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ORIGINAL ARTICLE

A Randomized Controlled Comparison of Tiotropium and Ipratropium in the Treatment of Chronic Obstructive Pulmonary Disease

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Abstract

The study was designed to compare the effectiveness of two anticholinergic currently available Tiotropium 18μg with Ipratropium 40 μg administered through Metered Dose Inhaler.

The study was conducted in outpatient department of the National Institute of Diseases of the Chest & Hospital, Dhaka, for a period of two years, starting from January 2005 to December 2006.

A standard proforma with questions was designed and filled to select patients with moderate to severe COPD. The patients were selected according to the predetermined criteria. To establish the diagnosis and for pretreatment evaluation, necessary baseline investigations were done. P value <0.05 was taken as significant in all analysis. The patients were allocated in two treatment groups by simple random sampling using random number table. 45 random numbers were selected from random number table and assigned in group A. The rest are assigned to group B. Patients in group A were treated by Inhaler Triotropium once daily + inhaled Ipratropium matched placebo four times daily and the rest in group B were treated Tiotropium matched placebo once daily + Ipratropium 40 μg four times daily. There were 87 males and 3 females. Mean age was 60.62±10.03 in group A and 57.24±10.26 in group B. The majority of the study patients fell within the range of 50-70 years. All were smoker. Both groups were homogenous in respect to age, sex, level of education and socio-economic condition.

Clinical evaluation, peak expiratory flow rate (PEFR), FEV1, FVC and FEV1/ FVC were done. Post-treatment evaluation including pulmonary function test were done on day 8, day 21 and day 42. No other bronchodilator was allowed during this study period except an open level inhaled short acting beta 2 agonist, the use of which was allowed on demand and also recorded. At the end of study Mini COPD health score questionnaire was asked and the score calculated.

There were statistically significant improvement in trough PEFR, FEV1 and FVC in group A compared to group B.

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At the end of day 8 it was 0.0702±0.013, 0.0581±0.012, 6.5349±1.39 respectively in group A and 0.0235±0.011, 0.0095±0.004 and 2.0930±0.81 respectively in group B. (p<.001). The mean difference of Trough FVC, FEV1 and PEFR from baseline on day 21 was 0.0810±0.013, 0.0617±0.013, 6.9756±1.46 respectively in group A and 0.0241±0.010, 0.0095±0.004 and 2.0488±0.77 respectively in group B (p<.001). There is a small increase in all parameters. At the end of 6 week the mean difference of Trough FVC, FEV1 and PEFR at the end of day 42 was 0.0910±.014, 0.0772±.012, 7.1282±1.51 respectively in group A and 0.0263±0.011, 0.0095±0.004and 2.0488±0.77 respectively in group B (p<.001).

The composite score of "Mini COPD health score" was 51.38±1.29 in group A and 53.44±2.08 in group B. The difference is statistically significant (p<0.001) and better in Tiotropium group.

The use of concomitant salbutamol was 1.49±0.63 in group A and 1.26±0.54 in group B. The difference of which is not statistically significant (p>0.05).

Tiotropium in a dose of 18 μg inhaled once daily MDI was significantly more effective than 40 μg ipratropium four times daily in improving trough PEFR, FEV1 and FVC as well as Mini COPD health score over 6 weeks period. These data support the use of tiotropium as first line treatment for the long term maintenance treatment of patients with airflow obstruction due to COPD.

Introduction

COPD is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease for years and die prematurely from it or its complications. COPD is currently the fourth leading cause of death in the world.

