Original Article

The Effectiveness Comparison of Salmeterol/Fluticasone Propionate and Formoterol Fumarate/Budesonide on the Level of Asthma Control in Moderate Persistent Asthma

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Abstract

Background: Asthma is a prevalent chronic respiratory disease, affecting approximately 1–18% of the population worldwide. Despite its high prevalence, a substantial proportion of patients have partially controlled asthma, and limited data on the level of asthma control remain a significant concern. This study aimed to compare the effectiveness of salmeterol/fluticasone propionate and formoterol fumarate/budesonide in achieving asthma control levels according to the ACQ-GINA criteria.

Methods: A retrospective cohort study was conducted using 61 medical records from January 2017 to December 2019. Patients with moderate persistent asthma received either salmeterol/fluticasone propionate or formoterol fumarate/budesonide for at least three months. Statistical analysis was performed using Fisher's exact test.

Results: A total of 61 patients were included. Most patients had partially controlled asthma (70.5%), followed by well-controlled (19.7%) and uncontrolled asthma (9.8%). No statistically significant difference in asthma control was observed between the two treatment groups (*P*=0.057).

Conclusion: Within the limitations of this retrospective cohort study, no statistically significant difference in asthma control was observed between salmeterol/fluticasone propionate and formoterol fumarate/budesonide.

Keywords: asthma control level, effectiveness comparison, formoterol fumarate/budesonide, moderate persistent asthma, salmeterol/fluticasone propionate

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INTRODUCTION

Asthma is a prevalent chronic respiratory disorder, affecting an estimated 1–18% of the population worldwide. The disease is characterized by recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing, with variable airflow obstruction.[1] In the United States, the prevalence of asthma in 2018 was approximately 24 million individuals, representing 7.7% of the total population, highlighting its substantial contribution to global respiratory morbidity and mortality.[2] In Asia, the prevalence of asthma is less clear, but a 2014 journal review estimated it to be less than 5% of the adult population.[3]

Meanwhile, in Indonesia, according to the 2018 Basic Health Research (RISKESDAS) by the Ministry of Health, the asthma prevalence was 2.4%, with the highest age group being over 75 years (5.1%) and an overall relapse rate of 57.5%.[4] According to data reported by the Centers for Disease Control and Prevention in 2019, 60.1% of adults with asthma in the United States were classified as having uncontrolled asthma, with a higher prevalence observed among women (63.1%) compared with men (54.7%).[5] A 2013 cross-sectional study in the Asia-Pacific region with 3630 respondents found that only 7.6% had controlled asthma, 29.8% had uncontrolled asthma, and 62.6% had partially controlled asthma.[6]

Objective assessment of asthma control requires tools like the Global Initiative for Asthma (GINA) guidelines, which provide simple screening tools widely used across all ages in primary care.[1] These include the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ).[7] Asthma control must pay attention to symptom management, and factors such as poor adherence, incorrect inhaler use, socioeconomic and psychological factors, environmental exposure, smoking, and comorbidities can lead to poor asthma control.[1] Factors such as age, a history of atopy to multiple allergens, severe asthma, and allergic rhinitis are significant risk factors for uncontrolled asthma.[8]

According to the Global Initiative for Asthma (GINA), combination therapy with an inhaled corticosteroid and a long-acting β_2-agonist (ICS/LABA) is recommended for asthma treatment using the maintenance and reliever therapy (MART) approach, particularly for adolescents and adults requiring Step 3 or Step 4 management.[1] Therapy such as Formoterol/budesonide has a rapid onset of action due to its moderately lipophilic properties and is administered twice daily as fixed maintenance therapy. While salmeterol in the fluticasone propionate/salmeterol combination has a slower onset of action and lower intrinsic efficacy and is prescribed as regular maintenance therapy twice daily, consistent with GINA recommendations.[1,9]

Both formoterol/budesonide and fluticasone propionate/salmeterol are available in dry powder inhaler (DPI) forms, which are generally easier to use than pressurized metered-dose inhalers (pMDIs). However, DPIs have limitations, such as the need for proper inhalation technique and the inability to refill the devices.[10] A 2018 multi-center study in Japan (ACQUIRE-2) revealed that 41.4% of asthma patients used ICS/LABA inhalers.[11]

Despite the high prevalence of uncontrolled and partially controlled asthma contributing significantly to healthcare costs, there is a lack of data on asthma control levels and medication usage patterns in Asia, especially regarding ICS/LABA therapy. Comparative data on the real-world effectiveness of fluticasone propionate/salmeterol and formoterol fumarate/budesonide on asthma control, especially in the Indonesian population, are currently limited.

