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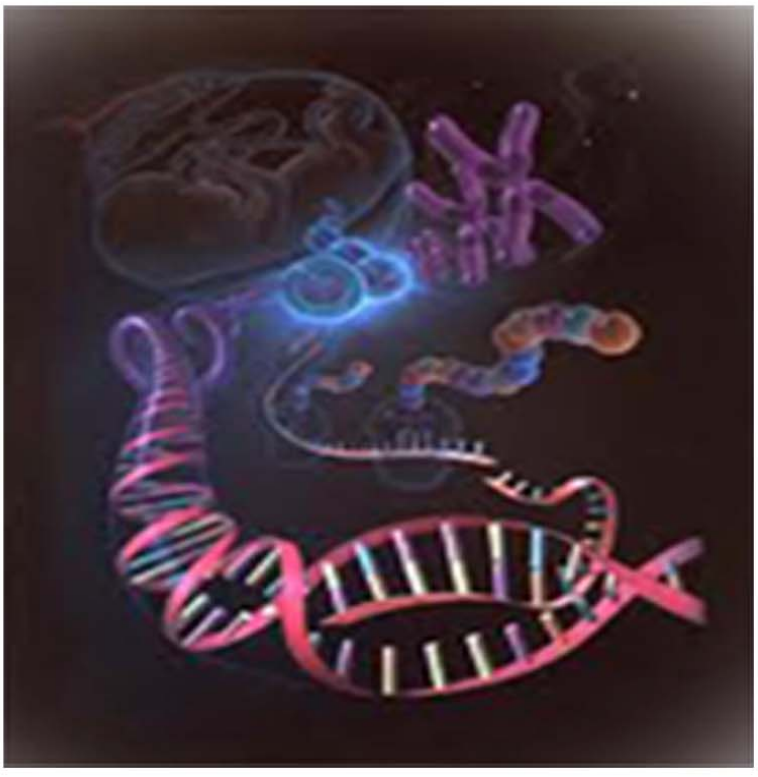

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Research Paper

SAFETY AND EFFICACY OF TIOTROPIUM BROMIDE IN BRONCHIAL ASTHMA AND COPD PATIENTS, CROSS OVER STUDIES BY PLACEBO

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Asthma attacks all age groups but often starts in childhood. It isa disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. According to WHO Between 100 and 150 million people around the globe -- roughly the equivalent of the population of the Russian Federation -- suffer from asthma and this number is rising. World-wide, deaths from this condition have reached over 180,000 annually. Asthma and COPD are clinically defined airway disorders that individually have significant heterogeneity with regard to underlying pathogenesis and responses to therapy. Tiotropium is well tolerated, with a safety profile comparable with that of placebo. The parasympathetic nervous system plays an important role in autonomic control of airways and is believed to be largely responsible for resting but they bronchomotor tone in COPD. Hence the purpose of the present study was to evaluate the efficacy and safety of 18mcg Tiotropium metered dose inhalation, administered once daily for 14 weeks in patients with COPD and Bronchial asthma, cross over study with placebo. The over all results of our study suggests that Tiotropium in the dose of 18 mcg once daily via dry powder inhaler result in 24 h bronchodilation as well as consistent and sustained improvement for both the COPD and the bronchial asthma patients. It is safe and efficacious drug both clinically and spirometrically. Our study showed decrease in symptoms, decrease in rescue medication frequency and also reduce frequency of acute attacks.

Keywords: Bronchial asthma, COPD, Tiotropium, PLACEBO

INTRODUCTION

Asthma attacks all age groups but often starts in childhood.It isa disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. In an individual, they may

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occur from hour to hour and day to day. This condition is due to inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated. In an attack, the lining of the passages swell causing the airways to narrow and reducing the flow of air in and out of the lungs. Asthma cannot be cured, but could be controlled.The strongest risk factors for developing asthmaare exposure, especially in infancy, to indoor allergens (such as domestic mites in bedding, carpets and stuffed furniture, cats and cockroaches) and a family history of asthma or allergy. A study in the South Atlantic Island of Tristan da Cunha, where one in three of the 300 inhabitants has asthma, found children with asthmatic parents were much more likely to develop the condition.

