



## Comparison of Rapid Bronchodilatory Effects of Salmeterol and Formoterol in Patients with Moderate to Severe Asthma

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### ABSTRACT

**Backgrounds:** All of Long-acting  $\beta_2$ -agonists are beneficial in maintenance treatment of asthma but their use in relieving acute asthma attacks is not well known. The aim of this study was to compare rapid bronchodilatory effects of Salmeterol and Formoterol in patient with moderate to severe asthma.

**Methods:** It was a randomized, double blind, cross-over study on 60 patients with moderate to severe asthma. Patients randomly received 50 micrograms of salmeterol or 18 micrograms of formoterol and after one-week washed out period exchanged their medications. All patients undergone spirometry for four times (before receiving the drugs, as well as 3, 30 and 60 minutes after drug inhalation) and Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FVC percentage predicted value, FEV1/FVC, Peak Expiratory Flow Rate (PEFR) and PEFR percentage predicted value were measured.

**Results:** Both medications could significantly increase FEV1/FVC and PEFR at 3, 30 and 60 minutes after inhalation ( $P < 0.001$  compared to baseline). Three minutes after inhalation of salmeterol and formoterol, FEV1 increased by 8.7% and 12.2% respectively. Formoterol was associated with more increase in the amounts of FEV1 compared to Salmeterol.

**Conclusion:** This study showed that fromoterol has a more rapid onset of bronchodilating action compared with salmeterol at 3 minutes after inhalation. Both agents had significant increases in FEV1/FVC and PEFR compared to baseline with no significant differences between two drugs.

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### Introduction

Asthma is a chronic disease of airways. Prevalence of asthma is variable in various parts of the world. Prevalence of asthma among primary school students of Sari City, north of Iran was about 12% (1). Although long-acting

$\beta_2$ -agonists have evidenced effectual role in maintenance treatment of asthma but their effectiveness in improving acute asthma attacks are not clear (2). Along with its long duration of effects, some studies have reported that Formoterol has a rapid onset of effect similar to Albuterol (3). It was demonstrated that rapid bronchodilatory effects of formoterol and Terbutaline based on Forced Expiratory Volume in 1 second (FEV1), 15 minutes post-inhalation

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**Table 1.** Demographic and clinical features of the subjects (N = 60).

Variable	Findings
Age; X±SD years (Range)	33.05±17.94 (7-72)
Duration of asthma; X±SD Months (Range)	7.08±6.58 (1-30)
Female (%)	34 (57)
Male (%)	26 (43)
<b>Drugs used; n (%)</b>	
Fluticasone	57 (95%)
Salmeterol	35 (58.3%)
Ipratropium Bromide	10 (16.7%)
Theophylline	23 (38.3%)
Montelukast	19 (31.7%)
Formoterol	5 (8.4%)
Prednisolon	1 (1.7%)
Ketotifen	12 (20%)
Budesonide	5 (8.3%)
<b>Disease severity</b>	
Moderate	34 (57%)
Severe	26 (43%)

\*Disease severity was determined by spirometer based on spirometric values and demographic information

are comparable which shows formoterol's rapid onset of effect (4). In another study, the efficacy of 4.5 microgram formoterol and 0.5 microgram terbutaline in relieving symptoms of patients in persistent asthma were the same (5).

In a study conducted by Lotval and colleagues in 2001, intrinsic activity of formoterol was more than Salmeterol (6) while some other ones demonstrated that bronchodilatory and protective effects of salmeterol and formoterol are the same (7-8). Some studies suggest increased airway resistance during first minutes after salmeterol inhalation (9).

In view of controversial reports about rapid bronchodilatory effects of salmeterol and formoterol, we conducted this study to evaluate the rapid bronchodilatory effects of two aforementioned drugs.

## Patients and Methods

This double-blind cross-over study was conducted in the "Tooba" clinic in Sari city affiliated to Mazandaran University of Medical Sciences. The trial and its ethical points were reviewed and approved by research council of faculty of pharmacy (238-2009).

According to rate of symptoms, nighttime awakenings, need to use short acting beta-agonist and lung function (FEV1 and FEV1/FCV), patients with moderate to severe asthma who were under treatment for at least one month and had not smoked or used bronchodilators during preceding 24 hours were enrolled in the study.

