score between 0-5 so that the total score will range between 0 and 40. The higher a person's score, the higher the impact of COPD on the patient's health status. Filling out the questionnaire in the CAT is done directly by the patient.^{24,25,26,27}

Many parameters and methods are available for the purposes of assessing lung function. Impaired lung function can be tested using spirometry, the

value used to detect the disorder is characterized by a decrease in Forced Vital Capacity (FVC) and Forced Expiratory Volume in First Seconds (FEV1). Spirometry is an examination technique to determine lung function. The patient is asked to blow as hard as possible through a device that is connected to a spirometer machine which will automatically calculate the force, velocity and volume of air expelled, so that the condition of the patient's lung function can be known.^{28,29,30} The purpose of this study was to find out which therapy was more cost effective between budesonide/formoterol than fluticasone/salmeterol in terms of clinical symptoms using the CAT questionnaire and spirometry (FEV1/FVC ratio).

METHODS

Research Design

The research design was prospective observational study with pre-post design by conducting comparative study between budesonide/formoterol versus fluticasone/salmeterol in outpatient COPD patients in a hospital in Gresik Regency, from October 2019 to January 2020. The study used hospital perspective. And had received a certificate of ethics from the University of Surabaya No. 108/KE/XI/2019.

Research Variable

The effectiveness of budesonide/formoterol and fluticasone/salmeterol with FEV1/FVC ratio, CAT questionnaire, and the incidence of drug side effects. Side effects were adverse drug reaction (ADR) and monitored for 3 months, namely oropharyngeal candidiasis (signs: white patches or plaques on the tongue and mucous membranes of the mouth) and pharyngitis (signs: sore throat, difficulty swallowing). The costs used were direct medical costs, including drugs, medical service, physical service, laboratory service, hospital service, and costs incurred to treat the side effects of COPD drugs that arise. The cost of health services listed on the patient's payment receipt.

Population and Sample

The population was all patients who went to

the pulmonary polyclinic of hospital X in Gresik between October 2019 and January 2020. The samples were all COPD patients who had used budesonide/formoterol or fluticasone/salmeterol therapy for 3 months, with age criteria >40 years, and willing to be involved in the research for 3 months. The sampling method was carried out using purposive sampling method.

Data Collection and Analysis Method

The instruments used in the study were: CAT (COPD Assessment Test), for the assessment of lung function. Consists of 8 questions with a score of 0-5 per question (Total scores ranged between 0 and 40). The greater a person's score, the higher the impact of COPD on the patient's health status. Assessment of lung function/physiology using spirometry, the value used to detect impaired lung function/physiology is marked by a decrease in Forced Expiratory Volume in First Seconds (FEV1) and Forced Vital Capacity (FVC). Monitoring therapy for 3 months on the appearance of side effects of oropharyngeal candidiasis and pharyngitis with the Naranjo Scale. Pharmacoeconomic analysis by calculating ACER (Average Cost Effectiveness Ratio) by calculating the ratio of total cost to outcome, lung function (FEV1/FVC ratio) and clinical symptoms (CAT). Then proceed with a different test to see the outcome, namely FEV1/FVC ratio with t-test or Mann-Whitney test (ratio data scale) and CAT value with chi-square test (ordinal data scale).

RESULTS

Characteristics of Respondents

The results of data collection on COPD patients receiving budesonide/formoterol and fluticasone/salmeterol therapy at the pulmonary polyclinic of X Hospital in Gresik from October 2019 to January 2020. There were 38 respondents involved in the study.

From **Table 1**, it can be seen that the characteristics of respondents based on gender, respondents were more male (20 of 38) than female (18 of 38). Characteristics of age, the largest number of respondents were 61-70 years old (19 of 38). In

terms of type of work, more respondents are not working or have retired. Most respondents are those who have quit smoking (20 of 38). As for the characteristics of the incidence of drug side effects, neither side effects were found at all.

