



## Original Research Article

## Efficacy of tiotropium bromide inhalation in COPD and bronchial asthma patients for a period of 14 weeks

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## ABSTRACT

**Background:** Chronic Obstructive Pulmonary Disease affects more than 15 million Americans, with the majority of the patients more than 50 years old with current or past smokers.

**Objective:** To study the safety and efficacy of Tiotropium bromide inhalation in both COPD & Bronchial Asthma patients.

**Materials and Methods:** The present study was conducted in patients with stable as well as exacerbated COPD and Br. Asthma at Shadan Hospital, Telangana.

**Results:** Significant improvement in Forced expiratory volume with respect to baseline at the end of the 14<sup>th</sup> week. The maximum mean response in FEV<sub>1</sub> improved by 0.221, (68.03%) when the compared value of baseline 0.13L (p-value < 0.001) significant improvement in Bronchial asthma but little less effective compared to COPD treatment group. The Forced expiratory volume (FEV<sub>1</sub>), Forced vital capacity (FVC) and FEV<sub>1</sub>/FVC ratio were improved with respect to baseline.

**Conclusion:** Tiotropium via dry powder inhaler result in 24 hr bronchodilation as well as consistent and sustained improvement for both the COPD and the Bronchial Asthma patients.

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## 1. Introduction

Chronic Obstructive Pulmonary Disease is a potentially fatal, slowly progressive respiratory disease. In contrast to Bronchial Asthma, COPD is characterized by air flow obstruction that is not fully reversible. The signs and symptoms are chronic coughs, excessive mucous production, wheezing and shortness of breath after mild exertion.

In practice, COPD tends to be under diagnosed and undertreated, for a number of reasons. However, the availability of detailed and practical guidelines from the Global Initiative for Chronic Obstructive Lung Disease will be useful for improving COPD care through primary care needs to respond by developing systems to ensure these guidelines are implemented in practice.

Tiotropium bromide, long-acting, inhaled Anti cholinergic bronchodilator, selectively inhibits the muscarinic receptors involved in mucous secretion and bronchoconstriction. Long term clinical trials have demonstrated the efficacy of Tiotropium in patients with COPD.<sup>1,2</sup>

Tiotropium is well tolerated, with a safety profile comparable with that of a placebo. The parasympathetic nervous system plays an important role in autonomic control of airways and is believed to be largely responsible for resting the vagal tone in COPD.<sup>3-5</sup>

Bronchial Asthma is a chronic inflammatory disorder of airways. It is characterized by airflow obstruction that is typically reversible and by airway hyper responsiveness to various stimuli.

According to WHO, between 100 and 150 million people around the globe suffer from Bronchial Asthma and the number is rising.<sup>6</sup>

Tiotropium bromide is a semisynthetic derivative with Anticholinergic properties specific for muscarinic receptors

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(M<sub>1</sub>, M<sub>2</sub> and M<sub>3</sub>) in humans.<sup>7</sup>

While asthmatic patients with chronic bronchitis and emphysema have been included in this study, pure Asthma patients have not been studied with this medication. Therefore, it is difficult to recommend this medication for regular use in Asthmatics and impossible to recommend it as the “single bronchodilator” for the management of Asthmatic patients.

However, there is evidence that Tiotropium bromide improves airflow (FEV<sub>1</sub>) and blocks the bronchoconstrictive effects of Methacholine in patients with Bronchial Asthma.<sup>8</sup> While Tiotropium bromide cannot be recommended as ‘bronchodilator of choice’ in patients with Bronchial Asthma, it provides a measurable degree of bronchodilation and is well tolerated with no serious drug-related adverse effects.

Hence the purpose of the present study was to evaluate the efficacy and safety of 18 mcg Tiotropium a metered-dose inhalation administered once daily for 14 weeks in patients with COPD and Bronchial Asthma.