Pregnant women, patients who were less than 5 years old, under treatment with beta-blockers, had mild asthma and who had inhaled bronchodilators 24 hours before the study were excluded from the study.

Considering the study being double-blind, salmeterol and formoterol inhalers were marked as A and B. Neither physician nor patients knew the name of the A and B drugs. A code referred to salmeterol and B code referred to formoterol. At the end of the study the codes were released and results were analyzed.

Dosage used in this study was two puffs of salmeterol metered dose inhaler (Salmex, SinaDaroo, Tehran, Iran), total 50 mcg and two doses of formoterol turbuhaler (Oxis® , AstraZeneca, Switzerland), total 18 mcg. As a protocol the other puff was consider one minute after the first puff. Patients were provided with adequate information about the study and their spirometry was assessed after take in the consent.

Patients were divided into two groups. Group 1 used salmeterol inhaler and group 2 used formoterol inhaler with the dosage indicated above. After one-week washed out period the patients exchanged their groups. All subjects took spirometry (Chest hi 809, Japan) four times; before drug administration, and 3, 30 and 60 minutes after inhalation. Fluticasone, salmeterol, theophylline and montelukast were the most common drugs had been prescribed for patients. FEV1, its percentage predicted value, Forced Vital Capacity (FVC), its percentage predicted value, FEV1/FVC, Peak Expiratory Flow Rate (PEFR) and its percentage predicted value as well as percentage predicted value of Maximum Mid Expiratory Flow (MMEF), were measured.

Data was recorded in SPSS-16. Paired Samples T Test was used for comparing variables before receiving salmeterol and formoterol as well as 3, 30 and 60 minutes after receiving them. We also used repeated measure ANOVA for comparing spirometric variables at four phases (baseline, and 3, 30 and 60 minutes after inhalation). Statistical significance was established at  $P < 0.05$ .

## Results

According to inclusion and exclusion criteria, out of 60 patients, age between 7 to 72 years old with moderate to severe asthma were randomly selected and enrolled in the study. The mean age of patients was 33.05 (standard deviation, 18 years). Thirty patients were in group 1 (received salmeterol then formoterol) and 30 cases were in group 2 (received formoterol then salmeterol). After one-week washed out period, all subjects exchanged their medication.

Subjects' demographic information is depicted in Table 1. Mean age of the patients was 33.05 ± 17.94 ranged from 7 to 72 years. Mean duration of asthma was 7.08 ± 6.58 years ranged from 1 to 30 years.

**Table 2.** Peak Expiratory Flow Rate (PEFR) percentage predicted value before and after receiving salmeterol and formoterol, N=60.

Drug	Phase	X±SD	P-value €
<b>Salmeterol</b>	Before Inhalation	53.42±18.33	<0.001
	After 3 minutes	58.31±23.78	
	After 30 minutes	58.57±19.74	
	After 60 minutes	60.23±19.84	
<b>Formoterol</b>	Before inhalation	53.47±20.89	<0.001
	After 3 minutes	58.32±21.69	
	After 30 minutes	58.94±21.05	
	After 60 minutes	60.69±21.92	

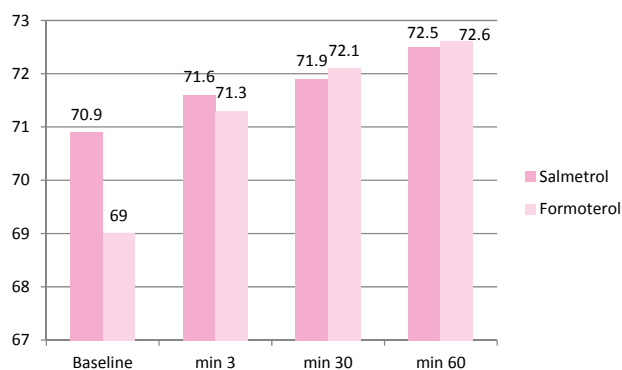
€: P-value; Repeated Measure Analysis of Variance

### FEV1/FVC Ratio

FEV1/FVC ratios before and after receiving salmeterol and formoterol are depicted in Figure 1. Mean FEV1/FVC before receiving salmeterol and formoterol was  $70.9 \pm 13.9$  and  $69 \pm 14.9$  respectively. There were significant increases in FEV1/FVC ratios 3, 30 and 60 minutes after inhalation of both drugs ( $P < 0.001$  for both drugs, Figure 1).