Outcome Profile: Lung Function Values and Symptoms

There were two outcomes of respondents in this study, namely lung function seen from the value of FEV1 and clinical symptoms seen from the value of CAT which was shown in **Table 2**. Pulmonary function in both the budesonide/formoterol and fluticasone/salmeterol groups by looking at the FEV1/FVC obtained Pvalues=0.007 explained that there was a significant difference between lung function in the two groups budesonide/formoterol and fluticasone/salmeterol. Meanwhile, for clinical symptoms by looking at the patient's CAT score, Pvalues=0.880 explained that there was no significant difference between the clinical symptoms of budesonide/formoterol and fluticasone/salmeterol.

In this study, the effectiveness of treatment was assessed based on a comparison of lung function and COPD symptoms. The total FEV1/FVC ratio in the fluticasone/salmeterol group (28.42 liters) was greater than in the budesonide/formoterol group (20.33 liters). The average FEV1/FVC ratio in the fluticasone/salmeterol group (1.58 liters) was greater than that in the budesonide/formoterol group (1.02 liters). The total CAT score in the budesonide/formoterol group (348) was greater than that in the fluticasone/salmeterol group (308). The mean FEV1/FVC ratio in the budesonide/formoterol group (17.4) was greater than in the fluticasone/salmeterol group (17.11). Fluticasone/salmeterol therapy was more effective than the budesonide/formoterol group in improving lung function (FEV1/FVC ratio), while budesonide/formoterol was more effective than the fluticasone/salmeterol group in improving clinical symptoms by CAT assessment (**Table 2**).

Mann-Whitney test on the effectiveness of the value of FEV1/FVC ratio, it was known that the value of Asymp. Sig. (2-tailed) of 0.007 was smaller than the probability (0.05.) Thus it can be said that there

was a significant difference between the use of fluticasone/salmeterol and budesonide/formoterol group (**Table 2** and **Figure 1**).

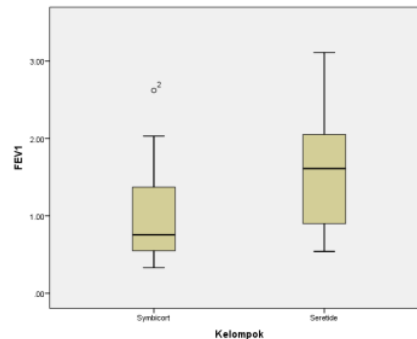


Figure 1. Test of Differences in Effectiveness of FEV1/FVC Ratio with Ratio Scale

There were 38 data that are all processed (no data is missing or missing), so the level of validity was 100%. The cross table that contained the relationship between drug therapy variables and CAT values. With ordinal data scale, fluticasone/salmeterol therapy (n:18) consisted of 5 people with mild group and 13 people with moderate-severe level. And budesonide/formoterol therapy (n:20) consisted of 6 people with mild group and 14 people with moderate-severe level. In the Pearson Chi-Square section, the Asimp.Sig value was 0.880. Because the Asimp.Sig value was 0.880>0.05, it can be concluded that there was no significant relationship between the drug and the CAT value. This meant that budesonide/formoterol and fluticasone/salmeterol have no correlation with CAT values (**Figure 2**).

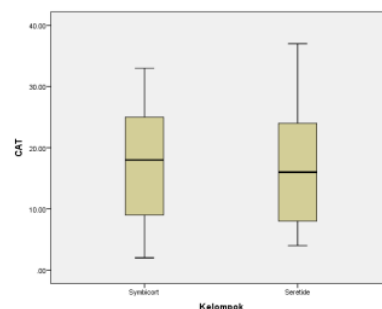


Figure 2. Test of Differences in Effectiveness of Clinical Symptoms Ratio with Ordinal Scale

Cost Profile

It was known that the costs for the two groups resulted in a $P\text{value}=0.069>0.05$ explaining that there was an insignificant difference between the costs of budesonide/formoterol and fluticasone/salmeterol. The costs used are direct medical costs, including drugs, medical service, physical service, laboratory service, and hospital service. Drug costs were the largest of the total costs. Average total cost in the budesonide/formoterol group (IDR. 301,730) was greater than in the fluticasone/salmeterol group (IDR. 278,604) (Table 3).

