

## Role of Long Acting $\beta_2$ Agonist Salmeterol, in Management of Mild to Moderate Asthmatic Patients

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### ABSTRACT

**Aim:** To evaluate the role of salmeterol as add-on therapy to inhaled corticosteroids in mild to moderate asthmatic patients.

**Study Design:** Randomized Clinical Trial

**Place and Duration of Study:** Study was conducted in Pharmacology and Therapeutics Department, Basic Medical Science Institute, Jinnah Post-graduate Medical Centre, Karachi for period of 8 months.

**Methodology:** Fifty mild to moderate asthmatic patients, age range 15 to 65, were divided in two groups. Patients of Study Group, were given combination of Salmeterol 50 $\mu$ g and Fluticasone propionate 250 $\mu$ g twice daily, patients of Control Group were given Beclomethasone Dipropionate 500 $\mu$ g twice daily. End points were reduction in Symptom Rating Score and improvement in Peak Expiratory Flow Rate (PEFR) checked fortnightly. Student paired test was applied to analyze data.

**Results:** In study group patients, the mean total symptom rating score declined markedly from score of 11.16 from baseline, to 0.41 ( $p < 0.001$ ) at the end of study and the mean PEFR elevated significantly from 189.4L/min $\pm$ 0.34 to 354.58L/min $\pm$ 0.15; P value  $< 0.001$ . While in Patients of control group, reduction in Mean total symptom rating score and elevation of Mean PEFR was non-significant i.e. total symptom score 11.04 from baseline to 5.29 and mean PEFR reduced from 182.60L/min $\pm$ 17.05 to 231.73l/min $\pm$ 13.84.

**Conclusion:** Salmeterol has a significant role in management of mild to moderate asthmatic patients.

**Keywords:** Beclomethasone Dipropionate, Fluticasone, Inhaled corticosteroids, Peak Expiratory Flow Rate, Salmeterol, Symptom Rating Score.

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### INTRODUCTION

Almost 300 million people worldwide are affected by asthma, thus, it is a global health issue. Apart from geographic variations, there are differences seen according to gender and age in outcomes such as hospitalizations, with highest rates in young boys and adult females<sup>1</sup>. Asthma is a chronic disease of respiratory system related to airways inflammation, hyper-reactivity and excessive production of mucus<sup>2</sup>.

Clinical diagnosis of Asthma is done on the history of recurrent events of breathlessness, wheezing, chest tightness feeling, with or without cough, usually in the early morning or at night<sup>3</sup>. Inhalational form of  $\beta_2$ -agonist, are routinely used as bronchodilators, to relieve asthma symptoms and have an essential role in the asthma management<sup>4</sup>.

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Frequent use of short-acting  $\beta_2$ -agonists alleviate symptoms in asthma patients prescribed "as-needed," but many patients use them more frequently or on routine basis.

Long-acting inhaled  $\beta_2$ -agonists are now available that provide sustained bronchodilation and are used as adjuvant to inhaled corticosteroids for asthma management<sup>5</sup>. Usage of salmeterol a long-acting bronchodilator, twice daily as add-on, has been observed to be better in achieving asthma control regarding symptoms and pulmonary function<sup>6,7</sup>, than monotherapy by albuterol four times daily<sup>8,9</sup>.

This effect may be due to fact that this regimen, causes suppression of airway inflammation<sup>10</sup>, thus, improving control of asthma by reduction in asthma symptoms and enhancement of pulmonary function<sup>11</sup>.

The object of this clinical study was to evaluate the effect of salmeterol as add-on therapy to inhaled corticosteroids in mild to moderate asthmatic patients.

### MATERIALS AND METHODS

This study was randomized, open-label, parallel group, and was carried out at the department of Pharmacology and Therapeutics, BMSI and in

Department of Chest Medicine, JPMC, Karachi. A total of 60, male and female patients, suffering from mild to moderate asthma, were registered for the study. The patients, aged between 15-70 years, were taking ICS therapy for asthma. Patients who were receiving systemic steroids or have been on systemic steroids in last 6 months; have had respiratory infections and given antibiotics in last 4 weeks; or suffering from diabetes, heart disease, hypertension, hepatic and renal diseases were excluded.