Between 100 and 150 million people around the globe—roughly the equivalent of the population of the Russian Federation—suffer from asthma and this number is rising. World-wide, deaths from this condition have reached over 180,000 annually. Asthma is not just a public health problem for developed countries. In developing countries, however, the incidence of the disease varies greatly. The costs of asthma to society could be reduced to a large extent through concerted international and national action. World-wide, the economic costs associated with asthma are estimated to exceed those of TB and HIV/AIDS combined. Asthma prevalence in the United States is estimated at approximately 30 million, and COPD prevalence may be as high as 24 million based on the latest National Health and Nutrition Examination Survey III.

The Present study showed Tiotropium was demonstrated to provide superior safety and efficacy relative to placebo in both COPD as well as Br. Asthma group in both clinical assessment score and spirometrically. Tiotropium is well tolerated, with a safety profile comparable with that of placebo. The parasympathetic nervous system plays an important role in autonomic control of airways and is believed to be largely responsible for resting but they bronchomotor tone in COPD (1-5). COPD and asthma are two different conditions are often confused.

Hence the purpose of the present study was to evaluate the efficacy and safety of 18mcg Tiotropium metered dose inhalation, administered once daily for 14 weeks in patients with COPD and Bronchial asthma, cross over study with placebo.

MATERIALS AND METHODS

The present clinical study was conducted in patients with stable as well as exacerbated COPD and Bronchial asthma in Andhra Pradesh Government General and chest Hospital from May 2005 to Feb 2006. A total of 120 patients, out of which 50 patients with mild to moderate COPD, 50 Bronchial asthma patients and another 20 patients each 10 with placebo study. They were diagnosed based on the clinical findings and pulmonary function tests. The study was conducted for a period of 14 weeks.

Study Design

This is an open label, randomized, parallel group study. The total number of patients in both COPD and Bronchial Asthma categories were randomized into 3 groups; had 50 patients bronchial asthma, 50 patients of COPD and 20 patients each disease with placebo.

Table 1: Pateint Groups	
Group I received	50 patients of COPD.Treated with 18mcg of Tiotropium.(2puffs/day).
Group II received	50 patients of Bronchial Asthma. Treated with 18mcg of Tiotropium inhaler.(2puffs/day).
Group III – (Group-IIIA & Group-III B)	Group-III A -10 patients of COPD and Group-III B,10 Bronchial asthma patientsBoth groups received, Inhalation with placebo 2 puffs / day , everyday morning.

Inclusion Criteria for Bronchial Asthma Patients

Patients with the following criteria were included in this study:

- Patients in the age group of 12 to 65 yrs of either sex.
- Patients with the history of episodic wheezing, difficulty in breathing, chest tightness, and cough with or without expectoration.
- Patients having nocturnal symptoms and family history of asthma.
- Patients with the history of seasonal and the diurnal variation.
- Patients with the history of non-smokers.

Inclusion Criteria for COPD Patients

- Patients in the age group of 40 to 70 of either sex.
- Patients with the history of cough, productive sputum and SOB.
- Patients with the history of smoking, 10 packs / year or more, FEV1 of 65 % or less of predict for age.
- Patients must be willing to give written informed consent and able to adhere to dose and visit schedule.
- Patients who are stable on inhaled corticosteroids are allowed to be enrolled and to remain on the treatment throughout the study.

Exclusion Criteria for both COPD and Br. Asthma Patients

Patients with the following criteria were excluded from the study:

- Patients in the age group of less than 12 and more than 80 years of either sex.
- Pregnant or lactating woman.
- Subjects quit smoking less than 3 months prior to the screening visit.
- Patients have clinically significant lung disease other than COPD and Bronchial Asthma e.g., Bronchectasis, acidosis, pulmonary fibrosis, tuberculosis, etc.
- Patients use oxygen >2 liters per min for >2 h /day.
- Subjects have had cancer diagnosed or treated within the 5 years.
- Patients require chronic or prophylactic treatment with antibiotics.
- Patients with symptomatic prostatic hyperplasia or bladder-neck obstruction.
- Subjects have clinically significant abnormalities on chest x-ray (Other than evidence of COPD / Br. Asthma) at the screening visit or within the previous year.
- Patients with H/O Allergic rhinitis, myocardial infarction, increased total blood eosinophile count in COPD group patients.

OUR CONTRIBUTION

In order to make this project as successful we concerned on various issues and information and contributed them to this paper.

