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Comparative Study Of Efficacy And Adverse Effect Profile Of Racemic Salbutamol With Levosalbutamol In Patients With Stable Chronic Obstructive Pulmonary Disease

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ABSTRACT

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a slowly progressive airwayobstruction characterized by expiratory airflow limitation that is not fully reversible. Short actingselective beta$_2$ agonists are used as first line drugs for the management of airway obstruction in patientswith stable disease.

AIM: To compare and evaluate the efficacy and adverse effect profile among two commonly used beta$_2$agonists, racemic salbutamol and levosalbutamol.

METHODS: A parallel, comparative and prospective study was designed to evaluate the effectiveness of2mg racemic salbutamol and 1 mg Levosalbutamol given orally thrice a day for a period of 21 days. Allthe patients underwent lung function assessment by spirometry before initiating the study and the samewere repeated every week thereafter. Subjective assessment of side effects was done at every follow upvisit. The results were analysed statistically.

RESULTS: Mean Forced expiratory flow in the first second (FEV1) before and after therapy in theracemic salbutamol group was 1.54 and 1.58 and in levosalbutamol group was 1.66 and 1.72 respectivelywith significant improvement in both the groups. Percentage of forced expiratory volume in the firstsecond (%FEV1) before and after therapy in racemic salbutamol group was 76.51% and 78.4% and inlevosalbutamol group 75.29 % and 78.43% respectively. Adverse affects such as palpitations, tremors,headache and anxiety were significantly low in levosalbutamol group.

CONCLUSION: Both racemic salbutamol and levosalbutamol are significantly effective in relieving thesymptoms of COPD but in terms of tolerability and safety, levosalbutamol was found to be superior tosalbutamol.

Key words: Levosalbutamol, beta2 agonists, spirometry, salbutamol, isomers

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease of the airway that is characterised by gradual loss of lung function associated with chronic cough, increased sputum production, shortness of breath and limitation of physical activity[1]. It is estimated that COPD becomes the third leading cause of death worldwide by 2030[2]. The risk factors for COPD include environmental factors like smoking, occupational exposures, air pollution, childhood respiratory infections. Characteristic symptoms of COPD include progressive dyspnoea, chronic cough with sputum production.

The ratio of forced expiratory volume in 1 second (FEV1) to functional vital capacity (FVC) reflects the rate of lung emptying. Presence of obstructive ventilator defect (COPD) is defined as the value of FEV1/FVC < 0.7. Classification of obstructive disease can be made according to the recent Global initiative for chronic obstructive lung disease (GOLD) guidelines, using the measured FEV1as percentage of the predicted FEV1 as given in the table 1. Patients with COPD assessment test (CAT) score < 10, history of exacerbations ≤ 1 and GOLD spirometric stage I or II are said to be stable or low risk. According to GOLD guidelines, stable patients are treated with either oral or nebulised $beta_2$ agonists.

S. no	GOLD SPIROMETRIC STAGE	SPIROMETRIC ANALYSIS
1	GOLD I	FEV1 ≥ 80 % of the predicted
2	GOLD II	50% ≤ FEV1< 80% predicted
3	GOLD III	30% ≤ FEV1< 50% predicted
4	GOLD IV	FEV1 < 30% predicted or FEV1 < 50% and respiratory failure

Table.no.1: Spirometric staging of COPD using %FEV1

The treatment of COPD is aimed at preventing disease progression, relieving symptoms, improving the quality of life, treating the exacerbations and improvement of survival. Along with drug therapy, patient education, cessation of smoking, good nutritional support and regular self directed exercises are recommended. The recommended choice of treatment in Gold staging I and II are short acting beta 2 agonist or anticholinergics.

The autonomic nervous system regulates the airway tone through the release of neurotransmitters that activate specific autonomic receptors. Activation of $beta_2$-adrenergic receptors on airway smooth muscle by epinephrine, a neurotransmitter of the adrenergic system leads to an increase in the intracellular concentration of cyclic-3′, 5′-adenosine monophosphate (cyclic AMP). This

increase in the concentration of cyclic AMP is associated with bronchial smooth muscle relaxation by reducing intracellular ionic calcium concentration [3]. Increased cyclic AMP concentration also inhibits the release of inflammatory mediators from mast cells and eosinophils.

