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COMPARATIVE STUDY OF TIOTROPIUM AND IPRATROPIUM IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS IN A TERTIARY CARE SOUTH INDIAN TEACHING HOSPITAL

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ABSTRACT

Objective: To compare the bronchodilator efficacy and safety of tiotropium and ipratropium in patients with Chronic Obstructive Pulmonary Disease (COPD) **Methodology:** The present study was a prospective randomized study conducted for 12 weeks. Eligible COPD patients were randomized in to two groups to receive either tiotropium 18 mcg once daily via metered dose inhaler (MDI) or ipratropium 40 mcg four times daily via MDI. Lung functions tests, baseline dyspnoea index (BDI) and transition dyspnoea index (TDI), health related quality of life (HRQoL), concomitant use of salbutamol were carried out to assess the lung function. **Results:** At the end of the study, a total of 70 patients (35 patients in Tiotropium and 35 patients in Ipratropium) completed the study. Both groups showed an improvement in lung functions, HRQoL and dyspnoea indices ($p<0.05$). Patients in tiotropium group showed a non significant improvement ($p>0.05$) in lung function compared to ipratropium group. Tiotropium group showed a significant improvement in dyspnoea indices ($p<0.05$) on 15th day follow-up compared to ipratropium. However, a non significant improvement in HRQoL and dyspnoea scores was observed in both groups. Concomitant use of salbutamol was found lower in the subjects of tiotropium group ($p>0.05$). Dry mouth was the common adverse effect observed in both groups. **Conclusion** Tiotropium in a dose of 18 mcg once daily via MDI showed a non significant improvement in dyspnoea, lung functions and all domains of SGRQ compared to ipratropium 40 mcg four times daily.

KEY WORDS: Tiotropium, Ipratropium, COPD, Safety and efficacy, HRQoL.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic disease of the lungs characterized by expiratory airflow obstruction. National Institute of Clinical Excellence (NICE) defines COPD as a disease characterized by airflow obstruction. The airflow obstruction is usually progressive, not fully reversible and does not change markedly over several months[1]. The obstruction is mainly due to bronchitis or emphysema. During the bronchitis stage, the disease affects the larger airways and in emphysema, the distal part of the lung, smaller airways and alveolar sacs get affected [2].

Currently, COPD is the second most common non infectious disease in the world, causing 2.7 million deaths annually, and global mortality is predicted to double by 2030[3]. In India it accounts for 2.8% of total deaths and is expected to rise to 6.5% deaths by 2020[4]. COPD causes progressive decline in lung function leading to increasing breathlessness, particularly on exertion. It is most often associated with smoking[1]. The diagnosis of COPD relies on the combination of suggestive signs and symptoms along with airflow obstruction on spirometry [4]. Although no permanent cure is available for COPD, various options are available for its management. Appropriate management of COPD decreases symptoms and improves quality of life, even in patients with severe disease. Important therapeutic goal include prevention and control of symptoms, reduction in frequency and severity of exacerbations, prevention and treatment of complications, improve health status, improve exercise tolerance and prevent disease progression. Bronchodilators are the mainstay in the treatment of COPD. Bronchodilators alleviate breathlessness through their direct effect on the airway, but these drugs also lead to reduction in pulmonary hyperinflation, increase mucociliary clearance and improve respiratory muscle function.

Since the cholinergic induced bronchoconstriction dominates symptoms in COPD, use of ipratropium bromide is an appropriate bronchodilator therapy due to its poor systemic absorption and minimal extra pulmonary side effects. Another anticholinergic agent, tiotropium bromide, with bronchodilating activity lasting for 24 hours or more, is also available in the market. It is used as once daily administration compared to ipratropium bromide 4 times a day and has a positive influence on patient's medication adherence behavior [5].

Health status is a broad term that encompasses the patients overall health, with emphasis on impact of impaired health on his or her quality of life. Measures of health status can be either

generic or disease specific. In patients with stable COPD, the spirometric response to bronchodilators, which is a physiologic outcome, is at best very modest. However, even in the absence of significant bronchodilation, an improvement in symptoms and exercise tolerance can be demonstrated. This can be quantified in a formal and standardized manner using questionnaires designed to measure Health-Related Quality of Life (HRQoL The St. George's Respiratory Questionnaire (SGRQ) is one of the most widely used disease-specific questionnaires used to measure HRQoL in COPD patients. The SGRQ total score reflects overall patient's health status[6]. The present study aims to compare the safety and efficacy of Tiotropium and Ipratropium in Indian setup. Most of the published literature has not simultaneously evaluated efficacy as well as effects on the health related quality of life in COPD patients.