Therefore, this observational study was conducted to compare the effectiveness of two ICS/LABA combinations on asthma control in patients with moderate persistent asthma, as defined by the Global Initiative for Asthma, at the Pulmonology Clinic of Prof. Chairuddin Panusunan Lubis Hospital, University of Sumatera Utara.[1]

METHODS

This retrospective observational analytic cohort study was conducted to compare the effectiveness of salmeterol/fluticasone propionate and formoterol fumarate/budesonide in achieving asthma control, as assessed using the Global Initiative for Asthma (GINA)–based Asthma Control Questionnaire (ACQ). The study was conducted at the pulmonary clinic of Prof. Chairuddin Panusunan Lubis USU Hospital in Medan, Indonesia, with data collection taking place from September 2023 to January 2024.

The study focused on patients with moderate persistent asthma who met the inclusion criteria: aged ≥18 years, diagnosed with moderate persistent asthma based on clinical and physical examination, and received salmeterol/fluticasone propionate or formoterol fumarate/budesonide therapy for at least three consecutive months. Moderate persistent asthma was defined in accordance with the Global Initiative for Asthma (GINA) as asthma requiring Step 3 treatment, defined by the regular use of low- to medium-dose ICS/LABA to achieve and maintain asthma control.

Exclusion criteria included diagnoses of COPD, Asthma-COPD Overlapping Syndrome (ACOS), Interstitial Lung Disease (ILD), lung cancer, cystic fibrosis, Allergic Bronchopulmonary Aspergillosis (ABPA), Eosinophilic Granulomatosis with Polyangiitis (EGPA), or active tuberculosis (TB), as well as those receiving other therapies such as immunotherapy or long-term anti-inflammatory medications.

Data were obtained from patient medical records and included demographic information (medical record number, age, gender, and education level) and disease characteristics (ICS/LABA therapy types and dosages, and asthma control assessment). The data utilized were patient medical records from January 1, 2017, to December 31, 2019. The total sampling technique was used, including all eligible patients treated at the clinic from January 1, 2017, to December 31, 2019. The sample size was 61 patients.

Variables in this study included independent variables such as ICS/LABA therapy types and dosages and demographic data such as age, gender, education level, and occupation. While the dependent variable was the asthma control level as measured by the ACQ.

Quantitative variables in this study included age (categorized as <55 years and ≥55 years), ICS/LABA therapy dosages (Salmeterol/Fluticasone Propionate 50/250 mcg and Formoterol/Budesonide 4.5/160 mcg), and asthma control levels (assessed using the ACQ, categorized as uncontrolled asthma with 3-4 "Yes" responses, partially controlled asthma with 1-2 "Yes" responses, and fully controlled asthma with 0 "Yes" responses).

Data processing involved editing for completeness and consistency, coding to quantify qualitative data, and cleaning to check data entries for errors. Data were analyzed using SPSS version 26. Univariate analysis used descriptive statistics to analyze demographic characteristics, asthma therapy types and dosages, and asthma control levels, with data presented as frequency distributions and percentages. Bivariate analysis used the Chi-Square test (or Fisher's exact test if assumptions were not met) to compare ICS/LABA therapy effectiveness on asthma control levels. Spearman's rho correlation was used to analyze relationships between demographic factors, device types, patient visits, and asthma control levels. Decision criteria included $P<0.05$ for significant differences or correlations and $P>0.05$ for no significant differences or correlations.

Measures to reduce potential bias included the use of a standardized data collection form to ensure uniform data extraction and the application of total sampling to include all eligible patients during the study period. However, potential sources of bias, such as unmeasured factors like medication adherence, inhaler technique, environmental exposures, and comorbidities that were not consistently documented in the medical records, may cause residual confounding. Furthermore, misclassification bias may be introduced by using ACQ-based assessments retrospectively.

The study received approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Sumatera Utara (No. 281/KEPK/USU/2024).

RESULTS

In this study, 61 individuals who met the inclusion and exclusion criteria were included. The demographic characteristics of the participants, including age, gender, and education level, are shown in Table 1.

Table 1. Subjects characterise

Characteristics	n	%
Age		
<55 years	39	63.9
>55 years	22	36.1
Gender		
Male	13	21.3
Female	48	78.7
Education Level		
No School/Unknown	8	13.1
Primary School	2	3.3
Secondary School (Junior and Senior)	31	50.8
Bachelor's Degree	20	32.8
Employment Status		
Unemployed	29	47.5
Employed	30	49.2
Student	2	3.3

The frequency distribution of ICS/LABA therapy usage shows that 33 individuals (54.1%) used the ICS/LABA Discs with a dosage of 50/250 mcg salmeterol/fluticasone propionate, while 28 individuals (45.9%) used the ICS/LABA Turbuhaler with a dosage of 4.5/160 mcg formoterol fumarate/budesonide.