In patients with chronic obstructive pulmonary disease (COPD) bronchodilators are the first line approach to treatment.[1] The spirometric response to bronchodilators such as β_2 agonists, anticholinergic agents and methylxanthines is, at best, very modest. However, even in the absence of significant bronchodilation an improvement in symptoms and exercise tolerance can be found.2

In COPD cholinergic vagal tone is thought to be the only reversible component of airway obstruction.[3] Currently, anticholinergics feature prominently in European and American guidelines.[1,4] The anticholinergic agent ipratropium is an effective and safe drug with few side effects and without signs of tolerance during chronic treatment. However, its duration of action is limited to 4–6 hours and the agent is a non-selective blocker of all muscarinic receptor subtypes.[3,5] Blocking of M2 receptors may account for some cases of paradoxical bronchoconstriction.[6]

Tiotropium is a quaternary ammonium compound which is structurally related to ipratropium.

In vitro work has shown that the compound has a unique kinetic selectivity for M3 and M1 versus M2 receptors and dissociates 100 times more slowly than ipratropium from M3 and M1 receptors.[7,8] Only a few clinical single dose studies have so far been published in patients with COPD and asthma, which confirm that tiotropium is a potent and long acting bronchodilator suited for once daily administration.[9-11] Long term studies of more than one month have not been reported. The present study was designed to evaluate and compare the efficacy and safety of tiotropium (18μg) from a dry powder inhaler (DPI) once daily and ipratropium (40μg) from a metered dose inhaler (MDI) four times daily in patients with stable, moderate to severe airway obstruction due to COPD. This study reports the first 13 weeks of a one year study with the focus on lung function.

Methodology

It is a prospective comparative study. This study was carried out in the Outpatient Department of National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, from January 2005 to December 2006. Patients with clinical diagnosis of COPD, as defined by the following inclusion and exclusion criteria were included in the study.

The sample size was 90 as there were drugs and placebo available for 90 patients. From Table,

reading down from α(two-sided) =0.05 and β=0.20 (the rightmost column), 44 patients per group are required to detect a standardized effect size of 0.6, which will enable us to detect a difference of 20% or more in FEV1 between two treatment groups.

A total of 105 patients were screened for the study and out of them 90 patients were enrolled in the study. But 10 patients dropped. We could not contact them. Finally there were 80 patients.

This was Hospital based randomized, double blind, double dummy, parallel group study. The patients were assigned into two groups (by random table). 45 number picked from random table were assigned group A and the rest were assigned group B.

Patients were required to have a clinical diagnosis of COPD according to the ATS criteria and stable airways obstruction. Only clinically clean cases without any complications were selected for this study.

Criteria of Inclusions:

1. Respiratory symptoms (cough, shortness of breath and sputum productions) for more than 1 year.
2. Patients were required to be a smokers and have at least of 10 pack-yr smoking history
3. Clinically stable airway obstruction
4. A forced expiratory volume in one second (FEV1) of < 80% of predicted normal values and a ratio of FEV1 to Forced Vital Capacity (FVC) of <70

Criteria of Exclusion:

1. If patients had a history of asthma, allergic rhinitis, atopy, or an increased total blood eosinophil count (>600 cells/cmm),
2. A significant disease other than COPD,
3. A recent history of myocardial infarction (<1yr), heart failure (<3yr) or cardiac arrythmia requiring drug treatment.
4. If the patients require regular daytime supplemental oxygen or were on doses exceeding the equivalent of 10 mg prednisone daily during the month prior to entering the study
5. Have had an upper respiratory tract infection in six weeks before screening.
6. Patients with a known hypersensitivity to anticholinergic drugs,

In the first phase, informed consent of the patient was obtained. A standard proforma was designed to fill up. The patients were identified as per inclusion and exclusion criteria.

A detailed history was taken, it was recorded in the proforma. In the second phase, a thorough physical examination was performed for pre-treatment assessment of patients.

