

# Investigation of the efficacy of generic and brand-name salmeterol/fluticasone combination in the management of asthma: a randomized comparative trial

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**Summary.** *Background:* Asthma is the most chronic inflammatory disease of the airways worldwide. Combination therapy with inhaled fluticasone and salmeterol is a common practice for the long-term management of asthma. Seretide<sup>®</sup> and Fluticort plus<sup>®</sup> are two available generic and brand name products of salmeterol/fluticasone. This study aimed to compare the efficacy and safety of these two drugs. *Materials and Methods:* In this randomized comparative, clinical trial, 80 asthmatic patients were allocated to Fluticort plus<sup>®</sup> (n=40) or Seretide<sup>®</sup> (n=40) for a period of 4 weeks. Patients with mild asthma were instructed to inhale one puff each 12 hours and those with moderate asthma two puffs every 12 hours. Respiratory volumes (assessed using spirometry), quality of life (assessed using St. George's Respiratory Questionnaire [SGRQ]) and control of asthmatic symptoms (assessed using asthma control test [ACT]) were evaluated at baseline and at the end of the study. *Results:* ACT score improved only in the Fluticort plus<sup>®</sup> group ( $p=0.012$ ) while it was not significantly changed in the Seretide<sup>®</sup> group ( $p=0.178$ ). In both treatment groups, FEV1, FEV1/FVC, and total as well as subscale SGRQ scores were significantly improved by the end of the study ( $p<0.05$ ). Seretide<sup>®</sup> more efficiently improved respiratory volumes and SGRQ score in comparison with Fluticort plus<sup>®</sup> ( $p<0.05$ ). *Conclusion:* Our comparative trial indicated that generic fluticasone/salmeterol product could improve respiratory volumes, quality of life but its efficacy is lower than the brand-name product. However, Fluticort plus<sup>®</sup> improved asthma control more efficiently compared with Seretide<sup>®</sup>. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** asthma, fluticasone propionate, salmeterol xinafoate, Fluticort plus<sup>®</sup>, Seretide<sup>®</sup>, generic, brand

## Introduction

Asthma is the most common chronic respiratory disease worldwide. According to WHO estimates, 255.000 people died because of asthma in 2005 and currently 235 million people have asthma. Available evidence shows that 8% of the population in the Eastern Mediterranean Region including Iran suffer from asthma and over 80% of deaths because of asthma occur in developing countries (1).

Asthma is characterized with inflammatory air-flow obstruction leading to shortness of breath, chest tightness, wheeze and coughs. Chronic airway inflammation causes airway hyper-responsiveness. This hyper-responsiveness is triggered by environmental factors such as cold air, allergens and smoking, leading to reversible obstruction (2).

Asthma is not curable but appropriate management can significantly contribute to the control of symptoms and complications, and improvement of life

quality. Bronchodilators are a major class of medications for asthma owing to their capacity to relax airway smooth muscles and causing a rapid relief. The most extensively used inhaled bronchodilators are  $\beta_2$ -adrenergic agonists that are available in short-acting (SABA e.g. salbutamol) and long-acting (LABA e.g. salmeterol) forms. Another important class of anti-asthmatic medications are anti-inflammatory agents that mitigate airway inflammation. The most commonly used anti-inflammatory drugs are inhaled corticosteroids (ICS) (3). It has been proved that combination therapy with LABAs and ICSs reduces the frequency and severity of asthmatic exacerbations, and improves long-term treatment more efficiently compared with ICS or LABAs alone (3-7). Moreover, concurrent administration has additional benefits in terms of cost and patient compliance, and has been recommended by the main available guidelines (8). Salmeterol/fluticasone is one of the most widely used combinations of this type and is FDA-approved. This combination is available in a single inhaler as a commercial brand-name (Seretide<sup>®</sup>) and generic (Fluticort plus<sup>®</sup>) products in Iran. Seretide<sup>®</sup> is marketed by GlaxoSmithKline (UK), and is more expensive than the generic product, Fluticort plus<sup>®</sup>, which is marketed by Medispray (India). With regard to the expiration of Seretide<sup>®</sup> patent in 2010, development of generic products provides an opportunity for increasing the availability of the drug, and reducing the consumer's costs. However, conducting comparative trials is a necessary step to confirm the efficacy and safety of generic products. In this study, we aimed to compare the efficacy and safety of brand-name and generic products of salmeterol/fluticasone in patients suffering from asthma.