Methodology

This study was a prospective open labeled randomized study and institutional human ethical committee of the hospital has approved the study. Written informed consent was obtained from all eligible patients before enrolling them into the study. The study had a one week run in period and a treatment period of 12 weeks. Clinical examinations and pulmonary function tests were done to confirm the diagnosis. Patient demographics including age, sex, occupation, smoking history; past medical history; symptoms, and medications were collected and documented in a suitably designed data collection form. During run in period, the patients were given an inhaled corticosteroid (ICS) on regular basis and salbutamol inhaler on regular and as and when required basis. After 1 week of run in period, patient's PFT was recorded to check the stability of the disease.

All enrolled patients were randomized to either tiotropium 18 mcg once daily or ipratropium 40 mcg, q.i.d for a period of 12 weeks. Both the study drugs were supplied as metered dose inhalers. During the study period, patients were allowed to use inhaled salbutamol 100mcg per actuation as regular and rescue medication and inhaled beclomethasone 200mcg two puffs twice daily as steroid therapy. Other β_2 agonists and inhaled anticholinergic medications (other than the study drugs) were not permitted. Patients were asked to keep of record of the number of times they used salbutamol as rescue medication.

Measurements

Spirometry

Pulmonary function was assessed prior to the start of the therapy by spirometry. Spirometry was performed according to ATS guidelines.[7] During four follow-ups, at day 15th, 30th, 60th and 90th day spirometry was repeated. Patients were asked to withdraw the rescue medication (salbutamol) six hours before PFT.

Dyspnoea

Dyspnoea was measured before and during treatment by the Baseline Dyspnoea Index (BDI). Scores range from grade 0 to grade 4. Changes in dyspnea from baseline were measured using the Transition Dyspnoea Index on a scale of + 3 to –3, at each follow-up. A change of 1unit from baseline dyspnoea was considered to be clinically significant. The BDI and TDI consist of three axes (functional impairment, magnitude of task, magnitude of effort) and the sum of these makes the focal score. [6]

Health-related quality of life

HRQoL was determined using the St. George's Respiratory Questionnaire. The SGRQ is a disease specific instrument that contains 76 items in three subscales (symptoms, activity and impacts). A lower score after study treatment represents an improvement. A change of 4 units is considered to be clinically significant [7,8,9].

Statistical analysis

Student t test and chi square test were done to check the significance of baseline demographic parameters. Analysis of covariance was used to check the significance in improvement shown within the group. Student 't' test was performed to assess difference in improvement shown by tiotropium over ipratropium at individual follow up. $P<0.05$ was considered to be statistically significant.

RESULTS

Patient demographics

A total of 70 patients were recruited with 35 patients in each arm. Demographic and baseline data in tiotropium and ipratropium groups are presented in Table.1. No statistical significant difference ($p>0.05$) between both the treatment groups was observed at baseline in pulmonary functions, smoking habits, dyspnoea and in the three domains of the SGRQ: symptoms, impacts, and activity. The overall quality of life measurement at baseline,

calculated by SGRQ total score, was also found to be similar between the two treatment groups.