After history taking and physical examination, following baseline investigations were done for full assessment of the patients. Base line investigations, that is data collected on day 1 prior to the administration of the study medication include

- Complete Blood count including total circulating eosinophil count.
- Sputum for
  - Eosinophil count
  - Acid Fast Bacilli
- Chest X-Ray (P-A view)
- PEFR (the best of the three measurements were taken)
- Spirometric evaluation for evidence of airway obstruction, and before and after salbutamol inhalation (2 puffs, 200 μgm) for reversibility :
  - FEV1 the best of three measurements were taken
  - FVC the best of three measurements were taken
  - FEV1/FVC

Study Design

The study had a run in period of one week and a treatment period of 6 weeks. FEV_1 and FVC measurements were performed after the first dose and after 8, 21, and 42 days of treatment. The patients continued to take the permitted medication for their COPD in stable doses, including methylxanthines, inhaled steroids, oral steroids up to 10 mg prednisone per day, and mucolytics. Long acting inhaled β_2 agonists, oral β_2 agonists, and cromolyn sodium were not allowed during the run in period as well as throughout the

study period. Anticholinergics were allowed during the run in period but were discontinued at the randomization visit. Patients were given open label salbutamol to use as rescue medication as necessary. They were allowed to increase or add oral steroids for two periods of seven days if necessary during exacerbations. At the randomization visit patients received either tiotropium 18 μg once daily + ipratropium matched placebo four times daily, or tiotropium matched placebo once daily + ipratropium 40 μg four times daily. Tiotropium was inhaled from the pMDI between 08.00 and 10.00 hours. Ipratropium (two puffs of 20 μg) was inhaled from a pMDI between 08.00 and 10.00 hours, at lunch, dinner, and when going to bed. Half of the patients were randomised into the tiotropium group and half into the ipratropium group.

Patients were given peak flow chart & were instructed to record the best recording out of 3 in morning and evening. In each visit patients peak flow chart was evaluated and physical examination was done and evaluated for any adverse effect.

The data collection through the above mentioned procedure were recorded systematically. All the data were collected from questionnaire forms and proforma. These data were then analyzed statistically by standard procedure to arrive at a definitive conclusion in respect to the objectives of the study. P value <0.05 was taken as significant in all analysis. Results were analyzed by conventional Chi-square test or Student's 't' test as applicable. Student 't' test was used to compare the quantitative difference between the groups and within the groups, viz. PEFR, spirometry analysis, etc. This quantitative data were presented in the table as mean ± standard error of mean (mean ± SEM). A chi-square analysis was done to compare the qualitative improvement and/or difference between groups.

Results

This was a prospective comparative study conducted in National Institute of Chest Disease and Hospital for a period of two years starting from January 2005 to December 2007. The main objective of the study was to assess the bronchodilator efficacy of Inhaled Tiotropium 18μgm/day and Inhaled Ipratropium 40 μgm 4 times a day in patients with COPD. Initially 105 patients were screened for the entry into the study. Of them 15 were not eligible for the study. Of the remaining 90 patients 45 were assigned to group A and the rest in group B. Patients in group A were treated by Inhaler Triotropium once daily + inhaled ipratropium matched placebo four times daily and the rest were treated tiotropium matched placebo once daily + ipratropium 40 μg four times daily.

Ten patients withdrew from the study before the completion. 2 for no contact, 1 for Lack of efficacy, 1 for adverse event, one for protocol violation in group A and 2 for no contact, 1 for adverse event, 1 for protocol violation and 1 for other reason. The withdrawal rates were similar in the two treatment groups-11.1% in both group.

Table-I

Age distribution of the study patients

Parameters	Study Patients				Total (N=90)		P value
	Group A(n=45)		Group B(n=45)				
Age in years	No	%	No	%	No	%	
<50	4	8.9	11	24.4	15	16.7	
<50-59	16	35.6	14	31.1	30	33.3	
60-69	16	35.6	13	28.9	29	32.2	
>70	9	20.0	7	15.6	16	17.8	
Mean±SD	60.62±10.03		57.24±10.26		58.93±10.23		0.118

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from unpaired student's t test

The mean age of the patients was 58.93±10.23years. The mean age of the group A patients was 60.62±10.03 and group B patients was 57.24±10.26 years and the mean age difference was not statistically significant (p >0.05) though the mean age of the group A was a little bit higher than the group B patients.