## 2. Materials and Methods

This study was conducted in patients with stable as well as exacerbated COPD and Bronchial Asthma at Shadan Hospital, Telangana State from May 2015 to Feb 2016. Permission for the study was obtained from the College authorities before commencement.

Out of 100 patients, 50 patients with mild to moderate COPD, 50 Bronchial Asthma patients were enrolled for study after inclusion & exclusion criteria for COPD and Bronchial Asthma. A written Informed Consent was obtained from the patient.

### 2.1. Inclusion criteria for COPD patients

1. Patients in the age group of 40 to 70 of either sex.
2. Patients with the history of cough, productive sputum and shortness of breath.
3. Patients with the history of smoking, 10 packs / year or more, FEV<sub>1</sub> of 65% or less of predict for age.
4. Patients must be willing to give written informed consent and able to adhere to dose and visit schedule.
5. Patients who are stable on inhaled corticosteroids are allowed to be enrolled and to remain on the treatment throughout the study.

### 2.2. Exclusion criteria for both COPD and bronchial asthma patients

1. Patients in the age group of less than 12 and more than 80 years of either sex.
2. Pregnant or lactating woman.
3. Subjects who quit smoking less than 3 months prior to the screening visit.

4. Patients having clinically significant Lung disease other than COPD and Br. Asthma eg. Bronchiectasis, Pulmonary fibrosis, Tuberculosis etc.
5. Patients using oxygen > 2 liters per min for > 2 hrs / day.
6. Subjects who have had cancer diagnosed or treated within the 5 years.
7. Patients requiring chronic or prophylactic treatment with antibiotics.
8. Subjects with significant renal, hepatic, cardiovascular (including cor pulmonale), metabolic neurologic, hematologic, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgement of the investigator, may interfere with the study or require treatment which may affect the evaluation of efficacy and safety of the drug study.
9. Patients with chronic narrow angle glaucoma.
10. Patients with symptomatic prostatic hyperplasia or bladder-neck obstruction.
11. Subjects who have clinically significant abnormalities on chest x-ray (other than evidence of COPD / Br. Asthma) at the screening visit or within the previous year.
12. Patients with H/O Allergic Rhinitis, Myocardial Infarction, increased total blood eosinophil count in COPD group patients.

### 2.3. Study design

This is an open-label, randomized, parallel-group study. The total number of patients in both COPD and Br. Asthma categories were randomized into 2 groups; 50 patients of Br. Asthma, 50 patients of COPD.

Group I received – 50 patients of COPD.

Treated with 18 mcg of Tiotropium. (2puffs/day).

Group II received – 50 patients of Bronchial Asthma.

Treated with 18 mcg of Tiotropium inhaler (2puffs/day)

A detailed history, Clinical Examination, investigation (baseline, ECG, X-ray Chest PA view) was taken.

### 2.4. Pulmonary function test

Baseline, after drug administration, on the 1<sup>st</sup> day, 3<sup>rd</sup> day, 7<sup>th</sup> day and every 2<sup>nd</sup> week up to 3<sup>1/2</sup> months.

All the patients were advised to take Salbutamol inhalation (100-150 mcg) as needed. All the drugs were given as metered-dose inhalation. Patients were shown inhalation techniques with spacers. They were advised to rinse their mouth after each inhalation. They were followed up 3 times in the 1<sup>st</sup> week after each inhalation and after that every 2<sup>nd</sup> week till a period of 14 weeks. At each visit, they were clinically assessed and PFT was done.

The Screening was done for the (cough, Wheeze, Breathlessness, The severity of nocturnal symptoms, frequency of use of rescue medication) parameters before

and after treatment.

The Score for cough, wheeze, breathlessness and severity of nocturnal symptoms<sup>9</sup> for Br. Asthma: 0 – No symptoms, 1 – Mild, 2 – Moderate, 3 – Severe

Score for frequency of use of rescue medication:<sup>10</sup>

0 – < 2 puffs / week

1 – < 2 puffs day

2 – 2 to 4 puffs / day

3 – > 4 puff / day

At each visit, patients were assessed for any adverse effects.