To made the patient report perfect and accurate we collected the particulars of the patient like Name, age, address, occupation, and out patient number were taken.

History

Detailed history was taken with special attention to the following points like Cough; Expectoration; Haemoptysis; Breathless-ness,wheezing; Nocturnal Awakening; Chest pain.

Personal History: History of Smoking, Drinking

Allergy History – Food, house dust, traffic dust, perfumes, soaps, powders, hair dye and other.

Past History

i. History as similar complains in the past.

ii. History of chronic bronchitis, pulmonary T.B., tropical pulmonary eosinophilia.

iii. Diabetis mellitus, Hypertension, Chronic renal failure.

iv. Malignancy.

Family History: History of bronchial Asthma/ COPD among 1st degree Relatives.

Treatment History

(a) History of bronchodilator therapy, H/O Hospitalization.

(b) Corticosteroid therapy.

After the history was taken, a detailed clinical examination was done.

Investigations

The following table contains the investigations were done:-

(Baseline, after drug administration, 5 times in the 1st day, 3rd day, 7th day and every 2nd week up to three and half months).

Blood examination, Sputum examination, chest x-ray, ECG were done to exclude other Conditions.

A written informed consent was obtained from the patient.

Table 2: Patient Information

1. **Blood Examination:**
   - a. Haemoglobin
   - b. Total count
   - c. Differential count
   - d. Absolute eosinophiles count
   - e. Erythrocyte sedimentation Rate
   - f. Peripheral smear
   - g. Random Blood Sugar
   - h. Serum Creatinine
2. Sputum Examination:
   - a. Eosinophilic Count.
   - b. A.F.B.
3. Electrocardiography.
4. Chest x-ray PA view.
5. Pulmonary function test.

Treatement Description:

Patient was given study number and included in one of the group:-

Group I: -COPD patients-(50 cases).

Drug - Tiotropium bromide inhalation.

Dose - 18 mcg, once daily.

Duration - 14 weeks.

Group. II: -Br. Asthma Patients. (50 cases).
Drug - Tiotropium bromide inhalation.

Dose – 18 mcg. Once daily.

Duration – 14 weeks.

GroupIII**:** GpIIIA : COPD patients treated with placebo,GpIIIB: Bronchial asthma patients treated with placebo . Either cases (10 each).

Drug – Placebo.

Dose – 2 puffs / day.

Duration: - 14 weeks.

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 1st week after that every 2nd week till a period of 14 weeks. At each visit, they were clinically assessed and PFT was done.

Monotoring

Screening was done for the following parameters before and after treatment: 1) Cough 2) Wheeze 3) Breathlessness 4) Severity of nocturnal symptoms 5) Frequency of use of rescue Medication.

Score for Cough, Wheeze, Breathlessness and Severity of nocturnal Symptoms (33) for Br. Asthma:-

O – No Symptoms

1 – Mild

2 – Moderate

3 – Severe

Score for frequency of Use of Rescue Medication (34).

O – <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. Hence the diagnosis of COPD can be confirmed with the help of spirometry. The differences between COPD and Asthma have an important bearing on treatment:

COPD: Backbone of treatment inhaled bronchodilators.

Asthma: Backbone of treatment inhaled corticosteroids.

RESULTS AND DISCUSSION

This study was done to see the safety and efficacy of Tiotropium bromide in both the cases i.e., mild to moderate COPD patients as well as mild intermittent and mild persistent asthma patients. In both the cases 18 mcg of drug was given through inhalation with spacer every day for a period of 14 weeks. Tiotropium is a long acting, once daily administered antimuscarinic drug, especially M_3 receptor blocker used as a bronchodilator. Bronchodilators are the main stay of pharmacotherapy for the patients with COPD (ERS Consensus Statement, 1995; American Thoracic Society, 1995; GOLD, 2001). For efficacy of any drug, the mechanism of action, route of administration, frequency of administration, onset of action, duration of action, symptomatic improvement and side effect profile, differentiates are equally important to differentiates that drug from various bronchodilator medication. In all aspect, Tiotropium bromide fulfils all these qualities. Generally, inhaled therapy has been performed over oral therapy due to the targeted delivery to the lung, superior spirometric results and superior tolerability. The presently available bronchodi-lators have provided symptomatic benefit to patients and an increasing recognition that treatment intervention is useful in patients with COPD. 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 h of action with once daily administration (Maesen *et al*., 1995; Littner *et al*., 2000). In our study, in both the cases that is mild to moderate COPD patients and mild intermittent and mild persistent bronchial asthma cases, Tiotropium bromide treatment produced significantly greater improvement in lung function

compare to the other bronchodilators or placebo. Patient compliance was good which 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.* (2003) have shown that after 4 weeks of treatment, patients treated with Tiotropium had reductions in FRC and improved inspiratory capacity vs placebo. O'Donnell and colleagues (2004) 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.