### Percentage predicted values of PEFR

Percentage predicted values of PEFR before and after receiving salmeterol and formoterol is depicted in Table 2. Both drugs significantly increased the percentage predicted values of PEFR 3, 30 and 60 minutes after inhalation ( $P < 0.001$ ).



**Figure 1.** FEV1/FVC before and after receiving salmeterol and formoterol (ANOVA,  $P < 0.001$  for both salmeterol and formoterol) FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity

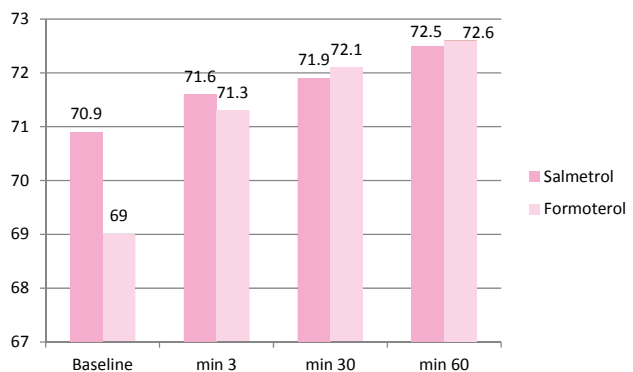
### Percentage predicted values of FEV1

Percentage predicted values of FEV1 before and after receiving salmeterol and formoterol are illustrated in Figure 2.

After 3 minutes inhalation of salmeterol and formoterol, FEV1 increased by 8.7% and 12.2% respectively. Criterion for reversibility of airway obstruction is at least 12% increase in FEV1 after administration of a short-acting bronchodilator (2); thus it could be concluded that formoterol caused rapid bronchodilatory effect and acted better than salmeterol in this field (Figure 2).

### Percentage predicted values of MMEF

Percentage predicted values of MMEF before and after receiving salmeterol and formoterol are depicted



**Figure 2.** FEV1 before and after receiving salmeterol and formoterol (ANOVA,  $P < 0.001$  for both salmeterol and formoterol) FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity

**Table 3.** Percentage predicted values of Maximum Mid Expiratory Flow (MMEF) before and after receiving salmeterol and formoterol, N=60.

Drug	Phase	X±SD	P value <sup>€</sup>
Salmeterol	Before inhalation	29.90±10.66	<0.001
	After 3 minutes	35.02±12.76	
	After 30 minutes	37.43±13.19	
	After 60 minutes	40.26±14.34	
Formoterol	Before inhalation	28.47±11.85	<0.001
	After 3 minutes	39.33±15.86	
	After 30 minutes	43.73±16.10	
	After 60 minutes	47.28±17.01	

€: P-value; Repeated Measure Analysis of Variance

in Table 3. Mean percentage predicted value of MMEF before administration of salmeterol and formoterol were 29.90±10.66 and 28.47±11.85 respectively. We observed significant increase in MMEF 3, 30 and 60 minutes after inhalation of both medications ( $P < 0.001$ ) (Table 3).

FEV1/FVC and percentage predicted value of PEFR at baseline and 3, 30 and 60 minutes after administration of two drugs were compared point to point (Table 4). Results denote that FEV1/FVC and percentage predicted value of PEFR were increased compared to baseline in both groups but there were no significant differences between two groups at baseline as well as 3, 30 and 60 minutes after drug inhalation.

## Discussion

Our study showed that formoterol could cause rapid bronchodilatory effect and acted better than salmeterol (FEV1 increase 3 minutes after inhalation; 12.2% verse 8.7% respectively). Of course, both drugs cause significant increases in FEV1/FVC and PEFR levels 3, 30 and 60 minutes but there was no significant difference between two groups.