Table.1. Demographic details of the study patients

Demographics (n=70)	Tiotropium (n=35)	Ipratropium (n=35)	p value
Age (Yrs)	60.57± 12. 17	57.28± 10.8	p>0.05
Gender* Male Female	31 04	28 07	p>0.05
GOLD Grading*	3	3	
Smoking History (Pack Yrs)	40.01 ± 41.53	42.3 ± 28	p>0.05
Duration of COPD (Yrs)	6.55 ± 10. 09	5.32 ± 5.77	p>0.05
Base Line Lung functions			
FVC	1.18± 0. 445	1.12 ± 0.49	p>0.05
FEV_1	0.80 ± 0.39	0.84 ± 0.42	p>0.05
FEV_1 / FVC	71.08± 15.91	74.54± 14.08	p>0.05
SGRQ scores			
Symptoms	66.79 ± 19.88	66.8 ± 23.1	p>0.05
Impacts	57.62 ± 25.78	58.4 ± 22.4	p>0.05
Activity	75.59 ± 19.76	76.95 ± 19.49	p>0.05
Total	64.84 ± 21.47	65.7 ± 20.2	p>0.05
Baseline Dyspnoea Index			
Functional Impairment	1.88± 0. 67	1.91 ± 0. 61	p>0.05
Magnitude of Task	1. 8 ± 0. 71	1.91± 0. 61	p>0.05
Magnitude of Effort	1.8 ± 0.71	1.85 ± 0. 60	p>0.05

All values are mean ± SD unless otherwise indicated*

p>0.05, non significant by 't' test

p>0.05, non significant by Chi square test

Spirometry

The baseline spirometric data were comparable between two groups. There was no significant statistical difference in FEV_1 and FVC at baseline, between the two groups (p>0.05). Both tiotropium and ipratropium have shown significant improvement (p<0.05) in FEV_1 from baseline with tiotropium showing a larger improvement in FEV_1 at the end of 3 months. However there was statistically no significant difference between both the groups (P>0.05) in FEV_1 at any stage of follow up (95% CI 0.03-1.03) Changes in FEV_1 among the two treatment groups, at different follow ups of the study, after treatment with 18 mcg tiotropium once daily or 40 mcg ipratropium four times daily via MDI are shown in Figure-1

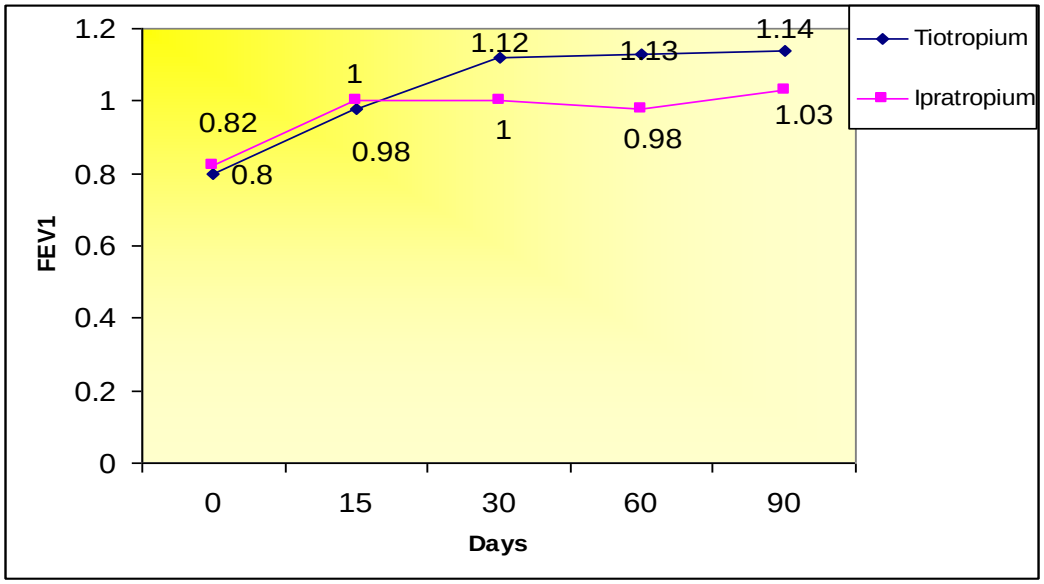


Figure 1: Changes in FEV_1 among two treatment groups at different stages of the study

Dyspnoea

Baseline Dyspnoea Index (BDI)

The assessment of baseline dyspnoea indices indicated that a moderate impairment (grade 2) was seen in each of the three domains: functional impairment (FI), magnitude of effort (ME), and magnitude of task (MT). Patients in the tiotropium group were more dyspneic (1.82) compared to ipratropium (1.89) group (Lower scores indicate more dyspnoea). There was no significant difference ($p>0.05$) among focal scores of the two treatment groups at baseline.