## Material and methods

### *Subjects*

This study was designed as a pilot randomized comparative trial. Out of 120 initially asthmatic subjects referred to the Respiratory Clinic of the Baqiyatallah Hospital (Tehran, Iran), 102 subjects were selected based on inclusion and exclusion criteria and randomized to receive either 250 microgram Fluticort

plus<sup>®</sup> (n=51) or Seretide<sup>®</sup> (n=51). Each puff of Fluticort plus<sup>®</sup> or Seretide<sup>®</sup> inhaler contains 25 micrograms of salmeterol and 250 microgram of fluticasone. Inclusion criteria were age between 30 and 70 yrs, diagnosis of mild to moderate asthma (according to clinical symptoms and spirometry) (9), no need for hospitalization, not being under concurrent treatment with other medications including  $\beta_2$  agonists and corticosteroids, and absence of Fluticort plus<sup>®</sup> or Seretide<sup>®</sup> contraindication. Exclusion criteria were history of systemic diseases, or cigarette smoking. Also, not consuming the allocated drug for more than 48 hours was considered as a criterion for being considered as "drop out". Each patient was aware of the type of drug he/she was receiving during the study. The study protocol was approved by the Ethics committee of the Baqiyatallah University of Medical Sciences and written informed consent was obtained from the participants.

### *Treatment*

Patients with mild asthma were instructed to inhale one puff each 12 hours and those with moderate asthma two puffs every 12 hours. Treatment duration in both groups was 4 weeks. During the study, treatment of patients in both groups was according to the Global Strategy for Asthma Management (GINA) guideline (10).

### *Evaluation*

Pulmonary function, control of symptoms and quality of life were evaluated at baseline and after 4 weeks of treatment in both groups. To assess pulmonary function, forced expiratory volume in the first second (FEV<sub>1</sub>), forced vital capacity (FVC), and FEV<sub>1</sub>/FVC ratio were measured using a Vmax20 spirometer (Chest Co., Italy). The spirometer was calibrated using a device provided by the manufacturer.

To assess asthma control, asthma control test (ACT) was performed. ACT is a quick numerical test for asthmatic patients 12 years and older. Its validity and reliability has been approved in different populations (11-14). The test includes 5 questions which ask how often the patient has symptoms, how often has

used rescue inhaler or nebulizer, how much of the time asthma kept the patient from getting as much done at work, school or home, and how the patient rates his/her asthma control during the past 4 weeks. A total score of 19 or less out of 25 demonstrates lack of proper control of asthma (15).

Quality of life was evaluated using St. George's Respiratory Questionnaire (SGRQ). Patients answered SGRQ (after receiving instructions about how to fill the questionnaire) in a calm place independently, in the presence of an observer. SGRQ has 76 items categorized in three subscales: "symptoms" subscale which asks about respiratory symptoms, their frequency and severity; "activity" subscale which asks about activities that cause or are limited by dyspnea and "impacts" subscale which asks about social functioning and psychosocial disorders due to lung disease. The overall score ranges between 0 to 100, and higher scores indicate a more severe impairment. SGRQ has been reported to be a sensitive, repeatable and numerical tool for evaluation of a range of disorders affecting quality of life in patients with respiratory diseases (16).

#### *Statistical analysis*

Data were analyzed using the SPSS software, version 18.0. Within-group comparisons were made using paired samples *t*-test (for normally distributed data) or Wilcoxon signed-ranks test (for non-normally distributed data). Comparisons of baseline and post-treatment values between the study groups was carried out using independent samples *t*-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data). Comparison of categorical variables between the two groups was made using the Fisher's exact test. A two-sided *p*-value of <0.05 was considered as statistically significant.

