Comparative study of pulmonary functions after administration of albuterol and levalbuterol in patients with moderate to severe bronchial asthma

Kavita Rathore1, Tarun Kumar Sharma2*, M. L. Aseri1, Sunil Kumar Mathur1, Rakesh Chandra Gupta3, Satish Kumar Vardey4, G. G. Kaushik5 and Maheep Sinha4

1Department of Pharmacology, J. L. N. Medical College, Ajmer, Rajasthan, India.  
2Department of Biochemistry, Pt. B. D. Sharma, University of Health Sciences, P.G.I.M.S., Rohtak (Haryana), India 124001.  
3Department of Respiratory Medicine, J. L. N. Medical College, Ajmer, Rajasthan, India.  
4Department of Biochemistry, S. M. S. Medical College, Jaipur, India.  
5Department of Biochemistry, J. L. N. Medical College, Ajmer, Rajasthan, India.

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β2 - adrenoceptor stimulants play a key role in the management of bronchial asthma. This study was carried out on 80 patients of moderate to severe bronchial asthma. Group I (n=40) received Albuterol 2.5 mg/2.5 ml and Group II (n=40) received Levalbuterol 0.63 mg/2.5 ml TDS for 4 weeks. Baseline and post-treatment evaluation of lung function, respiratory rate, Total leucocytes Count, Total eosinophils Count, Serum potassium and Heart rate were carried out. In group I, Forced Expiratory Volume in 1 s was increased from 1.565±0.53 to 1.74±0.64 L (p<0.05) and in group II it was increased from 1.48±0.91 to 2.10±0.70 L (p<0.05). Forced vital capacity and Peak Expiratory Forced Rate were also increased in both groups (p<0.05). Respiratory rate and Total eosinophil count were significantly decreased by both drugs. Total leucocyte count was decreased non-significantly by both drugs (p>0.05). Serum potassium was decreased in group I from 3.77±0.38 to 2.96±0.49 mEq/L (p=0.001) and in group II from 3.79±0.57 to 3.51±0.56 mEq/L (P=0.017). Heart rate was significantly increased by both drugs, but it was greater with Albuterol. Levalbuterol appears to be more effective with better tolerability in low dose as compare to Albuterol.

Keywords: Albuterol, Levalbuterol, bronchial asthma, bronchodilation, β2-agonists.

INTRODUCTION

Asthma is a chronic inflammatory disease associated with airway hyper-responsiveness and episodic wheezing characterized by breathlessness, chest-tightness, and cough, particularly at night or in the early morning. Various cells like eosinophils, T-cells, mast cells, basophils and neutrophils play an important role in pathophysiology of asthma (Hamid et al., 2003). Asthma also involves contraction of airway smooth muscles, airway wall remodeling, edema and hyper secretion of mucus, contributing significantly to bronchial obstruction. As a result the use of bronchodilators remains at the forefront of modern approaches to asthma therapy (Fernandes et al., 2004). β2. Agonists drugs are the most commonly used bronchodilators used in the treatment of asthma to relieve bronchospasm (Dollery, 1999). The most commonly prescribed β2 agonist is Albuterol (Salbutamol), was first described by Brittain et al. (1968). It is also known as racemic albuterol, 1:1 mixture of (R) - and (S) - albuterol, stereoisomers. R - and RS - albuterol have a 2:1 potency ratio for improvement in FEV1 in asthmatic patients and shows that S - albuterol is clinically inactive. Because the RS - albuterol mixture...
contains only 50 % R - albuterol, it is clear that the clinical
effect of albuterol resides with the R - enantiomer.
Furthermore, the therapeutic ratios of R- and R,S -
albuterol are very similar, suggesting that the S -
enantiomer of albuterol does not affect its therapeutic
ratio (Lotvall et al., 2001). The new evidence suggests
that (S) - albuterol is not inert, but rather may exaggerate
airway reactivity and cause loss of asthma control.
Specifically, (S) - albuterol increases intracellular calcium
(Yamaguchi and McCullough, 1996; Mitra et al., 1998),
enhances experimental airway hyper responsiveness to
spasmogens (Morley, 1996; Johansson et al., 1996) and
may have pro-inflammatory effects as gauged by eosinophil superoxide production in response to IL-5
(Volchek et al., 1998). (S) - albuterol is metabolized 10-
fold more slowly than Levalbuterol (Walle et al., 1996;
Boult et al., 1996). With repeated frequent dosing, this
slower metabolism increases the proportion of (S) -
albuterol than Levalbuterol in vivo and exposes the
patient to relatively more potential adverse effects of (S) -
albuterol than the beneficial effects of Levalbuterol.