The study was done for 12 weeks period and was preceded by run-in period of 2 weeks. Patients were assessed in the run-in period for eligibility and randomization based on specific criteria i.e., male or female patients diagnosed of having mild to moderate persistent asthma already taking ICS. During treatment period patients were randomized to either Study Group, given Salmeterol 25µg/Fluticasone 125µg inhaler (Salmicort), two puffs twice daily; or Control Group, given Beclomethasone Dipropionate inhaler, 250µg, two puffs B.D. for 12 weeks with fortnightly follow up visits.

Asthma diary (Symptom Rating Score) was given to every patient at the beginning of study and relevant information was noted on fortnightly visit. This diary contained questions regarding, day time symptoms as well as nocturnal awakenings, frequency of use of  $\beta_2$ -agonists, exacerbation of asthma, number of asthma free days and use of other resources when the asthma worsened.

Peak expiratory flow rate (PEFR) was measured by Micropeak. Peak flow meter. Reg. Design no. 2100423, Made in UK, on every visit and noted. The tolerability and safety of Salmeterol was checked by monitoring adverse events (asthma exacerbation), pulse and blood pressure at every clinic visit during the study.

All the readings were taken as mean  $\pm$ SEM. The efficacy measurement was the mean change in the symptom rating score and PEFR fortnightly during the study from baseline to end of study. Student paired test was used to analyze the data.

## RESULTS

Total 60 patients enrolled in study 50 were randomized to treatment groups, 25 in each group. Five patients withdrew from study during treatment period. One patient withdrew from Salmeterol group which is study group and two patients from ICS group which is control group because of non-compliance. Demographic data and baseline PEFR are given in Table 1. Patients in both groups were matched for age, sex and type of asthma they were suffering from. Male to female ratio was similar to international studies i.e. 25:75.

**Symptom Rating Score:** In Study Group there was significant reduction in patient-rated mean total symptom score, i.e. symptoms of wheezing, chest tightness and shortness of breath, compared with Control Group after each fortnightly treatment.

In Study Group mean total symptom score reduced significantly from baseline value of 11.16, to 0.41 ( $p < 0.001$ ) on day-90. Use of rescue medicine reduced from daily use to once per week by the end of study. Symptom free days increased from mean value of 2 to 12.16 ( $p < 0.01$ ) and mean of symptom free nights increased from 4 to 13 ( $p < 0.002$ ) in these patients at the end of study. In comparison in Control group, mean total symptom score reduction was non-significant i.e. from baseline value of 11.04, to 5.29 on day-90. Daily use of rescue medicine only decreased to 4-5/week by the end of study. Increase in symptom free days was from mean value of 2.2 to 5 ( $p$ -value not significant) and increase in mean of symptom free nights was from 3.78 to 6 ( $p$ -value not significant), at the end of study (Table II).

**Peak Expiratory Flow Rate:** Salmeterol as add-on therapy significantly improve PEFR, after each fortnight treatment while in patients of ICS group the improvement in PEFR was non-significant. By week 12 in Study Group (Salmeterol plus ICS), improvement in PEFR was 46.58% as compared to baseline value, while in Control Group (ICS), PEFR improved to only 21.2% in comparison to baseline observation (Table-III, Fig. I).