## **Results**

### *Flow of participants*

Out of the 102 randomized asthmatic patients, 80 (40 in each group) completed the study. The reasons

for drop outs were nasal dryness (4 subjects in the Fluticort plus<sup>®</sup> and 3 in the Seretide<sup>®</sup> group) and non-compliance with the study medications (7 subjects in the Fluticort plus<sup>®</sup> and 8 in the Seretide<sup>®</sup> group) (Figure 1). The number of drop-outs was not significantly different between the study groups ( $p>0.05$ ). Study groups were statistically comparable regarding age, gender, weight and disease duration (Table 1).

### *Spirometry*

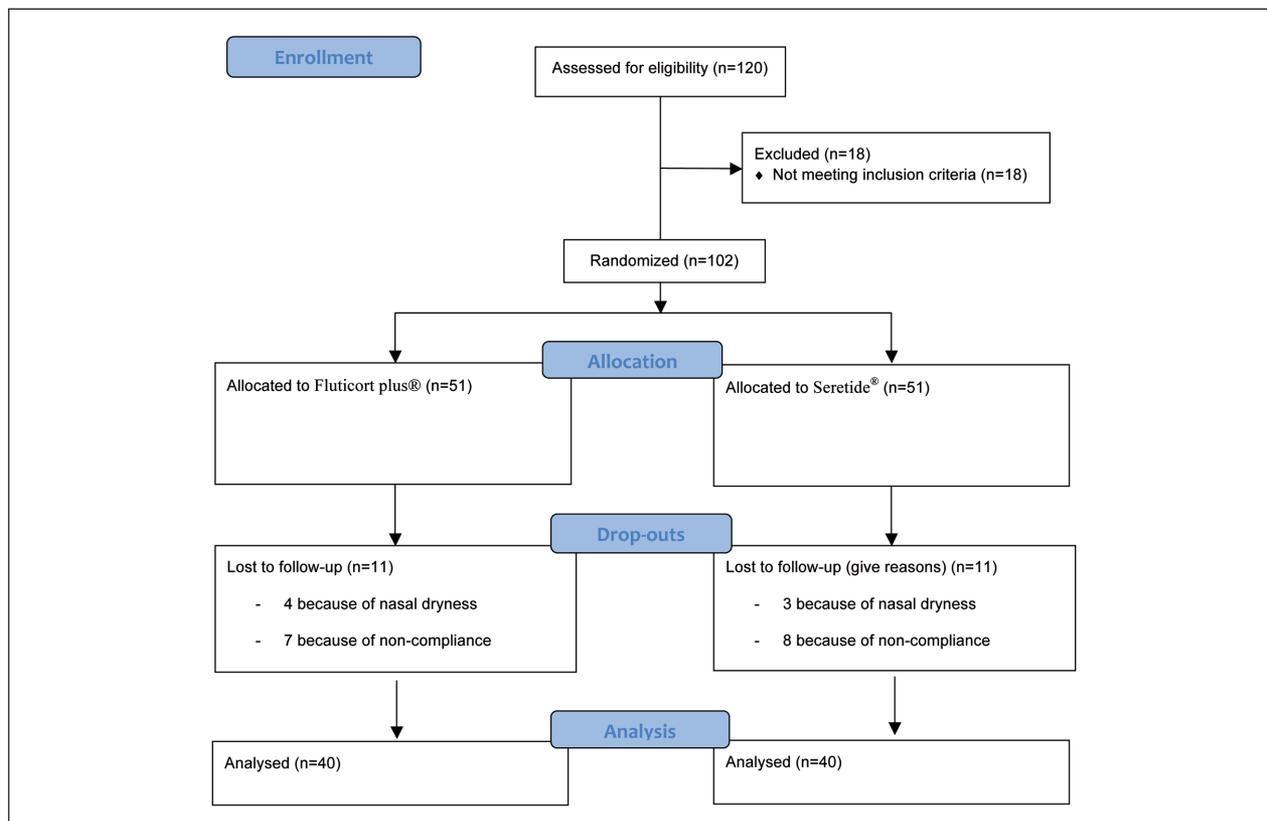
All three measured spirometric indices namely FEV1 ( $p<0.001$  in both groups), FVC ( $p=0.034$  in the Fluticort plus<sup>®</sup> and  $p<0.001$  in the Seretide<sup>®</sup> group) and FEV1/FVC ( $p<0.001$  in both groups) were significantly increased following 4-week treatment with either of the study medications. Between group comparisons revealed that although FEV1 ( $p=0.306$ ) and FEV1/FVC ratio ( $p=0.212$ ) were comparable between the groups at baseline, FVC was higher in the Fluticort plus<sup>®</sup> group ( $p=0.001$ ). On-treatment comparisons showed significantly higher values of FEV1 ( $p=0.029$ ) and FEV1/FVC ( $p=0.004$ ) in the Seretide<sup>®</sup> versus Fluticort plus<sup>®</sup> group, while FVC was comparable between the groups ( $p=0.068$ ) (Table 2).