However, many studies show the comparative effect
of Albuterol and Levalbuterol on lung functions and
checked the tolerability of these drugs (Khurfan et al.,
2011; Maiti et al., 2011; Ali et al., 2010; Pun et al., 2009;
Qureshi et al., 2005). But with the best of our knowledge
there is no such study which shows the effect of both the
drugs on lung functions (FEV1, FVC, PEFR) along with
Respiratory rate, Total leucocyte count, Total eosinophil
count, Serum potassium estimation and Heart rate
evaluation in moderate to severe adult asthmatic patients
in Indian settings, which was the aim of the study.

MATERIALS AND METHODS

Study population/subjects

This single blind prospective study was carried out on 80 patients of
moderate to severe bronchial asthma in the Department of
Respiratory Medicine, J.L.N. Medical College & associates group of
hospitals, Ajmer, Rajasthan. Patients were selected according to
the GINA guidelines, 2010 (Forced Expiratory Volume in 1 s
between 40 to 60 % of the predicted value) with 6 months history of
chronic stable asthma and who required pharmacotherapy at the
time of the enrollment visit (V1). Patients of either sex (18 year or
above ages) who were able to perform clinical assessment and
previously not kept on regular inhaled corticosteroids or other bronchodilators like Methylxanthines or Anticholinergic group for
last three weeks. Patients who required steroids for the treatment of
asthma exacerbations were allowed to take low dose oral steroids
therapy with prednisolone or its equivalent at 8 mg/day. If more
than 8 mg/day was required, the patient was discontinued from the
study. Patients must be nonsmoker and not suffering from any
other chronic disease/condition, were included in this study.
Patients of other acute or chronic pulmonary disease,
cardiovascular disease, tremor, seizure or CNS disorder, history of
carcinoma, drug abuse, hormonal or metabolite disorders, diabetes
mellitus, sensitive to Albuterol or Levalbuterol, patients with
unstable asthma and who have to change asthma therapy and
unwilling patients were excluded from the study.

Study design

A total of 127 patients were enrolled in the study. Out of 127, forty
seven patients withdrawn before randomization, 29 of whom did not meet enrolment criteria. 9 were withdrawn due to intolerable
adverse events (including asthma exacerbations) and have to change asthma therapy. 6 patients were lost during follow up or
withdrawn for other causes and 3 patients voluntary withdrawn from study and finally 80 patients were left who were randomized into
two groups and successfully completed the study. Out of 80 patients, 40 patients (Group I) continued to use inhaled Albuterol
(Salbair) 2.5 mg/2.5 ml TDS for 4 weeks, remaining 40 patients
(Group II) received inhaled Levalbuterol (Levolin) 0.63 mg/2.5 ml
TDS for 4 weeks. During the enrollment, visit (V1); all patients
underwent a complete clinical examination, respiratory function
tests (PEFR, Peak expiratory flow rate; FEV1, Forced Expiratory
Volume in 1 second; FVC, Forced Vital Capacity), reversibility
testing, TLC, TEC, respiratory rate, serum potassium and heart rate evaluation. After treatment, visit (V2); assessment included clinical
examination of the respiratory system, spirometry, general objective
examination, TLC, TEC, respiratory rate, serum potassium and
heart rate evaluation. At least three spirometry maneuvers were
performed and best reading were recorded and compared with pre-
treatment values. Both group patients were asked about the need
for rescue medication (low dose oral corticosteroids if necessary)
during study period. Written informed consent was obtained from
patients participating in this study. The study was approved by
the institutional ethical review committee.

Statistical analyses

All results were expressed as mean ± SD. Differences between
mean were calculated by sample Student’s t’ test using SPSS
version 17.0. Values of p < 0.05 were considered statistically
significant. Results obtained were compared by paired t’ test. Inter
drug comparison was done by unpaired t’ test.