BoehringerIngelheim 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 (Table 3). Casaburi *et al*. (2002) studied 921 patients to compare Tiotropium 18 mcg daily vs. placebo in a randomized controlled trial lasting 1year. Vincken *et al*. (2002) 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. Donahue *et al*. (2002) studied Tiotropium 18 mcg via dry powder inhaler Vs. salmeterol 50 mcg bid via metered-dose inhaler in a randomized, double-blind, double-dummy trial for 6 months. Brusasco and colleagues (Brusasco *et al*., 2003) compared 1,207 patients receiving Tiotropium or salmeterol or placebo in a randomized, double-blind, double-dummy trial for 6 months.

Casaburi *et al*. (2002) demonstrated that compared with placebo, Tiotropium reduced wheezing and shortness of breathe but not cough or chest tightness when using a severity score from 0 to 3. In the studies comparing Tiotropium and placebo, there was a statistically significant

Table 3: Summary of Major Treatment Studies With Tiotropium Bromide Inhaler in COPD

Reference	No	Duration	Comparison	Results
Casaburi *et al.* (2002)	921	1 yr	Tiotropium 18 mcg vs. placebo.	Reported that Tiotropium could reduce exacerbations by 14-24%vs placebo
Vincken *et al.*, (2002)	535	1 yr	Tiotropium 18mcg vs. ipratropium 40mcg qid	Reported that Tiotropium could reduce exacerbation by 14-24% Vs ipratropium
Donahue *et al.* (2002)	623	6 months	Tiotropium 18 mcg Vssalmeterol	Reported that there was a statistically significant improvement in TDI [44, 45].
Brusasco *et al.* (2003)	1,207	6 months	Tiotropium 18 mcg vs. salmeterol 50 mac bid	Compared with salmeterol, Tiotropium achieved a clinically relevant drop in SGRQ (i.e., a > 4-point drop)

Note: TDI - Transition Dyspnea Index, SGRQ – St. George Respiratory Questionnaire, FRC- Functional Residual capacity.

improvement in the TDI, (Casaburi *et al*., 2002; Vincken *et al*., 2002; and Donahue *et al*., 2002) whereas similar findings were found in one of the two studies that compared it with salmeterol but not the other.Tiotropium caused a significant improvement in the SGRQ score (a reduction of 4 or more points) compared with placebo (Casaburi *et al*., 2002; and Donahue *et al*., 2002) or ipratropium. Compared with salmeterol, Tiotropium achieved a clinically relevant drop in SGRQ (*i.e*., a >4-point drop), whereas salmeterol did not, but the difference between the two was not statistically significant. The Medical Outcomes Study Short Form-36 measures general health status rather than respiratory health specifically. In trials comparing Tiotropium with placebo and ipratropium, Tiotropium showed statistically significant improvement in the domains of role physical and physical health summary compared with the control agent.

Casaburi *et al*., (2002) and Vinken *et al*., (2002) reported that Tiotropium could reduce exacerbations by 14 to 24% vs placebo and ipratropium, respectively.Thespirometric response to drug administration has generally served as a useful initial standard to judge efficacy among bronchodilators. In addition to smoking cessation, bronchodilator therapy is the foundation of COPD medicated management. Current guidelines recommend regular anticholinergic therapy once symptoms became persistent. Ipratropium bromide has been used successfully for the past two decades and the early clinical development of the next generation anticholinergic drug, Tiotropium, has been reported recently .

The primary advantage of Tiotropium has been once-daily dosing, with 24 h effects established in single dose studies and a study of 1 month duration. A recent large trial Rennard *et al*. (2001) comparing with ipratropium bromide to solmeterol demonstrated that with ipratropium and solmeterol had a similar AUC for both FEV_1 and FVC from 0-12 h. The spirometric improvements with the novel anticholinergic Tiotropiumhave now been evaluated in separate comparative trials with two common used maintenance inhaled bronchodilators prescribed for the treatment of COPD or Bronchial asthma patients.