Beta2-adrenoceptor agonists are the first line of drugs used either orally or in the form of nebulisation in patients with stable COPD. They are developed based on the structure of endogenous epinephrine which is produced in the body as a pure single isomer R-epinephrine. Only the R- isomer fits into the three dimensional conformation of the beta 2 adrenoceptors. Salbutamol, the most commonly and widely used bronchodilator among all beta 2 agonists, is a chiral drug with two isomers R (levo) and S (dextro) in equal quantities [4, 5]. It has been the mainstay of treatment for airway obstruction since a very long time [6]. The R isomer, referred to as levosalbutamol is therapeutically active in opposing the bronchial smooth muscle contraction [7, 8]. It has greater binding affinity than the S–Salbutamol for the $beta_2$ adrenergic receptor and has a better therapeutic ratio than racemic salbutamol [9]. Levosalbutamol has 2 fold greater affinity for beta 2 adrenergic receptors and about 100 fold greater binding affinity when compared to S-Salbutamol.

S-Salbutamol on the other hand increases airway hyper responsiveness by a beta2 adrenergic independent mechanism and is thought to be pharmacologically inactive [8, 9]. Current studies indicate that the S isomer is devoid of bronchodilator activity [10]. It may also promote airway obstruction increasing mucous secretion by the airway epithelial cells leading to disturbances in mucociliary clearance [11]. S-salbutamol has been shown to promote the synthesis and release of numerous inflammatory mediators from mast cells, T lymphocytes and airway epithelial of cells. Levosalbutamol when administered as the single isomer is said to avoid all the potential adverse effect of (S) isomer because of its property of fitting into the three dimensional conformation of β2 adrenoreceptor proteins.

The short acting β2-agonists like salbutamol provide effective bronchodilatation over a 6 to 8 hour period. Salbutamol is metabolized in human tissues mainly in liver by sulfation and the inactive metabolites produced are rapidly excreted in urine. Rates of metabolism for the two isomers are different. R-isomer is metabolized about eight times faster than S-salbutamol leading to a longer half-life and increased accumulation of S-salbutamol in tissues with repeated dosing.

So the present study was taken up to compare the efficacy and safety of both the

drugs racemic salbutamol and levosalbutamol in patients with COPD.

METHODS:

The study was done in the department of Pulmonology, Siddhartha medical college, Vijayawada, after taking approval from the ethics committee. It was a prospective, randomised parallel study conducted in patients with stable COPD for a period of 3 weeks. An informed written consent was taken from all the patients included in the study. A total of 210 patients who met the inclusion and exclusion criteria were selected and randomly divided into two groups of 105 each. One group received oral racemic salbutamol in the dose of 2mg and the other group received oral levosalbutamol 1mg thrice a day. Before initiating the treatment, each patient was subjected to spirometric evaluation and the baseline readings were recorded

INCLUSION CRITERIA

1. Patients who were diagnosed with COPD clinically and spirometrically in the department of Pulmonology, Government general hospital, Siddhartha medical college, Vijayawada.
2. Patients, both male and female above the age of 35 years and below the age of 65 years suffering with COPD.
3. As salbutamol and levosalbutamol are given as mono therapy, COPD patients having FEV1 above 80% predicted (Stage I) and those with FEV1 ranging between 60-80% predicted (Stage II) only were included.

EXCLUSION CRITERIA

1. Patients below the age of 35 and above the age of 65 years.
2. Patients who had moderate/severe COPD or exacerbations in the last 4 weeks
3. Patients on inhaled or systemic corticosteroids at the time of screening
4. Patients with active respiratory disease other than COPD like tuberculosis, Bronchial asthma, pneumonias and acute bronchitis of different aetiology, lung malignancies and other chronic miscellaneous lung disorders.
5. Patients with compromised cardiac, renal and hepatic parameters.

Before initiating the study, all patients were assessed by history, clinical examination, chest X-ray and sputum examination. Data regarding smoking history and exacerbations in the past one year were recorded. Lung function tests that are important in diagnosing and monitoring COPD were performed by a simple non invasive and cost effective device spirometry.

Spirometric evaluation:

It measures the extent of airflow in and out of lungs. After sufficient practice, all the

patients were asked to take a deep inspiration and blow into a tube attached to the spirometer with a nose clip on their nose. A computerised sensor calculates the airflow and the results are graphically expressed. The graph demonstrates the patient's rate and volume of air that can be forced out of the lungs. The same spirometer was used throughout the study period. The test was performed in each patient every week and the readings were documented. Subjectively patients were enquired about the adverse effects at every visit. The same spirometer was used throughout the study period.