### 2.5. Pulmonary function test

Evaluation of lung disease by SPIROMETRY is the most widely used Pulmonary Function Test. Spirometry is a measure of airflow and lung volumes during a forced expiratory maneuver from full inspiration

Pulmonary Function Test is a powerful tool required in the assessment of respiratory conditions. In addition to helping with diagnosis, PFTs can help to make an objective assessment of severity and monitor the response to treatment.

### 2.6. Spirometry Provides three basic measurements

1. Forced vital capacity.
2. Forced expiratory volume in one second.
3. Forced expiratory ratio.

### 2.7. Statistical analysis

Data is presented in Mean + SD and percentages as applicable. Unpaired student's t-test was applied to test the level of significance.

P-value < 0.05 was considered as the level of significance.

Pulmonary Function Test: FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC%

1<sup>st</sup> Day:

Baseline, after 30 min; 60 min; 120 min; 180 min on 1<sup>st</sup> day, next 3 day, 7<sup>th</sup> day thereafter every 2<sup>nd</sup> week.

## 3. Results

Patients with Bronchial Asthma were randomized into two groups:

### 3.1. Group I

50 patients of Patients of Br Asthma This group of patients were treated with Tiotropium 18 mcg/day.

Patients were given Tiotropium bromide inhaler 2 puff/day, in the morning everyday upto 14 weeks. Each puff contains 9mcg of drug.

Patients diagnosed as both mild and moderate COPD numbering 50:

### 3.2. Group I

50 Patients of mild to moderate COPD, were treated with Tiotropium bromide, 2 puffs/day, upto 14 weeks.

In the COPD group with drug, two patients were excluded from the study owing to non-compliance and in the group.

All the patients were advised to take Salbutamol inhalation as needed. In case of Acute Br. Asthma, patients were first put on steroids, and after completion of their course of treatment with steroids, they were included in our study.

All the patients were followed up for 3 visits in the 1<sup>st</sup> week and after that every 2<sup>nd</sup> week for a period of 14 weeks to assess the clinical improvement reported by the patients (subjective) and Pulmonary Function Tests were done at each visit (objective)

### 3.3. COPD patients treated with tiotropium bromide

#### 3.3.1. Clinical improvement

Symptomatic improvement was observed in all three groups i.e., Cough, Shortness of breath, Wheeze and Nocturnal symptom severity has come down in regarding to baseline. The Frequency of rescue medication also decreased by mean a change of 78.2% in the period of 14 weeks with regard to baseline, (p < 0.001) A significant clinical improvement was observed in patients of COPD treated with Tiotropium.

#### 3.3.2. Spirometry assessment

In the spirometry assessment, values showed significant improvement in FEV<sub>1</sub> with respect to baseline at the end of 14<sup>th</sup> week. The maximum mean response in FEV<sub>1</sub> improved by 0.221, (68.03%) when compared value of baseline 0.13L (P Value < 0.001) At the endpoint maximum mean response of FVC value is 0.3 IL (48.78%) in comparison with baseline value of 0.16L (p-value < 0.001). The mean FEV<sub>1</sub>/FVC ratio also improved by 96% (57.63%) compared with baseline 61% (P value < 0.001). No adverse effects were reported in treatment group patients except the dry mouth in 10% of patients, after 3-4 weeks of treatment. These reports suggest that Tiotropium is very effective in COPD group especially elderly patients (ex-smokers) without any significant adverse effects except the dry mouth Tables 1, 2 and 3.

### 3.4. Bronchial asthma patients treated with tiotropium bromide

#### 3.4.1. Clinical assessment

In this group value showed clinically significant improvement but little less effective compared to COPD treatment group. In both the sexes not much difference in improvement had been observed. Clinically, the statistical

data shows 65-75% of improvement in Cough, Shortness of Breath, Wheeze, and Nocturnal severity of symptoms. The frequency of rescue medication was also decreased by 60% during the period of 14 weeks (Tables 1 and 2).

