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COMPARATIVE STUDY OF EFFECTS TWO β_2 ADRENERGIC AGONISTS ON BIOCHEMICAL PARAMETERS IN MODERATE TO SEVERE BRONCHIAL ASTHMA PATIENTS

Kavita Rathore [1], Neha Sharma*[2], M.L. Aseri [1], Sunil Kumar Mathur [1] and Sanjay Sankhla [1]

Department of Pharmacology, J.L.N. Medical College [1], Ajmer, Rajasthan, India
Department of Biochemistry, SRMS-IMS [2], Bareilly- 243202, Uttar Pradesh, India

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Correspondence to Author:

Neha Sharma

Department of Biochemistry, SRMS-IMS, Bareilly- 243202, Uttar Pradesh, India

E-mail: neha16.sharma@gmail.com

ABSTRACT:

Background: β2- agonist drugs are frequently prescribed in asthmatics. Apart from bronchodilation they affect biochemical and physical parameters of the body.

Method: Total 80 patients were divided into two groups. Group I (n=40) received Albuterol- 2.5mg./2.5ml. TDS and Group II (n=40) received Levalbuterol- 0.63mg./2.5ml, TDS via nebulizer for 4 weeks. Baseline and post-treatment estimation of biochemical parameters including, fasting and postprandial plasma glucose levels, serum Na+, serum K+ levels, lipid profile, Monitoring of systolic and diastolic BP and adverse drug effects evaluation were carried out.

Results: Significantly changes were in serum lipid profile and blood glucose in both the groups but increase was more in group I. Serum K+ level was decreased significantly ($p<0.05$) in both groups but decrease was more in group I patients. The fasting and postprandial plasma glucose levels were significantly increased in both the groups but increase was more in group I. Systolic BP increases and diastolic BP decreases after administration of both drugs. There was no significant change observed in Serum Na+ level after administration of both drugs. After administration of both the drugs, an increase was observed in serum Lipid profile level. Adverse drug profile showed that Levalbuterol produce less adverse effects as compare to Albuterol.

Conclusion: This study concludes that Levalbuterol is safer and it carries fewer incidences of adverse effects as compare to Albuterol.

INTRODUCTION: Asthma is a lung disorder that encompass virtually the entire spectrum of life i.e. it can involve all age groups from infancy to geriatric age group.

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The prevalence of asthma worldwide is around 300 million people with a mortality of around 0.3 million per year [1]. The overall burden of asthma in india is estimated at more than 15 million patients [2]. Pharmacotherapy is the main constituent for treating asthma.

The various pharmacological agents commonly used in asthma managements include β_2 adrenergic receptor agonists, methyl xanthenes, corticosteroids, mast cell stabilizers, leukotrienes inhibitors [1].

Out of these β2 agonists delivered to the airways by inhalation or by oral route, provide rapid and effective reversal of acute airway obstruction caused by bronchoconstriction [3]. Apart from beneficial effects, there are some significant adverse drug reactions with β_2 agonists. Tremor and tachycardia are common adverse effect; however tolerance generally develops to tremors. Arterial O_2 may fall when treatment of acute exacerbation of asthma begun; this may be due to drug induced pulmonary vascular dilation.

When given parentally, these drugs also increase concentrations of glucose, lactate and free fatty acids in plasma and decrease the concentration of K^+. In some diabetic patients hyperglycemia may be worsened by these drugs and higher insulin may be required [4]. They can induce mild appetite suppression, headache, nausea and sleep disturbances [5].

Albuterol and Levalbuterol are β_2 agonist drugs. Albuterol is a racemic mixture of R, S enantiomers [6] and levalbuterol is a new drug, an R-isomer of racemic Albuterol. It was introduced firstly in United States as brand name XOPENEX and approved by FDA in 1999. Apart from bronchodilation both the drugs causes β_2 receptor mediated side effects.

Many studies have been conducted to study the effect of both the drugs on pulmonary parameters but there were a few studies available to compare both the drugs on the basis of biochemical, physical and adverse reaction profile. Till now, this is a matter of huge argument that whether Levalbuterol is safer than Albuterol or not. In view of the aforementioned controversial literature, it was decided to evaluate the biochemical, physical and adverse drug reaction profile in Indian population.