Table 2. Comparison analysis on the effect of ICS/LABA type on asthma control levels

ICS/LABA	Asthma control status			*P*
	Uncontrolled asthma	Partially controlled	Fully controlled	
Salmeterol/fluticasone propionate	2 (6.1%)	21 (63.6%)	10 (30.3%)	0.057
Formoterol fumarate/budesonide	4 (14.3%)	22 (78.6%)	2 (19.7%)	

Furthermore, the frequency distribution of asthma control levels after ≥3 months of treatment shows the highest proportion of partially controlled asthma, with 43 individuals (70.5%). This is followed by the group with fully controlled asthma, comprising 12 individuals (19.7%), and the group with uncontrolled asthma, consisting of 6 individuals (9.8%).

The analysis on the effect of ICS/LABA type on asthma control levels was conducted using Fisher's exact test (2x3 contingency table) because both datasets are unpaired categorical data and there were 2 cells (33%) with an expected count of less than 5. The significance value obtained was *P*=0.057, indicating there is no statistically significant difference in the effectiveness of ICS/LABA salmeterol/fluticasone 50/250 mcg and ICS/LABA formoterol fumarate/budesonide 4.5/160 mcg on asthma control levels. The analysis results can be seen in Table 2.

DISCUSSION

The characteristics of the subjects showed a higher proportion of females, a high school education level, unemployment, comorbidity of hypertension, and most were using fluticasone propionate/salmeterol (with the most common dose being fluticasone/salmeterol 50/250 mcg). The higher proportion of females is consistent with a real-world study conducted by Davis et al, which analyzed US health data from 2013 to 2016 and found that 62.1% of 428 asthma patients were female.[12] The higher proportion of female patients can be related to genetic polymorphism factors, hormonal influences during puberty, such as early menarche, which can increase the risk of asthma from adolescence to adulthood, higher atopic conditions in women, and immunological factors that may be associated with increased production of IFN-gamma induced by estrogen in women.[13]

Socioeconomic conditions, such as education level and employment status, have also been reported in studies. Mulyanto et al stated that high school education and income levels tend to have similar results to this study. This is related to therapy choices and the ability and willingness of patients with asthma symptoms to seek treatment.[14]

The comparison between treatment groups did not reach statistical significance (*P*=0.057), indicating no evidence of a difference in asthma control between patients receiving salmeterol/fluticasone propionate and those treated with formoterol fumarate/budesonide. This differs from the study by Cheng et al in the REACT prospective cohort study, which observed that controlled asthma levels were achieved in the group using the budesonide/formoterol combination compared to the group using salmeterol/fluticasone, although neither group reached a clinically significant minimal important difference (MID).[15]

A different study by Kuna found that using the formoterol/budesonide combination for both reliever and maintenance doses was superior in controlling asthma and reducing the risk of emergency room treatment (exacerbation events) compared to using the salmeterol/fluticasone combination, even though both combinations showed similar improvements in lung function, asthma maintenance, and asthma-related quality of life.[16]

The GOAL (Gaining Optimal Asthma Control) study in 2004 found that the fluticasone-salmeterol combination therapy achieved better asthma control at both fully controlled and partially controlled asthma levels compared to using ICS alone (*P*<0.005).[17] A systematic review by Gibson et al reported that asthma control significantly improved with the use of ICS/LABA combination therapy compared to ICS alone, with the salmeterol ICS/LABA combination being the most used in this review. The efficacy of

adding LABA to ICS use significantly affected asthma control levels (P<0.001).[18]

On the other hand, the OPTIMA and FACET studies also revealed that the combination of budesonide and formoterol resulted in improved asthma control levels and reduced exacerbation events.[19,20] This systematic review generally indicates that using the ICS/LABA-salmeterol combination significantly affects asthma control levels. Therefore, both types of ICS/LABA-salmeterol/fluticasone propionate and formoterol fumarate/budesonide-are equally effective in influencing asthma control and are consistent with the treatment guidelines.[1] However, the use of budesonide-formoterol has advantages as both a reliever and maintenance therapy and can serve as a rescue therapy during exacerbation attacks.

LIMITATIONS

This study has several limitations. Primarily, its retrospective design prevents tracking factors influencing asthma control over time, which would require a prospective approach. Additional limitations include unequal distribution, a small sample size for each variable, the potential use of medications other than salmeterol/fluticasone propionate and formoterol fumarate/budesonide by respondents, and the lack of detailed tracking of medication adherence and proper use of inhaler devices.

CONCLUSION

This study did not demonstrate a statistically significant difference in effectiveness between salmeterol/fluticasone propionate (50/250 µg) and formoterol fumarate/budesonide (4.5/160 µg) in terms of changes in asthma control following at least three months of treatment among patients with moderate persistent asthma.

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CONFLICT OF INTEREST

All the authors declare that there are no conflicts of interest.

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