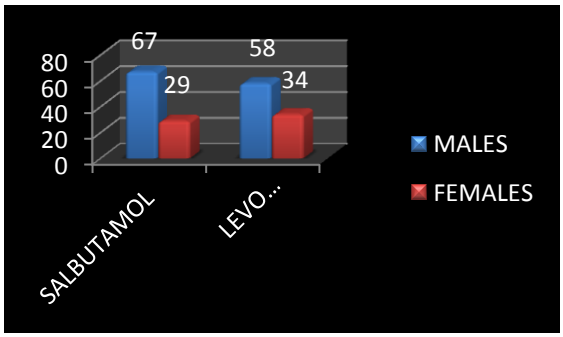
Statistical analysis:

The data were analyzed statistically using Students t test and Chi square test. A p value < 0.05 was considered to be significant.

RESULTS: Out of the total 210 patients, 157 (%) were male and 73(%) were female .Due to non compliance and failure to come for subsequent follow-up visits, 22 patients (9 from salbutamol group and 13 from levosalbutamol) were excluded from the study. A total of 96 patients from racemic salbutamol group and 92 patients from levosalbutamol group (188 patients in total) completed the study. Graph.no:1 shows the distribution of both the sexes in the two groups. No significant difference was found in the distribution of both the sexes in the study groups as shown in the table no.2

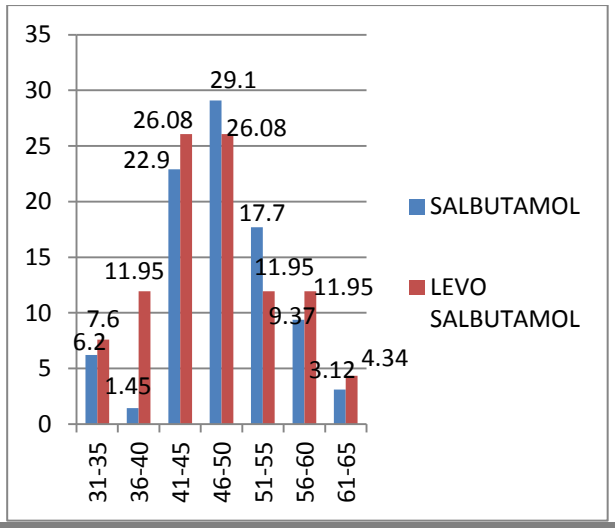
	SALBUTAM	LEVOSALBUTA
	OL GROUP	MOL GROUP
Males	67	58
Females	29	34
Total	96	92
Chi^2 TEST	Chi^2 value:0.9602	
P Value	0.3271	
Inference	Not significant	

Table no.2: Sex wise distribution of patients among both the groups.



Graph no- 1: Sex distribution in both the study groups

Mean age group of patients in the racemic salbutamol group and levosalbutamol group was 46.92 ± 7.2 and 46.54 ±7.6 respectively. There was no significant age wise difference between the two groups.

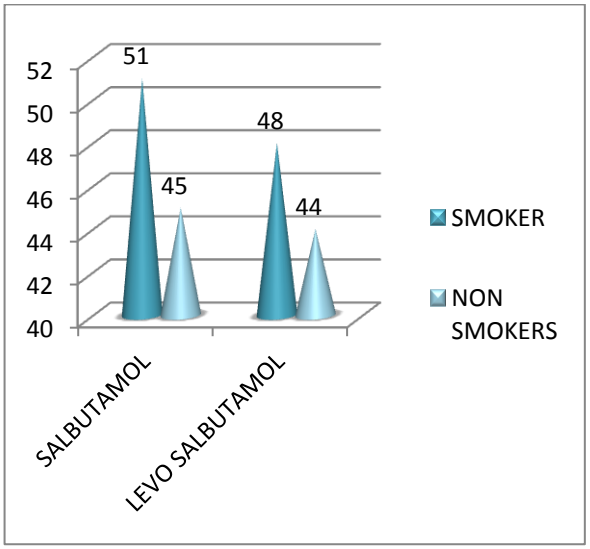


Graph no-2: Age wise distribution of patients in both the groups (figures in percentages)

History of smoking was taken from all the patients .Habit of smoking was present in 53.12% (51) of patients on racemic salbutamol and 52.17 % (48) of patients receiving levosalbutamol as shown in the Graph. no.2. Difference between distribution of patients who smoke in both the study populations was not significant (p value <0.05). All the patients of both the groups with the habit of smoking were males (100%).

History of smoking	Salbutamol group	Levosalbutamol group
Smokers	51 (53.12 %)	48 (52.17%)
Non smokers	45 (46.88 %)	44 (47.83%)
Chi ^{2} value	0.017	
P Value : 0.8961 (>0.05)	Inference: Not significant	

Table no.3: Distribution of patients with the habit of smoking among both the groups.