Table I: Demographic and baseline characteristics of patients

Groups	Total Patients		Age (Mean) Range(15-65)	Gender		Type of Asthma		PEFR L/min( $\pm$ SEM)
	Remained	Left		Male	Female	Mild	Moderate	
Study	24 (96%)	1(4%)	34	6(25%)	18(75%)	13(54.16%)	11(45.83%)	189.4( $\pm$ 16.4)
Control	23 (92%)	2(8%)	35	6(26%)	17(73.91%)	12 (52.1%)	11 (47.8%)	189.8( $\pm$ 17.0)

Values are expressed in Mean ( $\pm$ SEM) (Percentage)

SEM: Standard Error of Mean

PEFR: Peak Expiratory Flow Rate

L/min: Liters per minute

Table II: Reduction in Individual Symptom Rating Score among Both Groups from Day 0-90

Groups	Symptom Rating Score	Day 0	Day 90	P-value
<b>Study Group</b>	Day time symptoms. Mean(SEM)	6.6( $\pm$ 0.21)	0.41 ( $\pm$ 0.15)	<0.01
	Night time symptoms. Mean(SEM)	4.4 ( $\pm$ 0.15)	0.5 ( $\pm$ 0.12)	<0.001
	Use of rescue medicine.	Daily	Once/ week	
	No. of symptom-free days/fortnight.	2 ( $\pm$ 0.14)	12.16( $\pm$ 0.15)	<0.01
	No. Of symptom-free nights/fortnight	4 ( $\pm$ 0.12)	13 ( $\pm$ 0.18)	<0.002
<b>Control Group</b>	Day time symptoms. Mean(SEM)	7.34( $\pm$ 0.16)	5( $\pm$ 0.2)	N.S
	Night time symptoms. Mean(SEM)	4.65( $\pm$ 0.14)	3.26( $\pm$ 0.12)	N.S
	Use of rescue medicine.	Daily	4-5/week	
	No. of symptom-free days/fortnight.	2.2 ( $\pm$ 0.15)	5 ( $\pm$ 0.14)	N.S
	No. Of symptom-free nights/fortnight	3.78( $\pm$ 0.12)	6 ( $\pm$ 0.16)	N.S

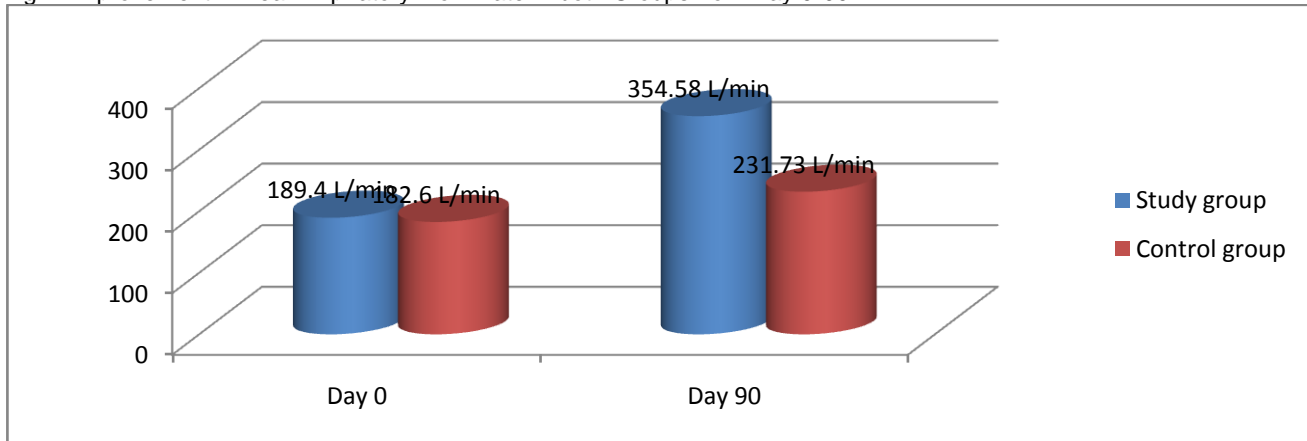
Values are expressed in Mean ( $\pm$ SEM) SEM: Standard Error of Mean P-value: Probability value  
 Negative (-) sign indicate reduction in asthma symptoms N.S: Not Significant