A 3-month trials with 288 COPD patients demonstrated that Tiotropium therapy was superior to ipratropium in improving FEV_1 and FVC. Compare with ipratropium, Tiotropium therapy produced higher predose through FEV_1 (130 ml), peak FEV_1 (50 ml) and average FEV_1 (80 ml) 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., Bronchial asthma and COPD patients. It shows more or less equal response in both the cases. Bronchodilator efficacy with Tiotropium, as with other inhaled anticholinergic medications, is generally sustained with no evidence of tolerance. In addition to objective measures of airflow, patients receiving Tiotropium reported significantly less SOB and wheezing. The degree of bronchodilation observed in this trial is significantly effective in the both cases. There are so many trials with Tiotropium in COPD patients. But very few trials are available to prove the efficacy of Tiotropium bromide inhaler in Bronchial asthma patients. But in our study, it was reported that Tiotropium is also effective in mild intermittent and mild persistent Asthma patients in both the aspect that is clinically as well as spirometric tests. Therefore, Tiotropium has the potential to provide superior bronchodilation with once daily dosing. Additionally, the sustained

airflow improvement throughout the dosing interval points the utility of Tiotropium as a maintenance drug. Further studies are necessary to determine whether the sustained improvement in airflow with Tiotropium might improve sleep quality, exercise tolerance and other quality of life measures in patients with both COPD and Bronchial asthma. British Thoracic Society (BTS) and modified Indian guidelines reported that Tiotropium bromide is useful only in case of severe persistentasthma. Present study supports the findings observed in the previous studies. 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.

SUMMARY

Tiotropium was demonstrated to provide superior safety and efficacy relative to placebo for both in clinical &spirometric assessment in COPD and Bronchial asthma patients. These observations were accompanied by better symptoms control and subjective global assessments as well as by less reliance on rescue medication with salbutamol. Other than the reported increase in dry mouth, Tiotropium was judged as safe and well tolerated drug during the 14 weeks of study. The result of this study suggests that Tiotropium should prove useful as once daily bronchodilator therapy in both Bronchial asthma and the COPD patients. The fundamental goal of asthma therapy is to reduce airway inflammation, where as in COPD it is symptoms relief. There are many similarities between patients with asthma and those with COPD with respect to the use of bronchodilators. The presence or absence of reversibility of the disease with bronchodilators does not distinguish asthma from COPD, as reversibility is noted in both diseases. While partial irreversible airflow obstruction is a hallmark of COPD, many patients with asthma have persistent obstruction, while many with COPD have a reversible component. Chronic inflammation underlines both diseases. Both conditions involve:

1. Decreased airflow perhaps slightly more in COPD, causing a slightly larger decrease in FVC.
2. Both cause obstruction with mucus and constriction of smooth muscle.
3. Both are effected by genetic- environmental interaction.

Because of these similarities and few differences in both the diseases, these two diseases were taken in our study with Tiotropium to evaluate the Safety and efficacy in Bronchial asthma and COPD patients. Total 120 patients were taken .Divided into 3 groups .Group-I, 50 patients of COPD treated with Tiotropium, 2nd group, 50 patients of Bronchial asthma treated with Tiotropium, 3rd Group-10 patients of Bronchial asthma treated with placebo and 10 patients COPD treated with placebo were taken.

The treatment group patients were given Tiotropium bromide inhaler 2puff per day everyday in the morning i.e. 18 mcg /day of dose for a period of 14 weeks.In the placebo group patients, placebo inhalation was given, 2puff / day.

These patients were from Out Patient Department of Government General and Chest

Hospital, Hyderabad.All the patients were advised to use a spacer and rinse their mouth thoroughly after each inhalation. All the patients were advised to use salbutamol inhalation (100mcg per puff) as needed.Two patients in COPD with drug group were excluded from the study owing to non-compliance.Three patients from COPD with placebo group were excluded from the study because these patients did not turn up for regular follow up.Out of all the 4 groups, Tiotropium bromide in COPD treatment group produced significantly greater improvement in $FEV_{1,}$ FVC and FEV_1/FVC% than the other groups. At the same time the present reports showed that there is a great improvement in spirometric as well as clinically in Br. Asthma group patients. To date, there have been few studies of the use of Tiotropium in asthma. However, one study demonstrated that Tiotropium was broncho-protective against methacholine induced bronchoconstriction for up to 48 h Rennard *et al*., 2001).