### *ACT*

As shown in Table 3, mean ACT score was significantly increased by the end of trial in the Fluticort plus<sup>®</sup> ( $p=0.012$ ) but not Seretide<sup>®</sup> group. Neither baseline ( $p=0.356$ ) nor on-treatment scores ( $p=0.187$ ) were significantly different between Fluticort plus<sup>®</sup> and Seretide<sup>®</sup> groups ( $p>0.05$ ).

### *SGRQ*

Total and subscale SGRQ scores were lower in the Fluticort plus<sup>®</sup> group at baseline, while on-treatment scores were higher compared with the Seretide<sup>®</sup> group. In both study groups, 4 weeks of treatment resulted in a significant improvement in the quality of life according to both total SGRQ score and subscale scores of symptoms, impact and activity (Table 3). The only exception was a significant increase in the impact subscale score in Fluticort plus<sup>®</sup> group ( $p<0.001$ ).



**Figure 1.** Flow diagram

**Table 1.** Baseline characteristics of the study groups

Characteristics	Fluticort plus®	Seretide®	<i>p</i> -value
Age (yrs)	47.87±11.35	48.35±10.55	0.847
Female (n)	21	19	0.823
Weight (Kg)	72.35±18.3	73.8±6.10	0.636
Height (cm)	167.25±10.27	173.3±7.15	0.003
Disease duration (yrs)	4.5±1.76	3.92±1.88	0.164

Values are expressed as mean ± SD or number.

#### Adverse events

No severe adverse event was reported in either of the study groups during the trial. There were 4 reports of nasal dryness in the Fluticort plus® and 3 in the Seretide® group. Overall, neither the frequency of reported adverse events nor the number of non-compliant subjects and drop-outs was significantly different between Fluticort plus® and Seretide® groups ( $p > 0.05$ ).

#### Discussion

Replacement of brand-name and generic drugs is a viable strategy to reduce the rising healthcare costs. In addition to the observation of standards in terms of content (active pharmaceutical ingredient and excipients), labeling and manufacturing, the efficacy, safety and quality of a generic drug must be equal to those of the brand-name drug in order to allow a bioequivalence judgment (17, 18). The motivation to reduce treatment costs through prescription of generic drugs has made healthcare systems in many countries, including Iran, to adopt generic policy (19-21). Bioequivalence of a generic drug with its brand-name counterpart must be demonstrated by appropriately designed randomized controlled trials and bioavailability studies to evaluate the non-inferiority of the generic product with regard to its efficacy and safety (22-29).

Asthma is the most common chronic respiratory disease worldwide and 80% of deaths due to asthma

**Table 2.** Respiratory volumes before and after treatment with study drugs

Variables	Fluticort plus®			Seretide®			p-value <sup>1</sup>	p-value <sup>2</sup>
	Mean±SD		p-value	Mean±SD		p-value		
	Pre	Post		Pre	Post			
FEV1	71.77±6.06	85.15±8.6	<0.001	70.35±6.29	89.57±9.11	<0.001	0.306	0.029
FVC	75.62±7.25	80.62±8.23	0.034	71.0±4.91	84.97±12.35	<0.001	0.001	0.068
FEV1/FVC	73.72±5.02	82.37±8.28	<0.001	72.17±5.96	87.9±8.27	<0.001	0.212	0.004

FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity.