Cost-Effectiveness Analysis Calculation

The ACER value of lung function between the fluticasone/salmeterol group (IDR. 176.465/Liter) was lower than that of budesonide/formoterol (IDR. 296.832/Liter). And the ACER clinical symptoms value between the fluticasone/salmeterol group (IDR. 16,283/score) was smaller than that of budesonide/formoterol (IDR. 17,340/score) (Table 4). It can be concluded that fluticasone/salmeterol was more cost-effective than budesonide/formoterol in improving lung function (FEV1/FVC ratio). Meanwhile, for clinical symptoms, fluticasone/salmeterol was a trade-off with budesonide/formoterol.

Table 1. Characteristics of Respondents

Characteristics:		Group:		Pvalue
		Budesonide/formoterol (n:20)	Fluticasone/salmeterol (n:18)	
Gender	Man	14	17	0.052
	Female	6	1	
Age (years)	40-50	1	0	0.526
	51-60	7	4	
	61-70	8	11	
	71-80	3	3	
	>80	1	0	
Job	Civil servant	0	1	0.441
	General employees	3	1	
	Self-employed	4	6	
	Other	13	10	
Smoking History	Quit smoking	7	13	0.005
	Smoke	2	0	
	Did not smoke	11	5	
Drug Side Effects	Exist	0	0	1.000
	No	20	18	

*) There was difference between the two groups

Table 2. Respondent Outcome Profile

Outcome:		Group:		Pvalue
		Budesonide/formoterol (n:20)	Fluticasone/salmeterol (n:18)	
Lung Function (Liters)	Total FEV1/FVC ratio	20.33	28.42	0.007
	Average FEV1/FVC ratio	1.02	1.58	
Clinical Symptoms	Total CAT	348	308	0.880
	Average	17.4	17.11	

Table 3. Cost Profile

Cost (in rupiah)		Group:		Pvalue
		Budesonide/formoterol (n:20)	Fluticasone/salmeterol (n:18)	
Direct medical cost (IDR)	Drug cost	154,424	142,737	0.069
	Medical service	24,094	12,655	
	Physical service	40,000	40,000	
	Laboratory service	58,212	58,212	
	Hospital service	25,000	25,000	
Average total cost (IDR)		301,730	278,604	

Table 4. Calculation Results of Cost-Effectiveness Analysis

CEA Calculation	Group:			
	Budesonide/formoterol (n:20)		Fluticasone/salmeterol (n:18)	
ACER lung function (IDR/Liter)	IDR	296,832 /Liter	IDR	176,465/Liter
ACER clinical symptoms	IDR	17,340/score	IDR	16,283/ score

DISCUSSION

There were more male respondents than female (Table 1). COPD patients were more common in men. COPD was a condition in which the lung airways become inflamed and narrowed and the air sacs became damaged. It was a major cause of morbidity and mortality around the globe.³¹ Smoking cessation was particularly important in male COPD patients because of much higher proportion of smokers and are more likely to have cough and sputum.³² These findings signify the importance of identifying and implementing gender-tailored symptom management strategies to relieve symptom burden in COPD patients to enhance their quality of life.³³

Age was often listed as a risk factor for COPD, but it was not clear whether healthy aging affects COPD or whether age reflects the cumulative amount of exposure over a lifetime. Patients with COPD at an early age or who had a strong relative history of COPD should be screened for risk for AAT deficiency, and if AAT concentrations are low, genetic (DNA) testing may be necessary.³⁴ The highest age range was 61-70 years (Table 1), for elderly. COPD morbidity increases with age. Although the development of comorbid COPD can occur at a younger age. COPD was also more common at the age of >40 years than <40 years and was more common in males than females. Most of the increase in COPD mortality was due to the growing epidemic of smoking, decreased mortality from other common causes of death such as ischemic heart disease, infectious diseases.^{31,35,36,37} In developing countries, deaths from COPD are also increasing, this was associated with an increase in the number of people who consume cigarettes. COPD had been considered as a disease affecting the elderly, with a preponderance in male smokers.^{36,37,38}