### 3.4.2. Spirometric improvement

The FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC ratios were improved with respect to baseline. A significant effect was observed in FEV<sub>1</sub> compared with FVC and FEV<sub>1</sub>/FVC ratio when compared to the baseline within the period of 14 weeks of study i.e., maximum mean response of FEV<sub>1</sub> increased to 0.21L (49.96%) when compared to baseline of 0.14L (P<0.005), whereas FVC 0.31L (45.32%) with respect to the baseline 0.21L (P value<0.005). FEV<sub>1</sub>/FVC ratio was improved by 92.14% (55.82%) with respect to baseline by 59.286% (P value < 0.001).

No gross adverse effects were reported in these group patients except dry mouth after the treatment for 2-4 weeks duration. These results show significant improvement with Tiotropium in Br. Asthma patients both clinically as well as spirometrically.

**Table 1:** Mean score improvement of COUGH in COPD and bronchial asthma patients during 14 weeks

Time-period	Drug in COPD	Drug in Bronchial Asthma
Baseline	1.531+0.083	1.68+0.121
1 <sup>st</sup> week	0.742+145	0.946+324
6 <sup>th</sup> week	0.346+081	0.628+0.153
14 <sup>th</sup> week	0.183+0.93	0.46+0.136

**Table 2:** Mean score improvement of wheeze in COPD and bronchial asthma patients during 14 weeks

Time-Period	Drug in COPD	Drug in Bronchial Asthma
Baseline	1.861+100	1.840+0.082
1 <sup>st</sup> week	1.62+0.43	1.56+0.068
6 <sup>th</sup> week	1.14+0.028	1.06+0.048
14 <sup>th</sup> week	0.104+0.065	0.360+0.091

**Table 3:** Mean max response in FEV<sub>1</sub> in COPD and bronchial asthma patients during 14 weeks

Time-Period	Drug in COPD	Drug in Bronchial Asthma
Baseline	1.320+0.607	1.421+0.796
1 <sup>st</sup> week	1.520+0.452	1.58+0.458
6 <sup>th</sup> week	1.86+0.685	1.742+0.384
14 <sup>th</sup> week	2.218+0.694	2.131+0.734

**Table 4:** Mean max response in FVC in COPD and bronchial asthma patients during 14 weeks

Time-Period	Drug in COPD	Drug in Bronchial Asthma
Baseline	1.65+0.709	2.148+0.834
1 <sup>st</sup> week	1.832+0.21	2.24+0.126
6 <sup>th</sup> week	2.21+0.642	2.64+0.312
14 <sup>th</sup> week	3.112+0.715	3.134+0.854

**Table 5:** Mean max response in FEV<sub>1</sub>/FVC % in COPD and bronchial asthma patients during 14 weeks

Time-Period	Drug in COPD	Drug in Bronchial Asthma
Baseline	61.27+14.63	59.286+0.768
1 <sup>st</sup> week	65.24+0.467	62.14+0840
6 <sup>th</sup> week	74.62+0.864	72.56+0.452
14 <sup>th</sup> week	96.580+11.46	92.140+0.513

## 4. Discussion

Bronchodilators are the main stay of pharmacotherapy for the patients with COPD.<sup>11</sup> In both the groups 18 mcg of the drug was given through inhalation with spacer once daily, every day for a period of 14 weeks.

Tiotropium bromide proved all the required demands as a superior bronchodilator among the other bronchodilators.

Many single-dose and multiple-dose studies have documented a 24 hr of action with once daily administration.<sup>12</sup> In our study, in patients of both the groups, Tiotropium bromide treatment produced significantly greater improvement in lung function compared to the other bronchodilators. Patient compliance was also good which was 95% in all the groups.

The results obtained in our study are consistent with previous studies conducted with same drug in different approaches.