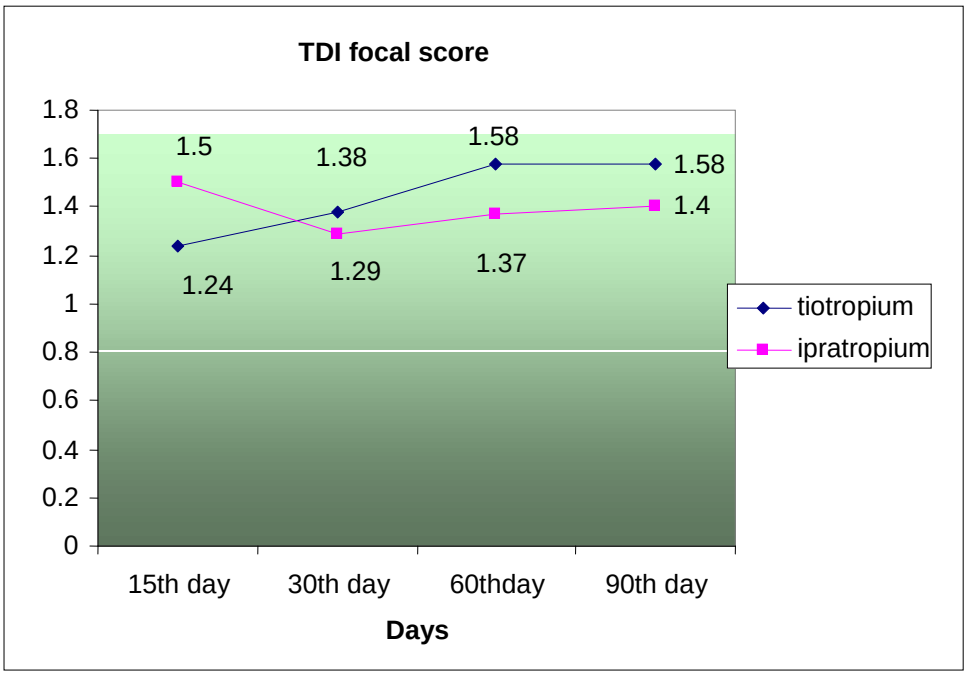
Table 2: Baseline dyspnoea index (BDI)

Domains	Tiotropium	Ipratropium
Functional impairment	1.88	1.91
Magnitude of task	1.8	1.91
Magnitude of effort	18	1.85
Focal score	**1.82**	**1.89**

Higher focal score shows lesser Dyspnoea

Transition Dyspnoea Index (TDI)

Clinically significant improvements in the TDI focal scores were achieved in patients of both groups after 15 days of treatment. Tiotropium showed a statistically significant improvement in TDI on 15^{th} day compared to ipratropium ($p<0.05$) with 95% CI ranging from -0.14 to -0.03. The changes in the TDI focal scores between the two different treatment groups are shown in figure 2.



A higher score denotes less dyspnoea.

Figure 2: Changes in the transition dyspnoea scores at different follow-ups

Health Related Quality of Life

The disease specific health related quality of life instrument SGRQ revealed that the patients enrolled in each drug group had similar range of impairment in QoL at base line. Health status of patients of both the treatment groups improved gradually and steadily over the study period. During the three months treatment period, the SGRQ total score decreased in both groups. Lower scores indicate better QoL. There was no stastically significant difference in the improvement in symptoms domain, impacts domain and activity domain of SGRQ after 90 days of treatment with ipratropium and tiotropium. 95 % CI (1.05 to 3.02) (figure 3).