MATERIALS AND METHODS:

Study Population/Subjects: This double 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 second between 40 to 60 % of the predicted value) with 6 months history of chronic stable asthma and who require pharmacotherapy at the time of the enrollment visit (V1). Patients of either sex (18 year or above ages) were included who 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 excluded from the study.

Patients who were nonsmoker and not suffering from any other chronic disease/condition, included in this study. Patient 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 or sensitive to Albuterol or Levalbuterol, patients with unstable asthma, who have to change asthma therapy and unwilling patients were excluded from the study.

Study design: After approval from institutional ethics committee total of 80 patients were randomized into two groups. 40 patients (Group I) continued to use inhaled Albuterol (Salbiar) 2.5mg/2.5mL three times a day for 4-weeks, remaining 40 patients (Group II) received inhaled Levalbuterol (Levolin) 0.63mg/2.5mL three times a day for 4-weeks. During the enrollment, visit (V1); all patients underwent a complete clinical examination, Baseline and post-treatment estimation of biochemical parameters including , fasting and postprandial plasma glucose levels, serum Na^+ , serum K^+ levels, lipid profile, Monitoring of systolic and diastolic BP and adverse drug effects evaluation were carried out. Both group patients were asked about the need for rescue medication (i.e. low dose oral corticosteroids if necessary) during study period. Written informed consent was obtained from patients participating in this study

Statistical analysis: All results were expressed as mean ± SD. Differences between means were calculated by samples 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 on different biochemical and physical parameters. Among them Plasma glucose (fasting) and post-prandial plasma glucose levels were significantly increased from 79.62 ± 4.80 mg/dL to 90.57 ± 5.35 mg/dL and 108.7 ± 8.37 mg/dL to 121.87 ± 8.12 mg/dL ($p < 0.05$).

Before treatment, the mean value of serum K^+ was 3.77 ± 0.38 mEq/L and after treatment it was 2.96 ± 0.49 mEq/L. The decrease in serum K^+ after therapy was statistically significant ($p < 0.05$). Albuterol did not alter serum Na^+ levels adversely and results were not significant ($p > 0.05$).

TABLE 1: EFFECT OF ALBUTEROL ON BIOCHEMICAL AND PHYSICAL PARAMETERS

Parameters	Pre-treatment (Albuterol)	Post-treatment (Albuterol)	p
Plasma glucose (fasting)(mg/dL)	79.62 ± 4.80	90.57 ± 5.35	0.001 S
Plasma glucose (post prandial)(mg/dL)	108.7 ± 8.37	121.87 ± 8.12	0.001 S
Serum Na+ level(mEq/L)	139.025 ± 3.37	140.0 ± 4.52	0.10 NS
Serum K+ level	3.77 ± 0.38	2.96 ± 0.49	0.001 S
Serum cholesterol	187.07 ± 9.78	184.07 ± 9.58	0.129 NS
LDL-cholesterol	131.10 ± 11.86	126.92 ± 11.26	0.07 NS
VLDL-cholesterol	17.97 ± 2.25	17.47 ± 2.19	0.26 NS
HDL-cholesterol	37.68 ± 4.72	38.10 ± 4.82	0.682 NS
Triglycerides	89.87 ± 11.26	87.37 ± 10.95	0.26 NS
Systolic blood pressure(mmHg)	127.28 ± 9.21	129.83 ± 8.44	0.001 S
Diastolic blood pressure(mmHg)	80.5 ± 5.95	78.5 ± 4.96	0.001 S

As shown in Table 1, Albuterol decreases the serum cholesterol and LDL-cholesterol. But results were statistically not significant ($p > 0.05$). The decrease in serum VLDL-cholesterol and triglycerides observed and a slight rise in HDL-cholesterol also observed after administration Albuetrol but results were not significant ($p > 0.05$). Albuterol increases systolic blood pressure from 127.28 ± 9.21 mmHg to 129.83 ± 8.44 mmHg in group I and diastolic blood pressure decreases from 80.5 ± 5.95 mmHg to 78.5 ± 4.96 mmHg ($p < 0.05$), (Table 1)

Table 2 shows that Levalbuterol also increase plasma glucose fasting from 84.37 ± 7.49 mg/dL to 89.52 ± 7.48 mg/dL and plasma glucose (post-prandial) from 119.90 ± 9.60 mg/dL to 124.52 ± 9.06 mg/dL ,results were statistically significant($p < 0.05$). Serum K^+ profile revealed that Levalbuterol also causes hypokalemia. Serum K^+ level decrease from 3.79 ± 0.57 mEq/L to 3.51 ± 0.56 mEq/L ($p<0.05$). Serum Na^+ level remain constent after Levalbuterol ($p>0.05$).