Moderate-to-severe COPD is frequently associated with significant hyperinflation that leads to stretch and compromise of the respiratory muscles and significantly increases the work of breathing. Reduction in hyperinflation frequently leads to reduced dyspnea and greater exercise tolerance. Bronchodilators can reduce hyperinflation by allowing for greater emptying and reductions in FRC or thoracic gas volume and increased inspiratory capacity. Celli et al.<sup>13</sup> have shown that after 4 weeks of treatment, patients treated with Tiotropium had reductions in FRC and improved inspiratory capacity.

O'Donnell and colleagues<sup>14</sup> demonstrated that compared with placebo, Tiotropium reduced hyperinflation and allowed for greater tidal volume recruitment during exercise on a constant work rate cycle ergometer, leading to a 21% improvement in endurance time and improved dyspnea index scores.

Boehringer Ingelheim Pharmaceuticals sponsored four studies that were published in major peer-reviewed journals that provide significant information regarding the efficacy of tiotropium in the treatment of COPD.

Vincken et al.<sup>15</sup> studied 535 patients randomly assigned to receive either Tiotropium 18 µg once a day or Ipratropium 40 mcg qid in a randomized, double-blind, double-dummy study for 1 year and reported that Tiotropium could reduce exacerbation by 14-24% vs Ipratropium.

Brusasco and colleagues<sup>16</sup> compared 1,207 patients receiving Tiotropium or Salmeterol or placebo in a randomized, double-blind, double-dummy trial for 6 months and when compared with Salmeterol, Tiotropium achieved a clinically relevant drop in SGRQ. (i.e., a > 4- point drop)

Donahue et al.<sup>17</sup> studied Tiotropium 18 mcg via dry powder inhaler vs Salmeterol 50 mcg bid via metered-dose inhaler in randomized, double-blind, double-dummy trial for 6 months and reported that there was a statistically significant improvement in TDI.

A recent large trial by Rennard Si et al.<sup>18</sup> comparing Ipratropium bromide to Salmeterol demonstrated that Ipratropium and Salmeterol had a similar AUC for both FEV<sub>1</sub> and FVC from 0-12 hour.

A 3-month trials with 288 COPD patients demonstrated that Tiotropium therapy was superior to Ipratropium in improving FEV<sub>1</sub> and FVC. Compare with Ipratropium, Tiotropium therapy produced higher pre dose through FEV<sub>1</sub> (130ml), peak FEV<sub>1</sub> (50ml) and average FEV<sub>1</sub> (80ml) over six serial measurement post dose.

In the present trial, Tiotropium was superior in all end points and is very effective in both the diseases i.e., Br. Asthma and COPD.

It shows more or less equal response in both the cases. Bronchodilator efficacy with Tiotropium, as with other inhaled Anti cholinergic medications, is generally sustained with no evidence of tolerance.

In our study, it was reported that Tiotropium is also effective in mild intermittent and persistent asthma patients in both aspects that is clinical as well as spirometric therefore, Tiotropium has the potential to provide superior bronchodilation with once daily dosing.

No adverse effects were reported in any of the treatment groups, except in very few cases i.e., <10% dry mouth was seen. Local adverse effects like oral candidiasis was not observed in any of the treatment groups. This might be due to the use of spacer and thorough rinsing of mouth after each inhalation. Spacer decreases oropharyngeal deposition of drug and also minimized the risk of oral candidiasis. The dose used in the present study is well tolerated and no adverse effects reported in our study.

## 5. Conclusion

Our study suggests that Tiotropium in a dose of 18 mcg once daily via dry powder inhaler result in 24 hr bronchodilation

as well as consistent and sustained improvement for both the COPD and the Br. Asthma patients. It is safe and efficacious drug both clinically and spirometrically. This study showed decrease in symptoms, decrease in rescue medication frequency and also reduce frequency of acute attacks.

## 6. Source of Funding

None.

## 7. Conflict of Interest

None.

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