RESULTS

Both the groups were identical, subjects in both groups
comprise 80 cases out of which 44 patients (55 %) were
male and 36 patients were female (45 %).

Table 1 shows effect of Albuterol and Levalbuterol on
FEV1. In group I FEV1 was not significantly increased
from 1.565±0.53 to 1.74±.64 L (p > 0.05) and in group II
it was significantly increased from 1.48±0.91 to 2.10 ±
0.70L (p < 0.05). Inter drug comparison was also
significant.

FVC was significantly increased in group I from 2.30±0.76 to 2.65±0.83 L and in group II from 2.22±0.90
3.10±0.98 L (p < 0.05; Table 2) respectively. Inter drug
comparison shows effect was more significant with
Levalbuterol as compare to Albuterol.

Before treatment, the mean value of PEFR was
3.32±1.03 and 3.40 ± 2.10 L/s in Group I and Group II
respectively and after treatment it was 3.83±1.47 and
4.34 ± 0.93 L/s in Group I and Group II. The improvement
in PEFR after therapy in both groups was statistically
significant (p < 0.05) but there was greater improvement
in PEFR in group II than group I (Table 3).

Table 4 shows the significant decrease (p < 0.05) in
Table 1. Effect of both drugs on FEV\textsubscript{1} (L).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albuterol</th>
<th>Levalbuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>1.565 ± 0.53</td>
<td>1.48 ± 0.91</td>
</tr>
<tr>
<td>Post treatment</td>
<td>1.74 ± 0.64</td>
<td>2.10 ± 0.70</td>
</tr>
<tr>
<td>P* = 0.145 (NS)</td>
<td>P** = 0.612 (NS)</td>
<td>P** = 0.021 (S)</td>
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</table>

Table 2. Effect of both drugs on FVC (Litres).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albuterol</th>
<th>Levalbuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>2.30 ± 0.76</td>
<td>2.22 ± 0.90</td>
</tr>
<tr>
<td>Post treatment</td>
<td>2.65 ± 0.83</td>
<td>3.10 ± 0.98</td>
</tr>
<tr>
<td>P* = 0.03 (S)</td>
<td>P** = 0.03 (S)</td>
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</tbody>
</table>

Table 3. Effect of both drugs on PEFR (L/s).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albuterol</th>
<th>Levalbuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>3.32 ± 10.3</td>
<td>3.40 ± 2.10</td>
</tr>
<tr>
<td>Post treatment</td>
<td>3.83 ± 1.47</td>
<td>4.34 ± 0.93</td>
</tr>
<tr>
<td>P* = 0.05 (S)</td>
<td>P** = 0.005 (S)</td>
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</table>

Table 4. Effect of both the drugs on respiratory rate (per min).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albuterol</th>
<th>Levalbuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>26.75 ± 4.63</td>
<td>25.78 ± 3.88</td>
</tr>
<tr>
<td>Post treatment</td>
<td>23.21 ± 3.26</td>
<td>22.77 ± 2.84</td>
</tr>
<tr>
<td>P* = 0.001 (S)</td>
<td>P** = 0.001 (S)</td>
<td></td>
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</tbody>
</table>

Table 5. Effect of both drugs on TLC (cells/mm\textsuperscript{3}).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albuterol</th>
<th>Levalbuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>8511.10 ± 1179.09</td>
<td>8775 ± 1607.41</td>
</tr>
<tr>
<td>Post treatment</td>
<td>8381.87 ± 1683.89</td>
<td>8623 ± 1608.98</td>
</tr>
<tr>
<td>P* = 0.66 (NS)</td>
<td>P** = 0.64 (NS)</td>
<td></td>
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</tbody>
</table>

Table 6. Effect of both drugs on TEC (cells/mm\textsuperscript{3}).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albuterol</th>
<th>Levalbuterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>398.22 ± 125.90</td>
<td>404.72 ± 111.70</td>
</tr>
<tr>
<td>Post treatment</td>
<td>352.75 ± 124.71</td>
<td>356.25 ± 111.07</td>
</tr>
<tr>
<td>P* = 0.07 (NS)</td>
<td>P** = 0.034 (S)</td>
<td></td>
</tr>
</tbody>
</table>

respiratory rate by both the drugs which were increased during obstruction of airways. In group I it was from mean initial values 26.75±4.63 / minute to 23.27±3.26/minute (p < 0.05) and 25.78±3.88 to 22.77±2.84/ min (p < 0.05) in group II respectively.