Lipid profile evaluation shows that Levalbuterol also decreases the serum cholesterol, LDL-cholesterol, VLDL-cholesterol and triglycerides but decrease was not significant ($p>0.05$). After administration of Levalbuterol HDL-cholesterol level was increased but results were not significant ($p>0.05$). Before treatment, the mean value of systolic blood pressure was 126.08 ± 10.58 mmHg and after treatment it was slightly increased to 128.25 ± 9.57 mmHg. Diastolic blood pressure was slightly decreased from 79.93 ± 5.23 mmHg to 78.2 ± 4.43 mmHg ($p<0.05$).

TABLE 2: EFFECT OF LEVALBUTEROL ON BIOCHEMICAL AND PHYSICAL PARAMETERS.

Parameters	Pre-treatment (Levalbuterol)	Post- treatment (Levalbuterol)	p
Plasma glucose (fasting)(mg/dL)	84.37 ± 7.49	89.52 ± 7.48	0.001 S
Plasma glucose (post prandial)(mg/dL)	119.90 ± 9.60	124.52 ± 9.06	0.017 S
Serum Na+ level(mEq/dL)	139.15 ± 3.68	139.31 ± 3.64	0.505 NS
Serum K+ level	3.79 ± 0.57	3.51 ± 0.56	0.017 S
Serum cholesterol	187.20 ± 17.17	180.93 ± 16.42	0.06 NS
LDL-cholesterol	128.01 ± 19.37	125.31 ± 18.27	0.53 NS
VLDL-cholesterol	19.29 ± 3.53	18.12 ± 3.44	0.107 NS
HDL-cholesterol	39.72 ± 5.36	40.48 ± 5.43	0.53 NS
triglycerides	96.45 ± 17.68	90.64 ± 17.20	0.103 NS
Systolic blood pressure(mmHg)	126.08 ± 10.58	128.25 ± 9.57	0.01 S
Diastolic blood pressure(mmHg)	79.93 ± 5.23	78.2 ± 4.43	0.001 S

Table 3 shows the comparison of Albuterol and Levalbuterol on pretreatment baseline values of different parameters.

As shown in **Table 4**, comparative studies of Albuterol and Levalbuterol on biochemical and physical parameters reveal that after treatment with Levalbuterol also have β_2 mediated effects like Albuterol. But interdrug comparison of plasma glucose level fasting and postprandial levels shows that increase in these levels were more with Albuterol as compare to Levalbuterol ($p<0.05$).

TABLE 3: PRE-TREATMENT VALUES OF BIOCHEMICAL AND PHYSICAL PARAMETERS IN BOTH GROUPS

Parameters	Pre-treatment (Albuterol)	Pre- treatment (Levalbuterol)	p
Plasma glucose (fasting)(mg/dL)	79.62 ± 4.80	84.37 ± 7.49	0.001 S
Plasma glucose (post prandial)(mg/dL)	108.7 ± 8.37	119.90 ± 9.60	0.001 S
Serum Na+ level(mEq/dL)	139.025 ± 3.37	139.15 ± 3.68	0.85 NS
Serum K+ level(mEq/dL)	3.77 ± 0.38	3.79 ± 0.57	0.85 NS
Serum cholesterol	187.07 ± 9.78	187.20 ± 17.17	0.96 NS
LDL-cholesterol	131.10 ± 11.86	128.01 ± 19.37	0.395 NS
VLDL-cholesterol	17.97 ± 2.25	19.29 ± 3.53	0.053 NS
HDL-cholesterol	37.68 ± 4.72	39.72 ± 5.36	0.079 NS
Triglycerides	89.87 ± 11.26	96.45 ± 17.68	0.053 NS
Systolic blood pressure(mmHg)	127.28 ± 9.21	126.08 ± 10.58	0.50 NS
Diastolic blood pressure(mmHg)	80.5 ± 5.95	79.93 ± 5.23	0.62 NS