In the budesonide/formoterol group, most did not smoke (11 of 20). While in the fluticasone/salmeterol group, most of them had stopped smoking 13 of 18). A person who quits smoking showed an improvement in lung function in the future. This was consistent with a previous study that increased FEV1 in the first 6 and 12 weeks, in COPD patients after smoking cessation. In addition, both COPD patients and those with normal baseline respiratory function who quit smoking showed a significant increase in pulmonary transfer factor values for carbon monoxide from 6 weeks to 1 year of follow-up.³⁹ Side effects did not appear in all respondents. ICS (inhaled corticosteroid) together with LABA (long acting beta-2-agonist) reduced the risk of exacerbations in COPD. ICS, however, do have side effects where an increased risk of pneumonia is probably the most clinically important one.⁴⁰

COPD is diagnosed through spirometry, which can detect COPD even in people who do not yet have symptoms.⁴¹ Currently, there is no cure for COPD, although available therapy can improve symptoms, quality of life, and prevent acute worsening of the disease.³¹ Pulmonary function in both groups of budesonide/formoterol and fluticasone/salmeterol by looking at the value of FEV1/FVC ratio obtained P=0.007 explained that there was a significant difference between lung function in the two groups. As for clinical symptoms, by looking at the CAT score obtained P=0.880, it explained that there was no significant difference between clinical symptoms and the CAT value between budesonide/formoterol and fluticasone/salmeterol. Fluticasone/salmeterol was more cost-effective than budesonide/formoterol in improving lung function (FEV1/FVC ratio). Meanwhile, for clinical symptoms, fluticasone/salmeterol was a tradeoff with budesonide/formoterol (Table 4).

ACER of lung function between the fluticasone/salmeterol group was lower than that of budesonide/formoterol, and the ACER of clinical symptoms between the fluticasone/salmeterol group was smaller than that of budesonide/formoterol. ACER represents the average cost required to obtain clinical results. Based on previous research by Tamminen et al. to explore the cost-effectiveness of budesonide/formoterol maintenance and reliever therapy as compared to fixed combination therapies (budesonide/formoterol and salmeterol/fluticasone) with terbutaline as needed in the treatment of asthma in Finland. Budesonide/formoterol maintenance and reliever therapy may be considered in the treatment of moderate-to-severe asthma instead of conventional treatment with combination products in view of its good clinical efficacy and a high probability of cost-effectiveness in the Finnish setting.⁴²

While other studies that tested the effectiveness, by Robert et al., of the 6770 patients (3385 budesonide/formoterol and 3385 fluticasone/salmeterol), fewer budesonide/formoterol patients had claims for short-acting beta agonists (SABA) (34.7% vs 39.5%; $p < 0.001$) and ipratropium (7.8% vs 9.8%, $p < 0.005$) than fluticasone/salmeterol patients, but no substantial differences were seen in other clinical outcomes including tiotropium or nebulized SABA claims, COPD-related outpatient visits, or exacerbation events. There were no significant differences in total COPD-related medical costs in the 6-month period after initiation of combination therapy.⁴³

LIMITATION

The limitations of this study were the presence of several factors that can affect pulmonary function scores and clinical symptoms other than inhaler therapy used, such as the severity of COPD, and other therapies used for COPD or other therapies.

CONCLUSION

Fluticasone/salmeterol therapy was more cost effective than budesonide/formoterol in improving lung function in FEV1/FVC ratio. And

fluticasone/salmeterol was a tradeoff with budesonide/formoterol in clinical symptoms in ACT score. No drug side effects were found between fluticasone/salmeterol and budesonide/formoterol.

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Conflict of Interest

There is no conflict of interest.

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