As shown in Table 5 both the drugs did not significantly decrease the total leukocyte count. Total eosinophil count was not significantly decreased from 398.22±125.90 to 352.75 ± 124.71 cells/mm\textsuperscript{3} in group I (p > 0.05, Table 6) and significantly decreased from 404.72±111.70 to 356.25±111.07 cells/mm\textsuperscript{3} (p < 0.05, Table 6) in group II.

Before treatment, the mean value of serum potassium
level was 3.77±0.38 and 3.79±0.59 mEq/L in Group I and Group II respectively and after treatment it was 2.96±0.49 and 3.51±0.56 mEq/L in Group I and Group II. The decrease in serum potassium level after therapy in both groups was statistically significant (p < 0.05). But decrease was greater in group I than group II (Table 7).

As shown in Table 8 both the drugs significantly increased the heart rate and caused tachycardia. It was increased from 83.025±9.09 to 90.35±5.85 beats/minute (p < 0.05) in group I and 83.875±9.07 to 89.30±6.91 beats/minute (p < 0.05) in group II.

**DISCUSSION**

In present study we have compared the effects and efficacy of Salbutamol/Albuterol and Levalbuterol/Levosalbutamol in patients of moderate to severe asthma. Levalbuterol causes more bronchodilation with less side effects as compare to racemic albuterol because Levalbuterol is free from deleterious effects of (S) - albuterol. S - Albuterol does not activate β₂ adrenoceptors and have no clinically meaningful ability to relax airway smooth muscle and also does not modify activation of β₂ adrenoceptors by Levalbuterol so that for many years it was thought to be biologically inert. It suggests that the S - albuterol contained within the racemic albuterol exerts deleterious effects on pulmonary function. Several researchers gave reasons for that it may be due to racemic albuterol increases basal levels of intracellular Ca²⁺ and induces cell shortening and (S) - albuterol enhances the increase in intra cellular calcium induced by carbachol (Yamaguchi and McCullough, 1996). This is in direct contrast to the bronchodilator actions of Levalbuterol that has shown to decrease basal intracellular calcium (Baramki et al., 2002). The increase in intra cellular calcium caused by (S) - albuterol may hasten other adverse consequences. (S) - albuterol may cause an increase in Ca²⁺ in the microvasculature (Chetham et al., 1997). Some studies have indicated that the airway hyperresponsiveness produced by racemic albuterol resides with (S) - albuterol and this induction is not a function of β₂ receptor down regulation (Perrin-Fayolle et al., 1996). Furthermore, exposure to racemic albuterol induces airway hyper-responsiveness to a variety of spasmogens or antigens in animals (Jafarian et al., 1996). This hyper-responsiveness persists longer than the bronchodilator effects of the compound. S - Albuterol was found to increase airway responsiveness to methacholine for three hour after administration (Kelly, 2007). S - Albuterol enhances and Levalbuterol inhibits the contractile response of histamine and leucotrine C₄ (Schmekel et al., 1999). S - Albuterol also causes facilitation of acetylcholine release from dysfunctional prejunctional muscarinic autoreceptors (Zhang et al., 1998).

Thus, extensive evidence demonstrates that (S) - albuterol is not inert but might exacerbate airway reactivity and impairs the control of asthma. Because of the relatively slower metabolic sulfation of (S) - albuterol in comparison with (R) - albuterol, plasma concentrations of (S) - albuterol are several-fold greater and remain in circulation much longer after the administration of racemic albuterol (Gumbhir - shah et al., 1999). Moreover, (S) - albuterol appears to be preferentially retained in the lungs in comparison with (R) – albuterol (Dhand et al., 1999). Pharmacokinetically, it is well known that S - albuterol reaches higher circulating concentrations than R - albuterol after inhalation of the race mate. This is believed to be due to pre-systemic stereo selective metabolism of R - albuterol, which occurs in the gut and systemic circulation (Boulton et al., 1996) but not in the lungs (Ward et al., 2000).