TABLE 4: EFFECT OF ALBUTEROL AND LEVALBUTEROL ON BIOCHEMICAL AND PHYSICAL PARAMETERS AFTER TREATMENT

Parameters	Post-treatment (Albuterol)	Post- treatment (Levalbuterol)	p
Plasma glucose (fasting)(mg/dL)	90.57 ± 5.35	89.52 ± 7.48	0.48 NS
Plasma glucose (post prandial)(mg/dL)	121.87 ± 8.12	124.52 ± 9.06	0.17 NS
Serum Na+ level(mEq/dL)	140.0 ± 4.52	139.31 ± 3.64	0.46 NS
Serum K+ level(mEq/dL)	2.96 ± 0.49	3.51 ± 0.56	0.001 S
Serum cholesterol	184.07 ± 9.58	180.93 ± 16.42	0.304 NS
LDL-cholesterol	126.92 ± 11.26	125.31 ± 18.27	0.64 NS
VLDL-cholesterol	17.47 ± 2.19	18.12 ± 3.44	0.319 NS
HDL-cholesterol	38.10 ± 4.82	40.48 ± 5.43	0.06 NS
Triglycerides	87.37 ± 10.95	90.64 ± 17.20	0.316 NS
Systolic blood pressure(mmHg)	129.83 ± 8.44	128.25 ± 9.57	0.45 NS
Diastolic blood pressure(mmHg)	78.5 ± 4.96	78.2 ± 4.43	0.78 NS

Inter drug comparison of Serum Na^+ and K^+ levels were not significant ($p>0.05$) it shows that both the drugs have similar effects on these parameters. Inter drug comparison of lipid profile also shows not significant results this indicates that both drugs effects lipid profile in a similar way. Systolic blood pressure increases and diastolic blood pressure decreases after administration of both the drugs however inter drug comparison was not significant ($p>0.05$)

As shown in **Table 5**, the adverse reaction profile observed in both the groups was almost identical in terms of the effects observed and their incidence in each group. The various effects observed during study were nausea and vomiting (2.5% in each group), palpitations (17.5% in group I and 12.5% in group II), headache (5% in albuterol treated group and 2.5% in levalbuterol treated group), tremors (5% in each group), tachycardia (7.5% in each group). However, two patients (5%) in albuterol group only complained of nervousness whereas no such side effects were seen in levalbuterol treated patients.

TABLE 5: ADVERSE DRUG REACTION PROFILE OF BOTH THE DRUGS

Symptoms	After Albuterol (n = 40)	After Levalbuterol (n = 40)
Nausea &/or vomiting	1 (2.5%)	1 (2.5%)
Palpitation	7 (17.5%)	5 (12.5%)
Headache	2 (5%)	1 (2.5%)
Tremors	2 (5%)	2 (5%)
Legcramps	3 (7.5%)	2 (5%)
Tachycardia	3 (7.5%)	3 (7.5%)
Nervousness	2 (5%)	-

DISCUSSION: In the present study, we compared the physical, biochemical and adverse drug reaction profile of albuterol/salbutamol and its isomer levalbuterol/levosalbutamol. Short acting beta agonists (SABAs) are often used for asthma flares, as needed for rescue bronchodilation, following exposure to an allergen or irritant or in preparation for exercise in the presence of exercise induced bronchospasm [7]. SABAs are also used in mild COPD as needed and for wheezing of bronchospastic origin, and for relief of acute reversible airway obstruction.

The mechanism of the antiasthmatic action of β-adrenergic receptor agonists is undoubtedly linked to the direct relaxation of airway smooth muscle and consequent bronchodilation. Among all SABAs Albuterol is frequently used agent. It was first described by Brittain *et al* in 1968 [8]. It is a racemic mixture of R, S enantiomers [6]. The R-enantiomer is more active because of an optimal interaction between the "down" orientation of the β-0H group and the serine residue on the receptor. For albuterol, the R-enantiomer is at least 100 times more potent as a β_2-agonist than is the S-enantiomer [9]. Apart from bronchodilation Simulation of β_2- receptors results in widespread metabolic effects including increase in free fatty acids, insulin, lactate and fall in serum K+, Na+ level [10].

