

## Study Of Combination Therapy With Ipratropium Bromide And Levosalbutamol In Stable Chronic Obstructive Pulmonary Disease Patients.

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**Abstracts: Background:** This study compared the efficacy of levosalbutamol alone and ipratropium bromide alone with levosalbutamol and ipratropium bromide combined, through inhalational route in stable patients of chronic obstructive pulmonary disease (COPD). The study was carried out in 102 patients of COPD. Levosalbutamol inhalation was administered to 33 patients and ipratropium bromide inhalation was given to 31 patients. 38 patients were treated with combination of levosalbutamol and ipratropium bromide inhalation. Pulmonary functions were noted before and after 15, 30, 60, 120, 180 and 240 minutes of inhalation of these drugs. Bronchodilation was significantly more in patients treated with combination therapy as compared to patients treated with single drug separately. The effect was more sustained in combination therapy as it started declining after 120 minutes with levosalbutamol, after 180 minutes in ipratropium bromide and after 240 minutes with combination therapy. So it was concluded that combination therapy with levosalbutamol and ipratropium bromide is better in management of COPD patients than using either of agents alone. [Kamshette Y NJIRM 2015; 6(3):60-63]

**Key Words:** COPD, Ipratropium Bromide, Levosalbutamol

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**Introduction:** Bronchodilators play major role in treatment of chronic obstructive pulmonary disease (COPD) patients. The major groups of drug available in metered drug inhaler form are

1. Beta 2 agonists-
  - i) Short acting – e.g. Salbutamol, levosalbutamol, terbutaline.
  - ii) Long acting – e.g. formoterol, salmeterol
2. Anticholinergic-
  - i) Short acting – e.g. ipratropium bromide, oxitropium bromide
  - ii) Long acting – e.g. aclidinium bromide
3. Inhaled corticosteroids – e.g. Budesonide, fluticasone
4. Various fixed dose combinations-
  - i) Short acting beta 2 agonists with either anticholinergics or inhaled steroids
  - ii) Long acting beta 2 agonists with either anticholinergics or inhaled steroids.

Global initiative of chronic obstructive lung disease, in its 2014 update has given recent guidelines and says that 'combining bronchodilators with different mechanism and duration of actions may increase the degree of Bronchodilation with equivalent or lesser side effects.'<sup>1</sup> Though various combinations of these agents are used in treatment of COPD by pulmonologist many general practitioners still use

single drug inhalational therapy while treating COPD patients. As levosalbutamol-a beta adrenergic receptor agonist and ipratropium bromide-an anticholinergic belong to two different groups with different mechanism of action, it is reasonable to expect their additive and complimentary action when combined.

Many studies were conducted in past for studying this combinatory effect of salbutamol and ipratropium bromide<sup>2</sup> are available from India; not many reports are available for combined use of levosalbutamol and ipratropium bromide fixed dose combination in general practice.

The present study has been designed to compare the effect of combination therapy of beta agonist levosalbutamol and anticholinergic ipratropium bromide in stable COPD patients with either agent used alone.

**Material and Methods:** The study was conducted in outdoor department of pulmonary medicine at private pulmonary clinic. All patients selected were diagnosed as COPD according to GOLD criteria.<sup>1</sup> The evaluation was done based on history, physical examination, chest X rays and previous pulmonary function tests. Only patients with mild to moderate symptoms were included in this study.<sup>1</sup>

The patients were instructed to discontinue their bronchodilator therapy 24 hours prior to entry in the study. Patients were treated either with levosalbutamol (50 mcg) or with ipratropium bromide (20mcg) or with fixed drug combination of above two in metered dose inhaler in randomized manner. Forced expiratory volume in one second (FEV1) was recorded before and 15, 30, 60,120,180 and 240 minutes of inhalation of bronchodilator drugs.

**Results:** The study was carried out in 104 patients of COPD. Table 1 shows characteristics of study population. Levosalbutamol inhalation was administered to 33 patients and ipratropium bromide inhalation was given to 31 patients.40 patients were given fixed dose combination of levosalbutamol and ipratropium bromide.

**Table 1: Characteristics of study population**

	Levosalbutamol Group	Ipratropium bromide group	Levosalbutamol + Ipratropium bromide group	Total
Number of subjects	33	31	40	104
Age -range	43-61	41-64	40-62	40-64
Male sex	18	17	23	58
Female sex	15	14	17	46
Duration of disease (years)				
Range	10-32	12-34	11-35	10-35
Smoking habits				
Smokers	19	22	25	66
Non smokers	14	21	15	50

Table 2 shows the FEV1 values. All patients in the study had almost similar baseline FEV1 values.

