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Full Length Research Paper

Effects of Albuterol vs. Levalbuterol on Pulmonary Function in Moderate to Severe Bronchial Asthma: A Comparative Study

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β_2 - 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 leukocytes Count, Total eosinophil 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 leukocyte 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, β_2-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 fore front of modern approaches to asthma therapy (Fernandes et al., 2004). β_2- Agonists drugs are the most commonly used bronchodilators used in the treatment of asthma to relive bronchospasm (Dollery, 1999). The most commonly prescribed β_2- 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 FEV_1 in asthmatic patients and shows that S - albuterol is clinically inactive. Because the RS - albuterol mixture

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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; Boulton 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 shows the comparative effect of Albuterol and Levalbuterol on lung functions and checked the tolerability of these drugs (Khorfan et al., 2011; Maiti et al., 2011; Ali et al., 2010; Punj 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 leukocyte 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 (Salbiar) 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; FEV_1, 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 FEV_1. In group I FEV_1 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 to 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_1 (L).

Parameter	Albuterol	Levalbuterol	
Pre treatment	1.565 ± 0.53	1.48 ± 0.91	P**=0.612 (NS)
Post treatment	1.74 ± 0.64	2.10 ± 0.70	P**=0.021 (S)
	P*=0.145 (NS)	P*=0.001 (S)	

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

Parameter	Albuterol	Levalbuterol	
Pre treatment	2.30 ± 0.76	2.22 ± 0.90	P**=0.619 (NS)
Post treatment	2.65 ± 0.83	3.10 ± 0.98	P**=0.03 (S)
	P*=0.03 (S)	P*=0.001 (S)	

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

Parameter	Albuterol	Levalbuterol	
Pre treatment	3.32 ± 10.3	3.40 ± 2.10	P**=0.830 (NS)
Post treatment	3.83 ± 1.47	4.34 ± 0.93	P**=0.007 (S)
	P*=0.05 (S)	P*=0.005 (S)	

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

Parameter	Albuterol	Levalbuterol	
Pre treatment	26.75 ± 4.63	25.78 ± 3.88	P**=0.309 (NS)
Post treatment	23.21 ± 3.26	22.77 ± 2.84	P**=0.51 (NS)
	P*=0.001 (S)	P*=0.001 (S)	

Table 5. Effect of both drugs on TLC (cells/mm^3).

Parameter	Albuterol	Levalbuterol	
Pre treatment	8511.10 ± 1179.09	8775 ± 1607.41	P**=0.407 (NS)
Post treatment	8381.87 ± 1683.89	8623 ± 1608.98	P**=0.516 (NS)
	P*=0.66 (NS)	P*=0.64 (NS)	

Table 6. Effect of both drugs on TEC (cells/mm^3).

Parameter	Albuterol	Levalbuterol	
Pre treatment	398.22 ± 125.90	404.72 ± 111.70	P**=0.808 (NS)
Post treatment	352.75 ± 124.71	356.25 ± 111.07	P**=0.895 (NS)
	P*=0.07 (NS)	P*=0.034 (S)	

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^3 in group I ($p > 0.05$, Table 6) and significantly decreased from 404.72±111.70 to 356.25±111.07 cells/mm^3 ($p < 0.05$, Table 6) in group II.

Before treatment, the mean value of serum potassium

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

Parameter	Albuterol	Levalbuterol	
Pre treatment	3.77 ± 0.38	3.79 ± 0.57	P**= 0.854 (NS)
Post treatment	2.96 ± 0.49	3.51 ± 0.56	P**=0.001(S)
	P*=0.001(S)	P*=0.017(S)	-

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

Parameter	Albuterol	Levalbuterol	
Pre treatment	83.025 ± 9.09	83.875 ± 9.07	_
Post treatment	90.35 ± 5.85	89.30 ± 6.91	P**=0.5 (NS)
	P*=0.001 (S)	P*=0.003 (S)	-

p* for intra drug comparison and p** for inter drug comparison. (S) = Significant and (NS) = Non significant.

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 β_{2-} adrenoceptors and have no clinically meaningful ability to relax airway smooth muscle and also does not modify activation of β_{2-} 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 Ca^{++} 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 Ca^{++} 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 β_2- 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 C_4 (Schmekel et al., 1999). S - Albuterol also causes facilitation of acetylcholine release from dysfunctional prejunctional muscarinic autorecptors (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).

In Our study, we observed that improvement in lung functions (FEV_1, 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 β_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 β_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 tachyarrthmia because these agents tend to increase sympathetic activity and inhaled β_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 β_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 β_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.

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