In therapeutic doses there are several symptomatic adverse effects reported with Albuterol which includes tremor, anxiety, muscle cramps, headache and palpitations, however tolerance develops to many of these effects with regular treatment [11]. It can increase sympathic modulation in the cardiac autonomic activity; this increase activity can lead tachycardia, cardiovascular hypertrophy, hyper-tension, insulin resistance [12] and sometimes can precipitate cardiac arrhythmia [13]. Increase in ectopic activity in domiciliary use was reported in patients with COPD [14]. Inhaled Salbutamol enhances atrioventricular (AV) nodal conduction and decreases AV nodal, atrial and ventricular refractoriness in addition to its positive chronotropic effects. These alterations could contribute to the generation of spontaneous arrhythmias [15].

Levalbuterol is the pure R-isomer of racemic albuterol. Racemic albuterol is manufactured by a method that results in a 50: 50 mixture of R-albuterol and S-albuterol (R, S-albuterol).

Levalbuterol is synthesized by a manufacturing process based on resolution of R,S benzyl albuterol to prepare an optically pure form of the Stereoisomer R-albuterol [16].

Levalbuterol includes only the (R)-isomers. The (S)-isomer is considered the inactive isomer because of its limited binding to β_2-receptors, lack of bronchodilatation production and augmentation of inflammatory stimuli. The (R) – isomer is considered the active isomer because it binds to β_2-receptor sites, produces bronchodilation, and has no effect or possibly reduces inflammatory stimuli [17]. Levalbuterol metabolizes about 8-times faster than S-Albuterol so it has shorter half-life than racemic salbutamol [18].

(S)-albuterol has a 10- fold slower rate of metabolism than (R)- albuterol and with frequent dosing it can accumulates in patient's plasma and lung tissue in the absence of (R)-albuterol [19]. Levosalbutamol has approx. 2-fold greater affinity than racemic for β_2 adrenergic receptor and approx. 100 fold greater binding for than S- isomer of albuterol [20]. Levalbuterol use is safe, efficacious and provides increase in FEV_1 (Forced expiratory volume in 1 min)**.** There is significant improvement FEV_1 values compared with placebo, the Levalbuterol doses afforded better efficacy than equal doses of albuterol administered, as part of the of the racemic mixture. Administration of 0.63 mg levalbuterol of resulted in an improvement in lung function that was similar to 2.5 mg racemic albuterol and was associated with fewer total drug related side effects [21].

In our study, we found a significant rise in both the fasting as well as post prandial plasma glucose levels from their mean baseline values (Table 1& 2) in patients treated with either Albuterol or Levalbuterol. However inter drug comparison shows that increase in plasma glucose level (fasting and post prandial) was more and significant ($P<0.05$) in patients treated with Albuterol as shown in table 4. These results are in accordance with [21, 22]. Milgrom H *et al,* (2001) [23] also concluded that racemic albuterol (RAC) 2.5 mg caused significantly larger increase in serum glucose than Levalbuterol (LEV) 0.31 mg and LEV 0.63 mg on both day 0 and day 21 ($P \leq 0.43$) and significantly greater increases than RAC 1.25 mg on day 21 ($p=0.003$).

This rise in plasma glucose was due to firstly by stimulation of glycogenolysis, neoglucogenesis and inhibition of glycogen synthesis in liver as a result of stimulation of adenyel cyclase and rise in cyclic adenosine monophosphate (cAMP) in hepatocytes [24].

Secondly in pancreatic islets activation of β_2 receptors on β-cells increase glucagon secretion and that on β-cells increases insulin secretion both by raising intracellular cAMP however, augmentation of insulin secretion is weak [25].

There is increased catecholamine release in acute bronchial asthma because bronchial asthma is a stressful condition and it slightly increases plasma glucose levels. As β_2-agonist also cause increase level of catecholamine, so it results in increase in blood glucose and FFA level [26, 27].

Activation of enzyme glycogen phosphorylase causing glycogenolysis while glycogen synthetase enzyme is inhibited. Both action results in hyperglycaemia and hyper-lactacidemia, neoglucogenesis enhance this effect.

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 ($p = 0.017$, Table 4). Similar results were also observed by several researchers [16, 28, 29]. 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 [30].