Changes in FEV1 started appearing 15 minutes after inhalation of drugs and it started to declining after 120 minutes in patients treated with levosalbutamol, after 180 minutes in patients treated with ipratropium bromide and after 240 minutes in levosalbutamol plus ipratropium bromide combination.

Statistically significant differences were seen in FEV1 values in levosalbutamol and ipratropium bromide treated patients at 180 minutes ( $p < 0.05$ ) and at 240 minutes ( $p < 0.05$ ), with values significantly higher in ipratropium bromide treated patients at all these intervals.

Statistically significant difference were noted in all the intervals at 120,180 and 240 minutes ( $p < 0.05$ ) in combination therapy group as compared to any of one drug alone.

It was also noted that significant Bronchodilation was noted at 15 minutes in levosalbutamol treated patients but at all other intervals the percentage of Bronchodilation was significantly high in combination therapy group.

It was noted that the onset of action was almost similar in patients treated with levosalbutamol, ipratropium bromide and combination of the two, but the duration of onset was more prolonged in the patients treated with levosalbutamol plus ipratropium bromide.

**Table 2: Changes in FEV1 in three different study groups.**

Time interval	Levosalbutamol group	Ipratropium bromide Group	Combination (Levosalbutamol + Ipratropium bromide) treated group
baseline	48+ <sub>-10.1</sub>	43+ <sub>-10.5</sub>	45+ <sub>-13.2</sub>
15 minutes	55+ <sub>-10.2</sub>	51+ <sub>-10.3</sub>	51+ <sub>-12.4</sub>
30 minutes	57+ <sub>-9.8</sub>	55+ <sub>-8.9</sub>	57+ <sub>-11.7</sub>
60 minutes	59+ <sub>-8.9</sub>	58+ <sub>-9.7</sub>	63+ <sub>-12.1</sub>
120 minutes	57+ <sub>-11.1</sub>	61+ <sub>-10.5</sub>	66+ <sub>-11.8</sub>
180 minutes	54+ <sub>-10.2</sub>	60+ <sub>-11.2</sub>	67+ <sub>-13.2</sub>
240 minutes	51+ <sub>-10.1</sub>	56+ <sub>-10.2</sub>	64+ <sub>-12.4</sub>

**Discussion & Conclusion:** In this study we compared the the bronchodilator effects of combination of levosalbutamol and ipratropium bromide with those of levosalbutamol alone or ipratropium bromide alone. It was observed that the combination is more effective in Bronchodilation than the single agent used alone.

There are many studies available comparing the effects of salbutamol 100mcg and ipratropium bromide 80 mcg and have shown better results than single drug with this combination.<sup>2-6</sup>

With the availability of levosalbutamol, the R isomer of salbutamol which is more efficacious than racemic salbutamol in terms of improvement of PEFr,SPO2 and has less adverse effects like tachycardia and hypokalemia; the fixed dose combinations of levosalbutamol and ipratropium bromide are used.<sup>7-9</sup> These require lesser concentrations of ipratropium bromide (50mcg versus 100mcg) to achieve similar effects on Bronchodilation.

Ipratropium when added in combination with levosalbutamol resulted in improved maximal airflow and improvement in airflow was more long lasting.<sup>10-16</sup>

In our study it was noted that the effective Bronchodilation started at 30 minutes but the effect of any single drug started waning after two hours while the combination of levosalbutamol and ipratropium bromide gave sustained effect up to four hours.

Gross et al reported that anticholinergics have a longer duration of Bronchodilation than do beta agonist, the effect of which remains even after two hours.<sup>17</sup>

All these studies have included 40-80 mcg dose of ipratropium bromide. In our study we have found that even smaller dose of ipratropium bromide (20 mcg) gives optimum bronchodilation with FEV1 of 56+<sub>-</sub>10.2 and FEV1 of 64+<sub>-</sub>12.4 when used alone and in combination with levosalbutamol respectively.

The principal action of beta 2 agonists is in increasing cyclic AMP and produce functional antagonism to bronchoconstriction. The effect of short acting beta2 agonists usually wears off after 4-6 hours.<sup>18</sup> It is known that beta agonists are relatively more effective in distal airways.

The short acting Anticholinergics like ipratropium bromide block M2 and M3 receptors and modify transmission at preganglionic junction. The

bronchodilating effect of short acting inhaled anticholinergics lasts longer than short acting beta 2 agonists and may be apparent up to eight hours.<sup>19</sup> Anticholinergics are relatively more effective in proximal action in airways. Thus a combination has time duration benefit not seen by either drug alone.

In addition to this time duration benefit some other benefits are also achieved with this combination i.e. convenience of administration, lesser dose of anticholinergics giving lesser adverse effects and potential cost saving.<sup>20</sup>

Thus our study suggests that combination of inhalational therapy with levosalbutamol and ipratropium bromide is more beneficial than either of the agents used alone.

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