

A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF RACEMIC SALBUTAMOL AND LEVOSALBUTAMOL IN PATIENTS WITH ASTHMA

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Abstract

Keywords:

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Aim: The present study was conducted to compare the efficacy and safety of racemic salbutamol with levosalbutamol in patients of bronchial asthma

Methods: A prospective, randomized, open label 8 weeks study. After taking informed consent of 100 patients of either sex were randomly divided in to racemic salbutamol (group A) and levosalbutamol (group B) group of 50 patients each. At first visit (0 week) Spirometry parameters like FEV1, FVC, PEFR and heart rate changes were recorded before and 20 minutes after drug administration via MDI. Patients were prescribed the study drug for further 4 weeks for safety assessment. At 4 weeks spirometry parameters and heart rate changes were recorded before and 20 minutes after drug administration. At both the visits patients were interviewed for side effects. Results were analysed at 0 and 4 weeks.

Result: At 0 and 4 weeks mean percentage increase of FEV1, FVC, PEFR in levosalbutamol group after drug administration was significantly higher. Conclusion: Levosalbutamol was found to be more efficacious and safer than racemic salbutamol.

Introduction

Asthma is one of the most common chronic diseases in the world. It is estimated that around 300 million people in the world currently have asthma. The number of disability-adjusted life years (DALYs) lost due to asthma worldwide has been estimated to be currently about 15 million per year. Worldwide, asthma accounts for around 1% of all DALYs lost, which reflects the high prevalence and severity of asthma. The number of DALYs lost due to asthma is similar to that for diabetes, cirrhosis of the liver, or schizophrenia. It is estimated that asthma accounts for about 1 in every 250 deaths worldwide.¹

Globally, the economic costs associated with asthma exceed those of tuberculosis and HIV/AIDS combined. 2 Investigations have shown that the financial burden on patients with asthma in different Western countries ranges from \$300 to \$1,300 per patient per year³. According to the National Family Health Survey (NFHS)- the overall prevalence of asthma among adult men and women in India is 1,696 and 1,627 per 100,000 respectively.⁴

Various cells like eosinophils, T-cells, mast cells, basophils and neutrophils play an important role in pathophysiology of asthma.⁵ Asthma involves contraction of airway smooth muscles, airway remodelling, edema and hypersecretion of mucus, contributing significantly to bronchial obstruction.⁶ The predominant feature of asthma is the discomfort experienced upon breathing in the presence of excessive and inappropriate constriction of the airway smooth muscle (ASM). Although airway inflammation may play an important role in asthma, it is benign in the absence of airway narrowing.⁷

Bronchodilator drugs relax constricted airway smooth muscle *in vitro* and cause immediate reversal of airway obstruction in asthma *in vivo*. They also prevent bronchoconstriction (and thereby provide bronchoprotection). Three main classes of bronchodilator are in current clinical use are β_2 adrenergic receptor (β_2 AR) agonists (sympathomimetics), theophylline (a methylxanthine) and anticholinergic agents (muscarinic receptor antagonists).⁸ Salbutamol the short acting selective β_2 AR agonist is one of the most commonly used bronchodilator in the treatment of reversible airway obstruction.⁹ Salbutamol consists of racemic mixture of equal amounts (50:50) of two

enantiomers, (R)-salbutamol (levosalbutamol) and (S)-salbutamol.¹⁰(R)-salbutamol (levosalbutamol) has been shown to have a 2-fold greater binding affinity than racemic salbutamol and a 100-fold greater binding affinity than (S)-salbutamol for the β_2 AR¹¹. Other evaluations have suggested that (R)-salbutamol possesses the bronchodilatory, bronchoprotective, and ciliary-stimulatory properties of racemic salbutamol, while (S)-salbutamol does not contribute beneficially to the therapeutic effects of the racemate and was originally assumed to be inert.¹²

However, preclinical evaluations have shown that (S)-salbutamol has effects that work in opposition to (R)-salbutamol and may diminish the therapeutic effects of (R)-salbutamol.⁽¹²⁾ Preclinical studies have suggested that (S)-salbutamol might antagonise the smooth muscle relaxing actions of (R)-salbutamol (levosalbutamol) by increasing intracellular calcium levels.¹³ Few clinical studies have shown that use of racemic salbutamol is associated with significant increase in heart rate as compared to levosalbutamol.^{14,15}

Formulation containing only (R)-isomer of salbutamol (levosalbutamol) has been available in the market for the last few years. It is worthwhile to compare the efficacy and safety of racemic salbutamol and levosalbutamol in patients of asthma.