Among group A, the highest percentage was male (95.6%) and only 4.4% was female. Similarly in group B patients, highest percentage was male (97.8%) and only 2.2% female No statistically significant sex difference was found between two groups of patients (p>0.05).

Among the studied patients the highest percentage was farmer (27.8%) followed by Service holder (22.2%), Retired person (17.8%), Businessman (15.6%), Teacher (13.3%) and Housewife (3.3%). Analysis found no statistically significant difference of occupation between two groups of patients (p>0.05)

Among the studied patients the highest percentage was graduate (30%) followed by illiterate (25.6%), above graduate (17.8%), primary (13.3%) and secondary (13.3%) level of education. Analysis found no statistically significant difference of occupation between two groups of patients (p>0.05)

Table-II

Sex Distribution of the study patients

Parameters	Study Patients				Total (N=90)		P value
	Group A (n=45)		Group B (n=45)				
Sex	No	%	No	%	No	%	
Male	43	95.6	44	97.8	87	96.7	
Female	2	4.4	1	2.2	3	3.3	0.500

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from chi square test

Table-III

Distribution of the study patients by Occupation

Occupation	Study Patients				Total (N=90)		P value
	Group A (n=45)		Group B (n=45)				
	No	%	No	%	No	%	
Service holder	10	22.2	10	22.2	20	22.2	0.906
Businessman	6	13.3	8	17.8	14	15.6	
Teacher	7	15.6	5	11.1	12	13.3	
Retired	9	20.0	7	15.6	16	17.8	
Housewife	2	4.4	1	2.2	3	3.3	
Farmer	11	24.4	14	31.1	25	27.8	

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from chi square test

Table-IV

Distribution of study patients by smoking history in packyear

Duration of smoking in pack year	Study Patients				Total (N=90)		P value
	Group A (n=45)		Group B (n=45)				
	No	%	No	%	No	%	
<20	4	8.9	8	17.8	12	13.3	0.432
20-29	24	53.3	26	57.8	50	55.6	
30-39	15	33.3	10	22.2	25	27.8	
40+	2	4.4	1	2.2	3	3.3	
Mean±SD	29.27±8.40		26.32±7.23		27.80±7.93		

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from chi square test

Table-V

Distribution of study patients by duration of illness of COPD

Duration of illness (in years)	Study Patients				Total (N=90)		P value
	Group A (n=45)		Group B (n=45)				
	No	%	No	%	No	%	
1-2	13	28.9	14	31.1	27	30.0	0.725
3-4	15	33.3	16	35.6	31	34.4	
5-6	7	15.6	9	20.0	16	17.8	
>7	10	22.2	6	13.3	16	17.8	
Mean±SD	4.33±2.51		3.89±2.32		4.11±2.41		

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from chi square test

Table-VI

Distribution of study patients by previous treatment history

Prestudy medication (in years)	Study Patients				Total (N=90)		P value
	Group A (n=45)		Group B (n=45)				
	No	%	No	%	No	%	
Anticholinergic	30	66.7	29	64.4	59	65.6	0.824
Short acting β_2 agonist	38	84.4	41	91.1	79	87.8	0.334
Long acting $\beta_2$agonist	12	26.7	15	33.3	27	30.0	0.490
Theophyline	22	48.9	20	44.4	42	46.7	0.673
Oral Steroid	8	17.8	11	24.4	19	21.1	0.438
Inhaled Steroid	17	37.8	21	46.7	38	42.2	0.393

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from chi square test

Table-VII

Distribution of study patients by PEFR, FEV1, FVC, FEV1/FVC

Parameter	Study Patients		Total (N=90)	P value
	Group A(n=45) Mean ±SD	Group B (n=45) Mean ±SD	Mean ±SD	
PEFR (L/min)	244.07±20.89	249.18±19.09	246.63±20.06	0.229
FVC (L)	2.3±0.30	2.39±0.29	2.34±0.3	0.137
FVC(%)	65.13±2.1	65.61±1.8	65.37±2.0	0.256
FEV1	1.33±0.29	1.39±0.29	1.36±0.29	0.335
FEV1(%pred)	47±5.8	47±5.4	47±5.5	0.83
FEV1/FVC %	57±8	57±7	57±7	0.954