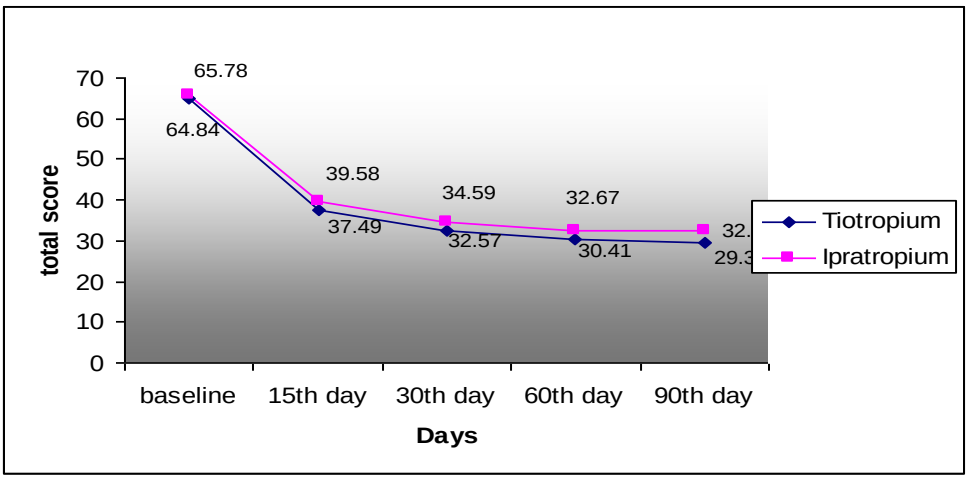


Figure 3: Changes in SGRQ total scores among two treatment groups at different stages of the study

The total scores explain the global or overall estimation of respiratory health.

A clinically significant improvement in both the treatment arms were observed within 15 days of treatment, which persisted throughout the treatment period.

Use of Salbutamol

On an average, patients receiving tiotropium had taken approximately 2.48 puffs inhalations of salbutamol per week, where as in ipratropium it was 2.96 inhalations per week. However there was no statistical significance ($p>0.05$) with 95% CI (-3.62 to 0.82) between the two treatment groups with respect to the need for salbutamol as rescue medication.

Safety

The only adverse event repeatedly reported related to study drugs was dry mouth, which was noted more frequently with tiotropium (57%) than with ipratropium (30%). None of the patients discontinued participation in the study due to adverse events. Other adverse drug reactions reported in the ipratropium group are cough and bitter taste.

DISCUSSION

COPD is characterized by irreversible obstruction; most of the patients show clinical benefits from bronchodilators. Thus bronchodilators are the mainstay of pharmacotherapy for patients with COPD. The three most widely used classes of bronchodilators are β_2 agonists, anticholinergic agents and methyl xanthines [3]. These agents have been proved to be useful in the management of patients with COPD. Since cholinergic vagal tone is thought to be the only reversible component of airway obstruction in COPD, current recommendations favour the use of inhaled anticholinergics along with long acting β_2 agonists in the maintenance therapy of patients with COPD. Ipratropium is a safe and effective anticholinergic agent with few side effects and with no signs of tolerance. However, as its duration of action is limited to 4-6 hours, the four times daily regimen leads to diminished compliance. Tiotropium, is the only available long acting anticholinergic agent, whose duration of action lasts 24 hours[10]. Very few randomized controlled trials comparing tiotropium and ipratropium were published as on date. The present study provides information on the bronchodilatory benefits of tiotropium in COPD patients compared with the older drug ipratropium, when given once daily. Dyspnoea indices and HRQoL were used as outcome measures in addition to spirometry, to evaluate the response to the study drugs. This was done because even in the absence of significant bronchodilation, an improvement in symptoms and exercise tolerance can be observed with bronchodilators.

Spirometry is a lung function test used to differentiate COPD from asthma and it is used as a tool to judge the response of the patient to different bronchodilators. Patients in both the groups showed a significant improvement in FEV_1 value ($p < 0.05$) throughout the study period from the baseline. The study results demonstrated superior effect in lung function improvement with once daily dosing of tiotropium when compared to ipratropium four times daily. In a study conducted by Vincken et al. also observed significant improvement in FEV_1 shown by tiotropium compared to ipratropium[10] . In another study conducted by J A Van Noord et al, patients on 18 mcg once daily of tiotropium showed a significant improvement in FEV_1 values compared to 40 mcg ipratropium four times daily[11]. There was an average difference of 100 ml improvement in lung function shown by tiotropium compared with ipratropium throughout this study. This improvement was not statistically significant ($p>0.05$) but most likely to be clinically significant. In addition, both in HRQoL and dyspnoea indices, tiotropium showed greater improvement than ipratropium.