The aim of this study was to explore and compare the efficacy and safety of racemic salbutamol and levosalbutamol in patients with asthma.

Materials and Methods

Study Design: This prospective, randomized, open label study was conducted in a tertiary care hospital attached to a medical teaching institute from January 2014 to June 2015. The study was approved by the Institutional Ethics Committee.

Inclusion criteria: Men and women patients between 18 and 60 years of age coming to the department of medicine and diagnosed with asthma according to the Global strategy for prevention and management (updated 2012) by Global Initiative for Asthma (GINA) diagnostic criteria¹⁶ showing a FEV₁ between 60% and 80% of the predicted value before administration of bronchodilator therapy and able to perform reproducible spirometry were included in the study.

Exclusion criteria : Patients with history of acute exacerbation of asthma respiratory tract infection within 4 weeks prior to study entry, Patients with history of life-threatening asthma requiring treatment with intubation and mechanical ventilation, pregnant and lactating women, smokers, ischaemic heart disease or cerebrovascular disease were excluded from the study.

Spirometry: After written informed consent from all the patients the patients were randomly allocated to either group A (racemic salbutamol group) or group B (levosalbutamol group) with the help of randomization software. Patients were asked to withhold anti-asthma medications for 24 hrs before the study visits.

Baseline data such as spirometry parameters like FEV₁, FVC, PEFr and heart rate were recorded during the first study visit (0 week). Spirometry was performed using Ultima Series™ automated spirometer. Three spirometry manoeuvres were performed and the highest value of three recordings were taken¹⁶. Patients were properly trained about the technique¹⁷ for use of metered dose inhaler (MDI). Patients in group A were given 2 puffs of racemic salbutamol via metered dose inhaler (100 µg per puff) and group B were given 2 puffs of levosalbutamol via metered dose inhaler (50 µg per puff). After 20 minutes of drug administration; repeat spirometry in each patient was performed to measure changes in FEV₁, FVC and PEFr. Also patients were examined and interviewed for change in heart rate and other side effects 20 minutes after drug administration.

Patients in group A and B were prescribed 2 puffs of racemic salbutamol (100 µg per puff) and levosalbutamol (50 µg per puff) respectively via metered dose inhaler twice a day for further four weeks starting from the day of first study visit for safety assessment¹⁸. Other reliever medications like anticholinergics, theophylline and long-acting β_2 agonists were discontinued. Patients received regular low-dose inhaled corticosteroids as controller medication.

Follow-up of all the patients was scheduled at 4 weeks after the first visit. Spirometry parameters and heart rate were recorded before drug administration. Spirometry, heart rate and side effect assessment was done 20 minutes after the study drug administration in each patient, as was done at first visit. Patients requiring additional doses of reliever medication and those suffering from any serious event including acute exacerbation during the study period were excluded from the study and managed accordingly.

Patients were explained about the expected side effects of the two drugs and asked to keep a record of the occurrence of any side effects during the study period in a patient diary.

Efficacy assessment

The primary efficacy endpoint was the percentage change in FEV₁ values taken 20 minutes post medication as compared to premedication in each group at first study visit (0 week) and at second study visit (4 weeks). The secondary efficacy endpoint was the percentage change in FVC and PEFR values taken 20 minutes post medication as compared to premedication in each group at first study visit (0 week) and at second study visit (4 weeks).

Safety assessment

Change in heart rate, 20 minutes post medication was compared to premedication heart rate in each group at first study visit (0 week) and at second study visit (4 weeks). Patients were interviewed and examined for the occurrence of side effects during the study visits. Patient diaries were also evaluated for the occurrence of adverse effects during the study period and their incidence in each group was recorded and compared

Results

Total 100 patients were enrolled in the study of which 50 patients were allocated to the racemic salbutamol group (group A) and 50 patients were allocated to levosalbutamol group (group B). During the study period three patients from racemic salbutamol group and five patients from levosalbutamol group were lost to follow-up. Five patients from racemic salbutamol group and three patients from levosalbutamol group required additional doses of reliever medication. One patient from racemic salbutamol group suffered from an acute exacerbation of asthma. Hence 9 patients from racemic salbutamol and 8 patients from levosalbutamol group were excluded from analysis. Thus 41 patients from racemic salbutamol group and 42 patients from levosalbutamol group completed the study (Fig 1). Demographic characteristics including age, sex, and height of both the treatment groups were comparable as there was no statistically significant difference between the two groups ($p > 0.05$) (Table no. 1).