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from unpaired student's t test

Table-VIII

Difference of Trough FVC, FEV1 and PEFR of study patients on Day 8

Parameter	Study Patients		P value
	Group A(n=43) Mean ±SD	Group B (n=43) Mean ±SD	
Difference of Trough FVC(L) on day 8	0.0702±0.013	0.0235±0.011	<0.001
Difference of Trough FEV1(L) on day 8	0.0581±0.012	0.0095±0.004	<0.001
Difference of Trough PEFR(L/m) on day 8	6.5349±1.39	2.0930±0.81	<0.001

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from unpaired student's t test

The mean difference of Trough FVC, FEV1 and PEFR at the end of day 8 was 0.0702±0.013, 0.0581±0.012, 6.5349±1.39 respectively in group A and 0.0235±0.011, 0.0095±0.004 and 2.0930±0.81 respectively in group B. The statistical analysis shows the difference of the both group is statistically significant (p<.001).

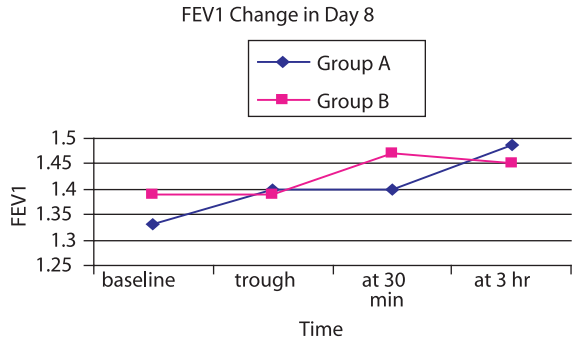

Fig.-1: *FEV1 at baseline, trough, 30 min and 3hr after taking medication in both group on Day 8.*

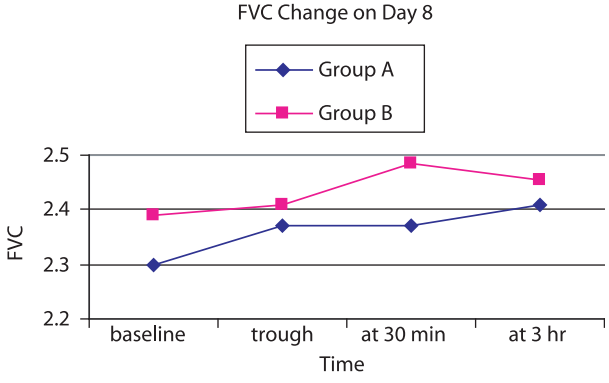

Fig.-2: *FVC at baseline, trough, 30 min and 3hr after taking medication in both group on Day 8*

Table-IX

Difference of Trough FVC, FEV1 and PEFR of study patients on Day 21.

Parameter	Study Patients		P value
	Group A(n=41) Mean ±SD	Group B (n=41) Mean ±SD	
Difference of Trough FVC on day 21	0.0810±0.013	0.0241±0.010	<0.001
Difference of Trough FEV1 on day 21	0.0617±0.013	0.0095±0.004	<0.001
Difference of Trough PEFR on day 21	6.9756±1.46	2.0488±0.77	<0.001

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from unpaired student's t test

The mean difference of Trough FVC, FEV1 and PEFR at the end of ay 21 was 0.0810±0.013, 0.0617±0.013, 6.9756±1.46 respectively in group A and 0.0241±0.010, 0.0095±0.004 and 2.0488±0.77 respectively in group B. The statistical analysis shows the difference of the both group is statistically significant (p<0.001).