**Table 7. Effect of both drugs on serum potassium (m Eq/L).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albuterol</th>
<th>Levalbuterol</th>
<th>p** for intra drug comparison</th>
<th>p** for inter drug comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>3.77±0.38</td>
<td>3.79±0.57</td>
<td>P**=0.854 (NS)</td>
<td></td>
</tr>
<tr>
<td>Post treatment</td>
<td>2.96±0.49</td>
<td>3.51±0.56</td>
<td>P**=0.001(S)</td>
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</table>

**Table 8. Effect of both drugs on heart rate (beats/minute).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Albuterol</th>
<th>Levalbuterol</th>
<th>p* for intra drug comparison</th>
<th>p** for inter drug comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre treatment</td>
<td>83.025±9.09</td>
<td>83.875±9.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post treatment</td>
<td>90.35±5.85</td>
<td>89.30±6.91</td>
<td>P**=0.5 (NS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P*=0.001 (S)</td>
<td>P*=0.003 (S)</td>
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</table>

p* for intra drug comparison and p** for inter drug comparison. (S) = Significant and (NS) = Non significant.
In our study, we observed that improvement in lung functions (FEV1, FVC, and PEFR) is greater with Levalbuterol than Albuterol. Similar results were found by some other studies also (Jantikar et al., 2007; Nowak et al., 2006). We also observed a significant reduction in respiratory rate (p < 0.05) by both drugs. The decrease in rate of respiration was because of relief in bronchial obstruction as shown by improvement in pulmonary function tests after therapy. This improvement leads to better oxygenation of blood and reduced respiratory drive (Barnes, 2008). However, some studies showed that reduction is not significant (Punj et al, 2009).

In our study, both the Albuterol and Levalbuterol decreased the total eosinophil count, which was increased in bronchial asthma. The decrease with Albuterol was not significant (p > 0.05) but decrease with Levalbuterol was significant (p < 0.05). Ezeamuzie et al. (1998) also confirmed that human eosinophils could be directly modulated by $\beta_2$ - adrenoceptors agonists. Both the drugs decreases Total leukocyte count also but results were not significant. There was a lack of studies which shows the effect of both the drugs on total eosinophil count which is an important parameter of respiratory functions.

There was a significant (p < 0.05) reduction in serum potassium level observed after administration of both the drugs but hypokalemia was greater with albuterol (p = 0.001) as compared to levalbuterol (p = 0.017). Similar results were also observed by Punj et al. (2009), Nowalk et al. (2006) and Nelson et al. (1998). The possible mechanism behind hypokalemia is, intracellular uptake of potassium into skeletal muscle by stimulation of membrane bound Na/K ATP-ase pump by $\beta_2$ - agonists (Lipworth et al., 1989).

In our study there was significant increase in heart rate observed after administration of both drugs (p < 0.05) but it was greater with albuterol. Our results were consistent with Nelson et al. (1998) and Milgrom et al. (2001). Lam et al. (2003) also observed an increase in heart rate but results were not significant. This increase in heart rate may aggravate tachyarrhythmia because these agents tend to increase sympathetic activity and inhaled $\beta_2$ - agonists shows positive chronotropic effects which leads to increase in AV nodal conduction, decrease in AV nodal, atrial and ventricular refractoriness. These alterations can contribute to the generation of spontaneous arrhythmias (Kallergis et al., 2005).

Elevated heart rate and decreased serum potassium may lead to cardiomyopathy, coronary artery disease, sudden cardiac arrest so these parameters should considered seriously during administration of $\beta_2$ - agonist drugs.

**Conclusions**

This study concludes that Levalbuterol has better therapeutic index than Albuterol. The 0.63 mg/2.5 ml Levalbuterol (R - albuterol) dose provided better efficacy with reduced systemic $\beta_2$ - agonist side effects as compared to 2.5 mg/2.5 ml of standard racemic albuterol or Albuterol. It also indicates that the bronchodilator effect of racemic albuterol (Albuterol) is due to R - albuterol and S - albuterol is considered as inactive but it is not yet clear and it needs further research.

**ACKNOWLEDGMENT**

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**REFERENCES**