Similar results have also been observed and reported by several studies, [21, 22, 23, 28, 31, 32].

Panchu D *et al,* (2003) [29] reported that in equipotent doses both Albuterol and Levalbuterol shows similar effects. But Levalbuterol shows better side effect profile. Both cause marked hypokalemia (P=0.24) but Levalbuterol shows better results as compare to Albuterol. Hypokalemia itself is associated with increased incidence of premature atrial beats and supra-ventricular arrhythmias. Most of the reported sudden deaths in young asthmatics could be due to beta-agonists induced hypokalemia and cardiac arrhythmias with corticosteroids and diuretics used concomitantly in cases of bronchial asthma which are known to cause hypokalemia, beta-2 agonists have an additive hypokalemia effect and may predispose to cardiac arrhythmias especially when patients receiving digitalis for any associated complications.

There was no significant change ($p>0.05$) in serum sodium which was increased slightly observed in both groups from its mean initial values. However, Kung M *et al,* (1984) [30] reported that some β_2 - agonist like terbutaline causes significant rise ($p<0.05$) in serum Na+ level but mechanism has not been explained.

In our study we found a slight decrease in serum cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides levels and slight improvement in HDL-cholesterol levels after administration of both β_2 agonists. However, results were statistically not significant ($p>0.05$, Table 1, 2 &4)

As evident from table 4, there was no significant difference ($p>0.05$) in the effects of Albuterol and Levalbuterol on systolic blood pressure and diastolic blood pressure. However, a mild increase in systolic BP and mild decrease in diastolic BP was noted in both the groups which was statistically significant ($p<0.05$)

The possible mechanism behind is that the rise in systolic and reduction in diastolic blood pressure would be due to direct stimulation of cardiac beta-1 receptors [33] and action on beta-2 receptors in vascular smooth muscle leading to peripheral vasodilation [34]. Similar results observed by [35] and [36].

β_2- agonists like Albuterol and Levalbuterol are well tolerated and quite safe drugs. But β_2-mediated side effects are present with both groups. In our study, we observed that incidence of nausea and vomiting were similar (2.5%, 2.5%) for both drugs. Palpitation was more observed (17.5%) in patients treated with Salbutamol as compare to Levosalbutamol (12.5%). The incidence of tachycardia observed, was similar in both groups. Tachycardia is due to stimulation of β_2 -receptors on vascular smooth muscle which leads to vasodilation and a reflex increase in heart rate with little effect of on stroke volume. The chronotropic effect of albuterol is considerably less than of a β_1-stimulant such as isoproterenol, which acts directly on cardiac β -receptors [37]. However, tolerance develops to many of these effects with regular treatment [11].

The incidence of headache was observed more in Albuterol group (5%) as within Levalbuterol group (2.5%), headache is caused by peripheral vasodilation [37]. Tremors were noted equally in both group. Tremor is caused by decrease recovery time following contraction of skeletal muscle [38]. Leg cramps were noted more in Albuterol group (7.5%) as compare to Levalbuterol group (5%). Nervousness was not so common and observed in only 2 patients (5%) of Albuterol group.

In present study, the overall incidence of side effects was considerably lower in Levalbuterol group than in Albuterol treated patients. Similar observation has been reported by Nowalk RM *et al* (2004)[28] and Raltson ME *et al* (2005)[39] who found in their study that β_2 - mediated side effects were less in LEV group as compare to RAC group. In another study, [21] observed β_2-adrenergic side effects for both treatments, these side effects were consistently lower with 0.63 mg Levalbuterol than with 2.5 mg racemic albuterol. Lotvall J *et al*, 2001 [31] and Milgrom H *et al*, 2001 [23] observed that above both drugs were well tolerated by patients.

However, in present study, the side effects were well tolerated by the patients and none of the patients was withdrawn from the study due to any adverse drug reaction with either of the drugs.

CONCLUSION: This study concludes that 0.63 mg Levalbuterol, R-isomer of Albuterol has better side effect profile and safer than Albuterol (2.5 mg) on the basis of some above mentioned biochemical, physical and adverse effects profile. But apart from above mentioned parameters like plasma glucose levels , Serum Na^+, K^+, Lipid profile, some other biochemical parameters like renal function tests, liver function tests were left to explore and yet to be explained.

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