Table III: Improvement in peak expiratory flow rate in both groups from day 0-90

Groups	Day 0	Day 90	P-value
<b>Study Group</b>	189.4 L/min ( $\pm$ 16.12)	354.58 L/min ( $\pm$ 7.61)	<0.001 HS
<b>Control Group</b>	182.60 L/min ( $\pm$ 17.05)	231.73 L/min ( $\pm$ 13.84)	N.S

Values are expressed in Mean ( $\pm$ SEM) SEM: Standard Error of Mean P-value: Probability value  
 HS: Highly Significant N.S: Not Significant L/min: Litres per minute

Fig. 1: Improvement in Peak Expiratory Flow Rate in both Groups from Day 0-90



## DISCUSSION

Symptomatic asthmatic patients, already receiving corticosteroid therapy require supplementary medicine. Inhaled corticosteroids and long-acting  $\beta_2$ -agonists have a complementary role in the management of asthma<sup>12</sup>. International guidelines suggest that long acting  $\beta_2$ -agonists should be added to inhaled corticosteroids in mild to moderate asthma<sup>13</sup>. This trial shows that adding salmeterol provided more benefit than ICS alone as clear by improvement in symptom rating score and PEFR. These results are consistent with the result of Cochrane review, with significant improvements in lung function, symptom control and quality of life<sup>14</sup>.

The decrease in symptom rating scores in our trial matches with the study conducted by Green et al<sup>15</sup> in 2006, pointing out the complex link between airway responsiveness and clinical presentation of asthma. Patients who received salmeterol as add-on

show improvements in all patient-rated symptom scores ( $P < 0.001$ ), decrease in use of rescue inhaler of albuterol ( $P < 0.001$ ), and a significant increase in number of symptom-free days ( $P < 0.001$ )<sup>16</sup>. Similar results regarding symptom free days and night are seen in another study conducted by Jeffery et al<sup>17</sup>.

Studies done by Bjermer et al and Wilson et al, have similar results as our study regarding improvement in peak expiratory flow rate<sup>13,18</sup>. In a meta-analysis, the results of many randomised clinical trials are summarized, including symptomatic patients with bronchial asthma on inhaled steroids who were given salmeterol as add-on or an increased dose of inhaled corticosteroids. Marked improvement in lung function was recorded in the salmeterol group, with a 28 l/min more increase in morning peak expiratory flow rate after six months of salmeterol plus inhaled steroid therapy than after increasing the inhaled steroid dose<sup>19</sup>.

Comparison of salmeterol and ICS combination with ICS alone, in this study is supported by the trials done by Bergmann et al and Zetterström et al, in which it is evident that combined salmeterol fluticasone (SFC) treatment resulted in significant elevation in PEFR and symptom control than doubling the fluticasone propionate (FP) dose. At the end of week 12, morning PEFR had elevated by 52 L/min from baseline in SFC receiving patients and by 36 L/min in patients on FP<sup>20,21</sup>.

Studies conducted by Murray and colleagues, Chan et al and Condemi and associates, show a significant improvement in both symptom rating score, PEFR and lung functions, when combination therapy of salmeterol and ICS is compared to doubled dose of ICS alone<sup>22,23,24</sup>.

## CONCLUSION

Using Salmeterol (LABA) as add-on therapy to inhaled corticosteroid has proven to be more effective in controlling asthma symptoms and improving lung functions than using ICS alone.