Table no. 1: Baseline demographic characteristics of patients

Variables	Racemic salbutamol group (N=41)	Levosalbutamol group (N=42)	p value
Age (years) [#] (Mean ± SD)	38.59 ± 9.56	38.21 ± 9.72	> 0.05
Sex**			
Male	25	24	> 0.05
Female	16	18	> 0.05
Height (cms) [#] (Mean ± SD)	158.51 ± 5.78	159.57 ± 6.25	> 0.05

[#] Unpaired t test, ** Z test

Baseline spirometry parameters FEV₁, FVC, PEFR and heart rate (HR) in the two treatment group were comparable as there was no statistically significant difference between the two groups ($p > 0.05$) (Table no. 2).

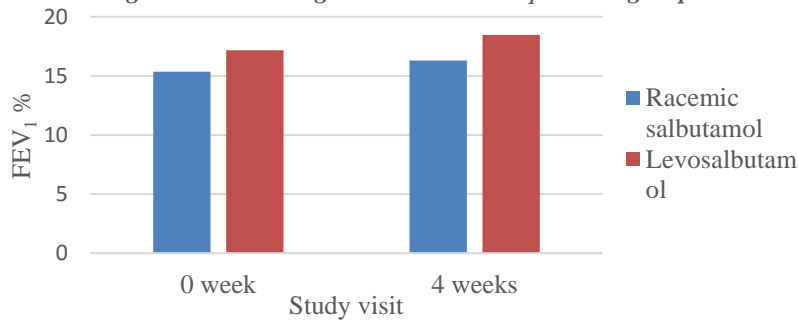
Table no. 2: Baseline spirometry parameters and heart rate (HR) of patients

Parameters	Racemic Salbutamol group (N=41)	Levosalbutamol group (N=42)	p value [#]
FEV ₁ (L)	1.68 ± 0.30	1.67 ± 0.32	> 0.05
FVC (L)	2.31 ± 0.45	2.34 ± 0.48	> 0.05
PEFR (L/min)	300.17 ± 52.37	290.49 ± 47.95	> 0.05
HR (beats/min)	73.07 ± 4.20	74.81 ± 4.58	> 0.05

[#]Unpaired t test, Figures are Mean ± Standard deviation

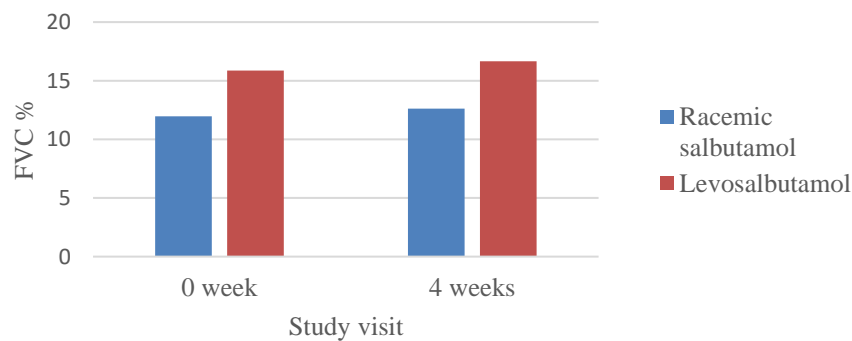
At 0 and 4 weeks the percentage increase of FEV₁ levels in levosalbutamol group (17.16% and 18.48% respectively) was significantly higher than racemic salbutamol group (15.36% 16.29% respectively) ($p < 0.01$) (Fig. no. 1).