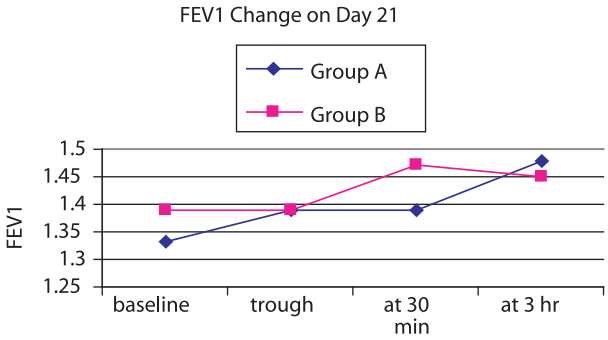

Fig.-3: *FEV1 at baseline, trough, 30 min and 3hr after taking medication in both group on Day 21*

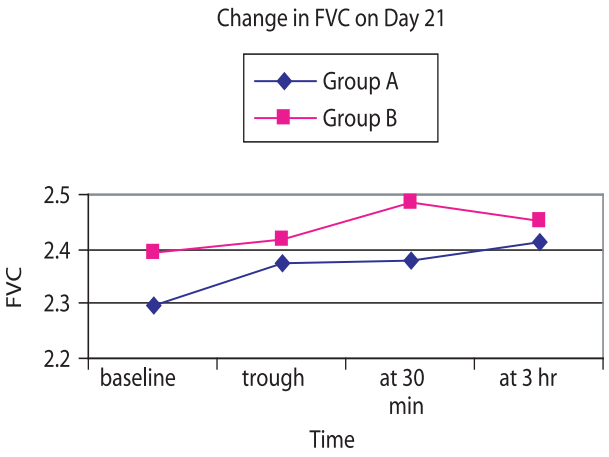

Fig.-4: *FVC at baseline, trough, 30 min and 3hr after taking medication in both group on Day 21*

Table-X

Difference of Trough FVC, FEV1 and PEFR of study patients on Day 42 (At the end of study).

Parameter	Study Patients		P value
	Group A(n=39) Mean ±SD	Group B (n=41) Mean ±SD	
Difference of Trough FVC on day 42	0.0910±0.014	0.0263±0.011	<0.001
Difference of Trough FEV1 on day 42	0.0772±0.012	0.0095±0.004	<0.001
Difference of Trough PEFR on day 42	7.1282±1.51	2.0488±0.77	<0.001

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium

Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium

p value reached from unpaired student's t test

The mean difference of Trough FVC, FEV1 and PEFR at the end of ay 42 was 0.0910±0.014, 0.0772±0.012, 7.1282±1.51 respectively in group A and 0.0263±0.011, 0.0095±0.004and 2.0488±0.77 respectively in group B. The statistical analysis shows the difference of the both group is statistically significant (p<.001).

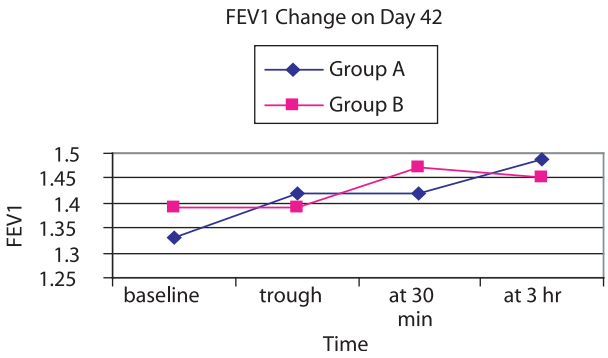

Fig.-5: *FEV1 at baseline, trough, 30 min and 3hr after taking medication in both group on Day 42*

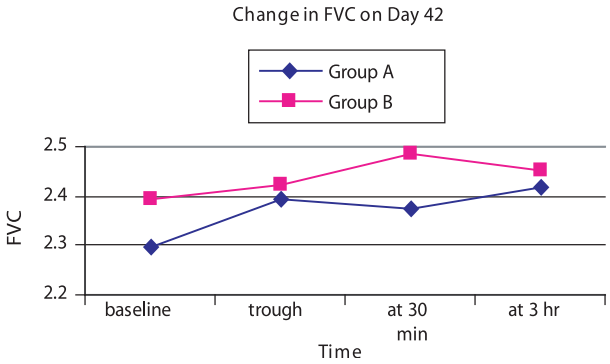

Fig.-6: *FVC at baseline, trough, 30 min and 3hr after taking medication in both group on Day 42*