Graph no-3.Distribution of patients with the habit of smoking among both the groups (figures in numbers)

Patients of salbutamol and levosalbutamol groups were given 2 mg and 1mg tablets respectively three times a day for a period of 21 days. During follow-up, all the patients were enquired about improvement or relief of symptoms and development of any adverse effects. On weekly assessment of spirometric analysis, improvement in lung parameters in both the groups, more in levosalbutamol group was observed as shown in table.no:4

spirometric parameter	Day	Salbutamol group (n= 96) Mean ± sd	Levosalbutamol Group (n= 92) Mean ± sd
FEV1	0	1.539 ± 0.678	1.662± 0.137
	7	1.545± 0.194	1.682± 0.143
	14	1.562±0.189	1.694± 0.147
	21	1.577± 0.197	1.719 ± 0.143
% OF FEV1 predicted	0	76.51± 5.23	75.29±6.33
	7	76.89± 4.76	76.38± 5.65
	14	77.71± 4.65	77.09± 5.08
	21	78.37±4.54	78.43±5.46

Table no.4: Improvements in the lung parameters among both the study groups.

Paired t test was applied to compare the values of FEV1 and % FEV1before and after the study period in each group separately. Improvements in FEV1 and %FEV1 values were statistically significant in salbutamol and levosalbutamol group as shown in table 5 and table 6 respectively.

Salbutamol group	Fev1		% Fev1	
Statistical analysis	Before	After	Before	After
Mean	1.539	1.577	76.511	78.37
Standard deviation	0.191	0.198	5.23	4.54
T value	14.066		14.291	
P value	< 0.0001		< 0.0001	

Table no.5: Improvement in the values of FEV1 and % FEV1 in salbutamol group

Levosalbutamol group	Fev1		%Fev1	
Statistical analysis	Before	After	Before	After
Mean	1.6627	1.7196	75.29	78.43
Standard deviation	0.1364	0.1427	6.28	5.46
T value	23.6956		23.6332	
P value	<0.0001		<0.0001	

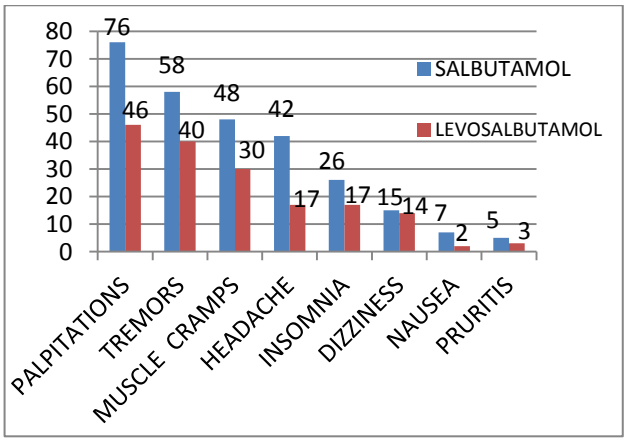
Table no.6: Improvement in the values of FEV1 and % FEV1 in levosalbutamol group

The predictable side effects with beta 2 agonists are palpitations, tremor, muscle cramps, restlessness and insomnia. Side effects seen with both the drugs in the study population were analysed using chi square test. Most common side effects seen in patients receiving salbutamol were palpitations (76%), tremors (58%), muscle cramps (48%) and headache (42%) which were significantly higher than those seen in levosalbutamol group as shown in the graph.no:4. Other side effects which were seen more in salbutamol group but not significantly different from levosalbutamol were insomnia, dizziness, pruritis and nausea.

Among all the side effects, palpitations was the most common side effect in both the groups but significantly higher in salbutamol group with a p value of < 0.0001.This was followed by tremors and muscle cramps. Patients with palpitations and tremors were

SIDE EFFECTS	SALBUTOMOL	LEVOSALBUTOMOL	p value
PALPITATIONS	76 %	46 %	0.0001
TREMORS	58 %	40 %	0.0201
HEADACHE	42 %	17 %	0.0001
INSOMNIA	26 %	17 %	0.1602
DIZZINESS	15 %	14 %	0.9383
PRURITIS	5 %	3 %	0.5084
MUSCLE CRAMPS	48 %	30 %	0.0155
NAUSEA	7 %	2 %	0.1003

Table no. 7: Adverse effects seen in both study groups



Graph no.4: Adverse effect profile of both the study groups (figures in percentages).

reassured and those with headache and muscle cramps were symptomatically treated with analgesics.

Discussion:

Beta 2 agonists are the commonly used medications in COPD and bronchial asthma in all dosage forms. For symptomatic relief, beta 2 agonists have paramount importance in COPD.