Fig no. 1: Percentage increase in FEV₁ in both groups



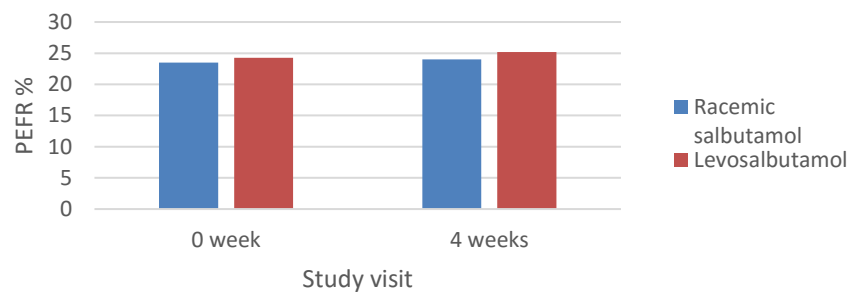
At 0 and 4 weeks the percentage increase of FVC levels in levosalbutamol group (15.86%, 16.67% respectively) was significantly higher than racemic salbutamol group (11.96%, 12.62%) (p < 0.01) (Fig no.2).

Fig. no. 2: Percentage increase in FVC in both groups

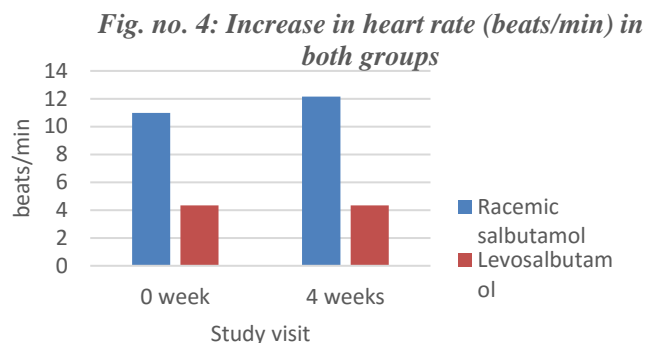


At 0 week the percentage increase of PEFR levels in levosalbutamol (24.27%) was not significantly higher than racemic salbutamol group (23.51%) (p > 0.05). At 4 weeks the percentage increase of PEFR levels in levosalbutamol group (25.21%) was significantly higher than racemic salbutamol group (24.01%) (p = 0.02) (Fig no. 3).

Fig. no. 3: Percentage increase in PEFR in both groups

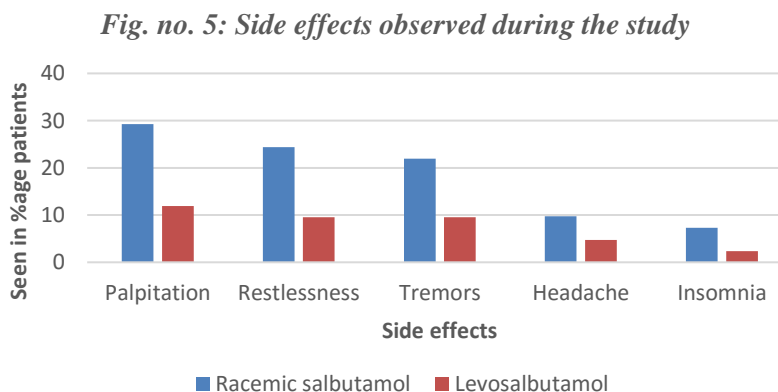


At 0 and 4 weeks there was significant increase in heart rate in racemic salbutamol group (10.98%, 12.15% respectively) than levosalbutamol group (4.33 %, 4.33 % respectively) ($p < 0.01$) (Fig. no. 4).



The side effects observed during the study period were palpitations, restlessness, tremors, headache and insomnia. During the study period 29.27% patients in the racemic salbutamol group and 11.90% in the levosalbutamol group complained of palpitations. 24.39% patients in the racemic salbutamol group and 9.52% patients in the levosalbutamol group complained of restlessness. The number of patients complaining of palpitations and restlessness was significantly high ($p < 0.05$) in patients of racemic salbutamol group than patients of levosalbutamol group.

There was no significant difference ($p > 0.05$) in the number of patients complaining of tremors, headache and insomnia between the two groups. The side effects were self-limiting and did not require discontinuation of drugs. (Fig no. 5)



Discussion

Asthma is one of the most common chronic diseases in the world. It is estimated that around 300 million people in the world currently have asthma.¹ The predominant feature of asthma is the discomfort experienced upon breathing in the presence of excessive and inappropriate constriction of the airway smooth muscle (ASM).⁷ Salbutamol the short acting selective β_2 AR agonist is one of the most commonly used bronchodilators in the treatment of asthma. Salbutamol consists of racemic mixture of equal amounts (50:50) of two enantiomers, (R) salbutamol (levosalbutamol) and (S)-salbutamol. Initially it was thought that the (S)-enantiomer of salbutamol was inert; however, more recent experimental work indicates that the (S)-isomer may have a deleterious effect in asthma.¹⁹