<sup>1</sup> Comparison between the two groups before treatment

<sup>2</sup> Comparison between the two groups after treatment

**Table 3.** ACT and SGRQ scores before and after treatment

Variables	Fluticort plus®			Seretide®			p-value <sup>1</sup>	p-value <sup>2</sup>
	Mean±SD		p-value	Mean±SD		p-value		
	Pre	Post		Pre	Post			
ACT	18.55±2.25	23.42±3.32	0.012	23.27±3.21	24.22±1.83	0.178	0.356	0.187
SGRQ								
Symptoms	18.9±4.13	12.95±2.84	0.023	26.1±9.50	7.27±1.81	<0.001	<0.001	<0.001
Impact	8.55±1.19	14.1±11.99	<0.001	18.47±7.45	6.85±1.65	<0.001	<0.001	<0.001
Activity	21.2±3.5	15.07±3.63	<0.001	23.4±5.05	13.27±2.45	<0.001	0.026	0.011
Total	27.15±5.13	17.0±3.57	<0.001	31.55±3.98	14.40±2.71	<0.001	<0.001	<0.001

ACT: asthma control test; SGRQ: St. George's Respiratory Questionnaire.

<sup>1</sup> Comparison between the two groups before treatment

<sup>2</sup> Comparison between the two groups after treatment

occurs in low- and middle-income countries. Hence, development of generic products with lower price, wider availability and equivalent safety and efficacy compared with the brand-name drugs might be a solution to provide asthmatic patients with proper treatment. Seretide®, a brand-name product, is the most common combinatory inhaler used in asthma management, and contains both ICs (fluticasone) and LABA (salmeterol).

This results of this study indicated that Fluticort plus®, as a generic product, improves spirometric function, quality of life and respiratory symptoms (according to the ACT scale) in asthmatic patients with mild to moderate disease. However, the degree of improvement in spirometric function and quality of life was found to be greater with Seretide®. In a previous study, Maneechotesuwan et al. investigated the anti-inflammatory effects of salmeterol/fluticasone combination

on sputum eosinophil count and fractional exhaled nitric oxide as primary and secondary outcomes, respectively. The results did not suggest any significant difference between generic and brand-name products in controlling asthmatic symptoms following 4 weeks of treatment (30). It is worth noting that in the present study, SGRQ total and subscale scores as well as FVC were significantly lower in the Fluticort plus® versus Seretide® group at baseline, and this might have partially confounded the above-mentioned results.

The present study has some limitations that deserve to be mentioned. First, this study was performed in a pilot scale and with a short-term duration of follow-up, and hence longer term studies are required to provide insight with respect to the comparative efficacy of drugs on asthma exacerbations. In addition, the findings of this study could provide useful information for the determination of size and equivalence margin

in future trials. Second, the study population was limited to patients with mild to moderate asthma and it is unclear whether the efficacy of generic and brand-name drugs is different in controlling more severe asthmatic symptoms. Third, the adherence to treatment, although being comparable between the study groups, was relatively low. Fourth, some of the parameters including SGRQ and FVC scores were different between the groups at baseline. Finally, antioxidant intake at baseline and during the period of study was not assessed. Owing to the documented role of oxidative stress in promoting airway inflammation and asthma severity (31, 32), between-group differences in antioxidant intake might have confounded the results.

In summary, the results of this comparative trial favored a higher efficacy of brand-name salmeterol/fluticasone versus the generic product, though the products were comparable in terms of safety. Since the disease symptoms and quality of life were improved by both products, the generic drug could be used as a cheaper treatment in asthmatic patients with mild to moderate symptoms. Nevertheless, future non-inferiority trials are required to compare the efficacy and safety of generic and brand-name drugs on a long-term basis.

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