Dyspnoea is the most frequent complaint of patients with COPD requiring medical intervention and is the most prominent symptom limiting the activity of daily living. In our study we have, incorporated dyspnoea as an outcome measure along with HRQoL and lung function assessment. The Baseline Dyspnoea Index/Transition Dyspnoea Index (BDI/TDI) is a validated questionnaire that quantifies and distinguishes changes in breathlessness over time in COPD patients. In a study conducted on 443 patients with symptomatic COPD (FEV_1 <65% pred.), it was found that tiotropium was superior to ipratropium in improving dyspnoea at all time points.[12] Similarly Donald Tashkin et al have shown that, the bronchodilating effects of tiotropium over ipratropium may be small but it is significant and the TDI scores show an improvement of high statistical significance.[13] The present study demonstrates that tiotropium was statistically superior to ipratropium on 15^{th} day follow-up which was assessed by the difference in mean TDI scores ($P<0.05$). Hence once daily treatment with tiotropium was found to be effective in reducing the dyspnoea, leading to a better improvement in activities of daily living compared to ipratropium.

The treatment for COPD is largely directed toward relief of symptoms and improvement in quality of life. Disease specific questionnaires may be more sensitive than the generic kind, because a high proportion of their content is directly relevant to the disease. The SGRQ is one of the most commonly used disease specific and validated instrument used to measure HRQoL in COPD patients. However it has a very weak correlation with lung function. In our

study, both treatment groups showed improved HRQoL as measured by effects on three domains; symptoms, impact and activity of the SGRQ. The total scores of both the groups decreased gradually over the 90 day study period ($p < 0.05$). This indicates that treatment with anticholinergics has a cumulative effect in improving QoL of COPD patients. At baseline the average of the total SGRQ scores of both groups was 65.31 units, while at the end of the study the drop (improvement in HRQoL) in their total SGRQ score was an average of 30.88, showing that both drug had a similar effect on the COPD patients. Studies conducted in developed countries have shown only small changes in the QOL scores relative to baseline. For example, in a study conducted by V Brusasco et al, while the total SGRQ scores improved by four units in tiotropium group the salmeterol group scores increased by only 2.8 units [13]. In our study population, COPD patients had a poor quality of life at baseline which is most likely due to the fact that they were treatment naïve at the time of inclusion in the study. In both the study groups, the greatest reductions in scores were seen in the symptoms domain, followed by the impact and then by the activity domains. However tiotropium shown a better result compared to ipratropium after 15 days of treatment ($p > 0.05$). The overall QoL improvement shown by tiotropium was found to be better than ipratropium even though there was only a difference of 100ml in lung function improvement, with a once daily dosage. Van Noord et al have also found similar result i.e. tiotropium improved SGRQ significantly than ipratropium in a one year randomized double blind study[12].

All study patients were provided with a regular dose of salbutamol, through out the study, and were also allowed to use it as and when needed basis to support the patient in decreasing the exacerbations. Findings of a meta-analysis suggest that use of beta agonists along with anticholinergics have decreased the severe exacerbations, hospital readmissions, and relative risk.[14] The different comparative studies of tiotropium and ipratropium indicate a low incidence of adverse events in the tiotropium group. No systemic cholinergic adverse effects were observed. The main drug related adverse event was dry mouth; it was generally mild and reported by 57% of the patients in the tiotropium group and 30% of the patients in the ipratropium group. None of the patients withdrew from the study because of this effect. Thus our study findings are supported by a study conducted by

J A Vanoord who did a randomized study, comparing the efficacy of tiotropium and ipratropium in the treatment of COPD. He observed that while 14.7% of the patients in tiotropium group reported dry mouth, the percentage of patients in the ipratropium group who

complained of this side effect was 10.3[15]. In conclusion, once daily dosing of Tiotropium has shown a better impact on patients' desired therapeutic outcomes.

In a recent Cochrane review, the authors compared the efficacy and safety of Ipratropium and Tiotropium bromide in COPD patients from the data published from various RCTs. The authors conclude that when compared to the Ipratropium, Tiotropium has shown better lung function, fewer exacerbations leading to hospital admissions, and improved quality of life. Similar adverse effect profile was observed in two groups. Thus the authors confirm that, Tiotropium is a reasonable choice in COPD over Ipratropium.[16]

CONCLUSION

Findings of the present study suggest that, long acting tiotropium has shown a significant improvement in FEV_1 scores, TDI scores and Health related quality of life in the COPD patients compared to ipratropium.

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