Clinical studies have demonstrated that bronchodilator and bronchoprotective effects of racemic salbutamol in asthma lie entirely with the (R) – isomer, moreover, in vitro cellular data implicated (S)-salbutamol as a possible cause of airway hyperactivity, bronchoconstriction or inflammation^{20, 21} perhaps induced by stimulating intracellular calcium accumulation and inhibiting adenyl cyclase.^{22, 23, 25} These preclinical findings have been confirmed in some clinical studies that shows a greater bronchodilation with levosalbutamol when compared to salbutamol when given either either as a long term therapy²⁵ (4 weeks) or when given in a single dose.²²

In the present study, bronchodilatory efficacy and safety of racemic salbutamol was compared to that of levosalbutamol in patients with asthma. A total of 100 eligible patients were enrolled in the study of which 50 patients were allocated to the racemic salbutamol group (group A) and 50 patients were allocated to the levosalbutamol group (group B).

Both the groups were comparable as regards age, sex distribution and height (Table 1). All patients were advised to stop all anti-asthma medications 24 hrs prior to study. Baseline data such as spirometry parameters like FEV₁, FVC, PEFR and heart rate were recorded during the first study visit (0 week). After obtaining baseline data group A and group B subjects were given racemic salbutamol 200 µg and levosalbutamol 100 µg respectively via MDI. After 20 minutes of drug administration repeat spirometry performed and patients were examined and interviewed for change in heart rate and other side effects. Patients in group A and B were prescribed racemic salbutamol (200 µg per puff) and levosalbutamol (100 µg per puff) respectively via metered dose inhaler for further four weeks starting from the day of first study visit for safety assessment¹⁸

In our study, at 0 week the mean percentage increase in FEV₁ and FVC after drug administration in levosalbutamol group was significantly higher than racemic salbutamol group (Fig no.1, 2), mean percentage increase in PEFR in levosalbutamol group was not significantly higher than racemic salbutamol group (Fig no. 3).

The mean percentage increase in FEV₁ and FVC in our study, at 0 week found in levosalbutamol groups were similar to those found in studies conducted by Khara et al.²⁴ The mean percentage increase in FEV₁ reported by Maiti¹⁸ et al. was greater in racemic salbutamol group as compared to levosalbutamol group. However the difference was not statistically significant.

Nelson et al.²⁵ conducted a 4 week study. Subjects were randomly assigned to receive nebulized racemic salbutamol, levosalbutamol or placebo. The mean percentage increase in FEV₁ after the first dose was significantly greater in the levosalbutamol group than that in the racemic salbutamol group (p = 0.03). This finding is similar to our study.

In our study, the mean percentage increase in FEV₁, FVC and PEFR after drug administration at 4 weeks was significantly higher in levosalbutamol group (Fig no. 1, 2, 3). At 4 weeks, Maiti et al.¹⁸, Khara et al.²⁴, and Kumar et al.²⁶ findings are similar to our study.

In our study, at 0 week and 4 week there was significantly higher increase in heart rate in racemic salbutamol group as compared to levosalbutamol group and the difference between the two groups was statistically highly significant (p < 0.01).

The side effects observed in both the groups in our study were consistent with the previous studies^{18, 25, 27, 28} (Fig no. 5). The most commonly noted side effects were palpitations, restlessness and tremors. The adverse events were self-limiting and did not require discontinuation of study drugs in the patients. The number of patients complaining of palpitations and restlessness was significantly higher in patients of racemic salbutamol group than in patients of levosalbutamol group (p < 0.05).

The majority of studies comparing racemic salbutamol and levosalbutamol have used nebulized formulations. The present study is one of the few studies to compare the bronchodilatory efficacy and safety of racemic salbutamol and levosalbutamol using metered dose inhaler (MDI). The study shows that levosalbutamol is a significantly better and safer bronchodilator than racemic salbutamol for use as reliever medication in asthma.

Conclusion

Thus we conclude that the levosalbutamol would be better choice in asthma compared with racemic salbutamol owing to its better efficacy and safety profile. The findings of this study should be confirmed by multicentric double-blind large population.

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