Lotvall and colleagues in the year 2001 studied on pharmacologic similarities and differences of  $\beta_2$ -agonists and reported that although salmeterol and formoterol are long-acting  $\beta_2$ -agonists but formoterol has a rapid onset of effect while initiation of bronchodilatory effects of salmeterol takes a while (6). After administration of a single dose, their effects last for 12 hours. Formoterol has higher intrinsic activity rather than salmeterol i.e. formoterol is a complete  $\beta_2$ -agonist while salmeterol is a partial agonist. Formoterol's high water solubility and its moderate lipophilic characteristics facilitate its rapid binding to  $\beta_2$  receptors of smooth muscles and lead to rapid bronchodilatory effects. Salmeterol is highly lipophilic and binds with  $\beta_2$  receptors slowly and has delayed onset of effect. Unlike Salbutamol which is a hydrophilic compound, salmeterol and formoterol are lipophilic drugs, reserved in airway tissues near  $\beta_2$  receptors and cause long-lasting effects.

Berger and colleagues in the year 2006 studied on efficacy of formoterol on relieving symptoms of asthma and prevention of exercise-induced bronchospasm and reported that formoterol is the only long-acting  $\beta_2$ -agonist which has a rapid onset of effect (during 3 minutes) which lasts for a long time (at least 12 hours) (10). In the year 2006 Hermansen and colleagues conducted a randomized, double-blind, cross-over study on 24 patients aged 7-15 years and compared rapid bronchodilatory effects of formoterol versus terbutaline on exercise-induced bronchospasm. Five minutes after exercise, individuals whom their FEV1 had decreased by at least 15% received the aforementioned drugs and their FEV1 was measured again after 3 minutes. Results showed that effects of a single dose of formoterol (9 mcg) on exercise-induced bronchospasm in children were similar to those of terbutaline. They suggested that formoterol is at least as effective as short-acting  $\beta_2$ -agonists and could be used as an effectual treatment in treating acute bronchospasm in children (11).

As mentioned above, the criterion of clinically-significant reversibility of airway obstruction is at least 12% increase in FEV1 value following administration of bronchodilators and if the increase could rise to 20%,

**Table 4.** Comparing FEV1/FVC and PEFR after administration of salmeterol and formoterol, N=60.

	Comparing FEV1/FVC Salmeterol versus Formoterol administration (P-value <sup>€</sup> )	Comparing PEFR Salmeterol versus Formoterol administration (P-value <sup>€</sup> )
Baseline	0.17	0.98
After 3 minutes	0.83	1
After 30 minutes	0.88	0.89
After 60 minutes	0.95	0.85

€: P-value; Paired Samples T Test to compare the values of salmeterol vs. formoterol at each time point.

FEV1: Forced Expiratory Volume in 1 second, FVC: Forced Vital Capacity, PEFR: Peak Expiratory Flow Rate

clinical conditions of the patient would significantly improve (12). Three minutes after administration, this figure was 8.7% for salmeterol and 12.2% for formoterol; that's to say formoterol could cause rapid bronchodilatory effects and acted better than salmeterol in this field.

Results of our study demonstrated that 3 minutes after inhalation of formoterol and salmeterol, MMEF was increased by 10.86% and 5.12% respectively. Both drugs could improve MMEF at a statistically significant manner, ( $P < 0.001$ ), while percentage increase of MMEF 30 minutes after inhalation of formoterol was two times more than that of salmeterol (15.26% vs. 7.53%).

In the year 2009, Cote and colleagues compared onset of bronchodilatory effects of 12 mcg formoterol (BD) and 50 mcg salmeterol (BD). During the 28-day treatment period, percentage increase of MMEF 5 and 30 minutes after inhalation of formoterol was significantly more than salmeterol (13).

Considering the results of this study, we conclude that both salmeterol and formoterol can significantly increase FEV1/FVC and PEFr at 3, 30 and 60 minutes after inhalation. Although these results after formoterol administration were more than that of salmeterol, the difference was not statistically significant. Rapid increase of FEV1, as a criterion of reversibility of airway constriction, was more favorable with formoterol compared to salmeterol. It could be concluded that, unlike salmeterol, formoterol can cause rapid bronchodilatory effects.

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