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## REFERENCES

- Lougheed M D. Variability in asthma: symptom perception, care and outcomes. *Can. J. Physiol. Pharmacol* 2007;85:149-154
- Kuperman D A, Huang X, Koth LL et al. Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. *Nature Medicine* 2002; 8: 885 – 889
- Strek M E. Difficult Asthma. *Proc Am Thorac Soc* 2006; 3: 116–123,
- Langley S J, Masterson C M, Batty E P et al. Bronchodilator response to salbutamol after chronic dosing with salmeterol or placebo. *Eur Respir J* 1998; 11: 1081–1085
- Hancox R J, Subbarao P, Kamada D et al.  $\beta_2$ -Agonist Tolerance and Exercise-induced Bronchospasm. *Am J Respir Crit Care Med* 2002; 165: 1068–1070
- Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D Pozzi E et al. Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma. *N Engl J Med* 2007; 356: 2040-2052.
- Bacci E, Franco AD, Bartoli ML, et al. Comparison of anti-inflammatory and clinical effects of beclomethasone dipropionate and salmeterol in moderate asthma. *Eur Respir J* 2002; 20:66-72
- Shapiro G, Lumry W, Wolfe J et al. Combined Salmeterol 50 µg and Fluticasone Propionate 250µg in the Diskus Device for the Treatment of Asthma. *AM J RESPIR CRIT CARE MED* 2000; 161: 527–534.
- D'Alonzo G E, Nathan R A, Henochowicz S et al. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. *J.A.M.A.*1994; 271: 1412- 1416
- Bacci E, Franco AD, Bartoli ML, Carnevali S, Cianchetti S, Dente FL et al. Comparison of anti-inflammatory and clinical effects of beclomethasone dipropionate and salmeterol in moderate asthma. *Eur Respir J* 2002; 20:66-72.
- Larj M J and Bleecker E R. Therapeutic Responses in Asthma and COPD: Corticosteroids. *CHEST* 2004; 126:138S–149S
- Currie GP, Jackson CM, Ogston SA, Lipworth BJ. Airway-stabilizing effect of long-acting  $\beta_2$ -agonist as add-on therapy to inhaled corticosteroids. *Q Med* 2003; 96: 435-440.
- Bjermer L, Bisgaard H, Bousquet J, Fabbri LM, Greening AP, Haahtela T, et al. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. *BMJ* 2003; 327: 1-6.
- Ram F, Cates C, Ducharme F. Long-acting  $\beta_2$ -agonist versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev* 2005; CD003137.
- Green RH, Brightling GE, McKenna S et al. Comparison of asthma treatment given in addition to inhaled corticosteroids on airway inflammation and responsiveness. *Eur Respir J*; 2006; 27: 1141-1151.
- Busse W, Nelson H, Wolfe J et al. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *J Allergy Clin Immunol*, 1999;103: 1075-1080
- Jeffery P K, Venge P, Gizycki M J et al. Effects of salmeterol on mucosal inflammation in asthma: a placebo-controlled study. *Eur Respir J* 2002; 20: 1378–1385.
- Wilson AM, Dempsy OJ, Sims EJ, Lipworth BJ. Evaluation of Salmeterol or montelukast as Second-Line Therapy for asthma not controlled with Inhaled Corticosteroids. *Chest*; 2001; 119: 1021-1026.
- Naedele-Risha R, Dorinsky P, Craig T J. Dual components of optimal Asthma therapy: scientific and clinical rationale for the use of long-acting  $\beta_2$ -agonists with inhaled corticosteroids. *JAOA*; 2001;101; 9: 526-533
- Bergman KC, Lindermann L, Braun R and Steinkamp G. Salmeterol/fluticasone propionate (50/250µg) combination is superior to double dose of fluticasone (500 µg) for the treatment of symptomatic moderate asthma. *Swiss Med wklly*; 2004; 134: 50-58.
- Zetterström O, Buhl R, Mellem H et al. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. *Eur Respir J* 2001; 18: 262–268
- Murray J J, Church N L, Anderson WH et al. Concurrent use of salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. *Allergy Asthma Proc*; 1999; 20(3): 173-180.
- Chan J, Hui R L, Spence M M. Effects on Resource Utilization of Adding Salmeterol in Combination or Separately to Inhaled Corticosteroids. *J Manag Care Pharm*; 2007; 13(1): 21-27
- Condemi J J, Goldstein S, Kalberg C et al. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Salmeterol Study Group. *Ann Allergy Asthma Immunol*; 1999; 82: 383-389.