Usually, beta 2 agonists are administered in the form of inhalers in both disorders in view of their adverse effect profile when used by other routes. In view of high cost of inhalation therapy in developing countries like India, patients of COPD opt for oral beta 2 agonists especially salbutamol in the form of tablet or syrup. These drugs are not only prescribed by doctors, but are also available as over the counter medications.

Salbutamol, a short-acting β_2-agonist is the most widely used bronchodilator in the treatment of COPD. It

consists of a racemic mixture of equal amounts of R and S enantiomers. These enantiomers have similar physical and chemical properties, but have different receptor specificity. Levosalbutamol has nearly two fold greater affinity for beta2 adrenergic receptor than S-salbutamol [9]. The bronchodilator properties of racemic salbutamol R, S have been shown to be attributed entirely to the R-enantiomer as it fits

into the three dimensional confirmation of beta2 adrenoreceptor proteins[5].

S-salbutamol was previously considered as an inert filler in the racemic mixture. Recently, various animal and human studies have shown that S-salbutamol is not inert but rather has deleterious effects on chronic administration. Chronic usage of racemic salbutamol may lead to loss of effectiveness and clinical deterioration. Clinical studies have demonstrated that the bronchodilator effects of racemic salbutamol in subjects with asthma and COPD lie entirely with the R-isomer [10, 12]. This causes an increase in the therapeutic index of levosalbutamol when compared to racemic salbutamol. These divergent pharmacologic properties form the rationale for the advantages of levosalbutamol over racemic salbutamol in the treatment of COPD and other airway disorders. Formulation of salbutamol containing only R (levo) isomer has been available since the last few years following its approval by FDA (Food and Drug Administration) in 1999 for clinical use in asthma and COPD patients as a single isomer.

In developing countries like India, oral racemic salbutamol is the most commonly used beta 2 agonist as the first line drug in the treatment of COPD. Poor economic background, financial constraints of the patients to opt for inhalational therapy, lack of awareness on the safety profile and easy availability of the drug as an over the counter medication also contributes to its chronic usage. Also cost difference between the two drugs used in the study was not significant (<5%). In this scenario, this study has been conducted to compare the efficacy and safety of salbutamol (racemic) with levosalbutamol administered orally to patients of stable COPD.

In the present study, out of a total of 210 patients, 188 completed the study out of which 96 patients were on salbutamol and 92 patients were on levosalbutamol. With respect to the spirometric variables, patients showed gradual improvement on 7^{th}, 14^{th} and 21^{st} days of treatment in both the groups. It was observed that 1mg of oral levosalbutamol administered thrice a day produced better bronchodilator response than that of 2 mg racemic salbutamol in subjects with stable COPD. The spirometric variables showed significant improvement in FEV_1 and %FEV values in both the groups but more in the levosalbutamol group. These improvements in FEV1 are comparable to a previous multicenter, randomized, double blind, parallel study done in 2006 by James F.Donohue et al on subjects with COPD, where nebulised levosalbutamol was compared with racemic salbutamol and placebo. Also, levosalbutamol showed significant bronchodilatation compared to salbutamol and placebo

adverse effects observed in both the study groups were mild in nature and did not require hospitalisation. Levosalbutamol group had significantly lesser side effects compared to racemic salbutamol which can be attributed to its greater affinity towards beta 2 receptors and structural similarity to endogenous epinephrine. With respect to adverse effect profile, levosalbutamol was found to be superior to racemic salbutamol.

Not many studies are available on the safety profile of oral salbutamol and levosalbutamol in patients of COPD. Also, in majority of the studies available, inhalational route was used for administration of these drugs.

CONCLUSION: Levosalbutamol is an effective bronchodilator whose primary mechanism of action is unimpeded by S-salbutamol. Therefore, when compared with racemic salbutamol, clinically comparable bronchodilation can be achieved by levosalbutamol with doses that substantially cause less beta-mediated side effects. Based on the results of this study, we conclude that levosalbutamol would be a better choice in patients with stable COPD as it shows similar therapeutic efficacy and superior safety profile when compared to racemic salbutamol in patients with COPD. Because the study had the limitations of being non blinded and conducted in a single-centre, the findings of this exploratory study should be confirmed by multicentric, randomized, double-blind, large population studies. Also as oral racemic salbutamol is the most common bronchodilator used in India in the treatment of COPD, more studies are needed to confirm the present findings following which, steps should also be taken to replace the production of salbutamol and its combination preparations with levosalbutamol. Also awareness should be created in the community to encourage the usage of levosalbutamol in place of racemic salbutamol.

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