Symptoms scores and rescue salbutamol use were reduced in both the diseases .No asthma-exacerbation were reported in any of the treatmentgroups. No adverse effects were reported in any of the treatment groups except mild dry mouth.

Safety: The safety profile indicates a low incidence of adverse event ie mild dryness of mouth in Tiotropium group. During the study, 10% of patients with Tiotropium in COPD group (5 of 50 patients) reported mild dryness of mouth.The only event regarded as drug related was dry mouth (10%) which was generally mild. It had a median onset of 3-4 weeks and continued throughout the treatment period. In case of Bronchial asthma group (6%) patient also showed dry mouth as an adverse event.

No patients discontinued from the study because of dry mouth. There were no serious adverse events were observed in our study. No differences were noted between treatment groups for changes in laboratory values, ECGs or results of physical examination. No significant changes in heart rate or blood pressure were detected after study drug administration in any of the groups. So dryness of mouth was the only consistent side effect noted in our study. There are no known major drug interactions. Ipratropium bromide should not be used with Tiotropium as they will compete for the same receptors and reduce the effectiveness of Tiotropium.Patients with narrow-angle-glaucoma, prostatic hypertrophy, bladder neck obstruction, or renal impairment should use anticholinergic drugs with caution. Patient compliance was 95% in all the treatment groups.

CONCLUSION

The Present study showed Tiotropium was demonstrated to provide superior safety and efficacy relative to placebo in both COPD as well as Br. Asthma group in both clinical assessment score and spirometrically.In the spirometric assessment with Tiotropium in COPD treatment group (n-48), reports showed significant improvement in FEV_1 i.e., 0.22L, in FVC 0.31L and FEV_1/FVC ratio was improved by 96% with respect to the baseline, which is statistically significant ($P<0.001$). Clinically symptomatic improvement was observed in cough, SOB, wheeze and nocturnal severity of symptoms. Frequency of rescue medication was also decreased by mean change score of 0.45 (78.2%) with regard to baseline score 2.10 ($P<0.001$) during the period of 14 weeks. In case of Bronchial asthma treatment group (n-50)

reports showed significant improvement in both clinically as well as spirometrically but less effective compared with COPD treatment group. In spirometric assessment, FEV_1 is improved by 0.21L, FVC by 0.31L and FEV_1/FVC ratio improved by 92.14% with respect to baseline which is statistically significant (P<0.005). Clinically, the mean score reports showed 60-70% improvement when compared to baseline.

These reports showed significant improvement with Tiotropium both clinically as well as spirometrically with fewer side effects i.e. mild dry mouth. Many studies are available with Tiotropium in COPD patients, which provides consistent reports of efficacy and safety of this drug but very few studies are available with Tiotropium in Bronchial asthma patients. However, it will be important to perform further comparative studies with large sample in multi centric studies, using Tiotropium in all the stages of Bronchial asthma patients to evaluate the safety and efficacy of the drug and also to document the role of Tiotropium in Bronchial asthma. Inspirometric as well as clinically, placebo in COPD group patients (n-7) and Bronchial asthma group patients (n-10) showed very less improvement, which is statistically not significant. The improvement observed was superior to placebo 2puff/day with MDI. The overall results of our study suggests that Tiotropium in the dose of 18 mcg once daily via dry powder inhaler result in 24 h bronchodilation as well as consistent and sustained improvement for both the COPD and the Bronchial asthma patients. It is safe and efficacious drug both clinically and spirometrically. Our study showed decrease in symptoms, decrease in rescue medication frequency and also reduce frequency of acute attacks. Patient's compliance was good in all the 3 groups of patients.

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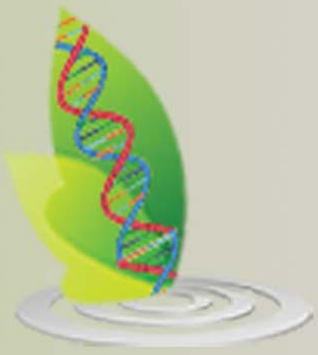

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