MINI COPD Quality of Life Score

Each patient was evaluated by Three 7 scale questionnaire for COPD related Quality of Life as 0 for Never, 1 for almost never, 2 for a little of the time, 3 for some of the time, 4 for a good bit of time, 5 for Most of the time and 6 for All of the time. And One 5 scale questionnaire where 0 for Not at all, 1 for Slightly limited, 2 for Moderately limited, 3 for Quite a bit limited and 4 for Extremely limited. Another 5 scale questionnaire where 0 for not at all, 1 for Mildly, 2 for Somewhat, 3 for Moderately and 4 for Severely. In another questionnaire 0 for not at all, 1 for Mildly, 2 Moderately, 3 for Severely and 4 for I could not do activities at all. A questionnaire also with 5 scale had 0 for excellent, 1 for Very good, 2 for Good, 3 for Fair and 4 for Poor.

The Mean Mini COPD health score at the end of the study was done. The score was 51.38±1.29 in group A and 53.44±2.08 in group B. The difference is statistically significant (p<.001).

Concomitant daily use of β_2 agonist was 1.49±0.63 in group A and 1.26±0.54 in group B. Though the use was a bit higher in group A but it was not statistically significant (p>.05).

Table-XI

Mean distribution of Mini COPD health score and concomitant use of â$_2$ agonist of study patients on Day 42 (At the end of study).

Parameter	Study Patients Group A(n=39) Mean ±SD	P value Group B (n=41) Mean ±SD	
Mini COPD health score	51.38±1.29	53.44±2.08	<.001
Concomitant daily use of β_2 agonist	1.49±0.63	1.26±0.54	.070

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from unpaired student's t test

Table-XII

Mean difference of trough and evening PEFR on Day 8, 21 and 42.

Parameter	Study Patients Grpoup A(n=39) Mean ±SD	Group B (n=41) Mean ±SD	P value
Difference of morning and evening PEFR on day 8	2.18±0.70	1.00±0.53	<0.001
Difference of morning and evening PEFR on day 21	1.88±0.56	1.00±0.53	<0.001
Difference of morning and evening PEFR on day 42	1.41±0.50	1.00±0.53	<0.001

Group A : Patients treated by Inhaler Tiotropium + Placebo of Ipratropium
Group B : Patients treated by Inhaler Ipratropium + Placebo of Tiotropium
p value reached from unpaired student's t test

The mean difference between trough and evening PEFR gradually decreased from day 8 to day 42 as the evening PEFR gradually increased through this period as compared to trough PEFR in group A which was 2.18±0.70, 1.88±0.56 and 1.41±0.50 respectively on day 8, day 21 and day 42 . But it group B the difference remained the same 1.00±0.53 throughout the study as the trough as well as evening PEFR remained almost static during this period. The difference of the mean was statistically significant (p<0.001).

Discussion

This prospective study was done in which the bronchodilator effect of tiotropium has been investigated and directly compared with that of ipratropium in patients with moderate to severe airflow obstruction due to COPD.

The variables studied were trough FEV1, PEFR, FVC, post bronchodilator FEV1, PEFR, FVC at 30 min and 3 hr, concomitant use of inhaled â2 agonist and Mini COPD Quality of Life Score.

Initially 105 patients were screened for entry into the study. Of them 15 were not eligible for the study as they did not met the inclusion criteria. Total ninety patients were included in the study. The study patients were divided into two groups by picking forty five from random table and were assigned group A and the rest became group B. Patients in group A were treated by Inhaler Triotropium once daily + inhaled ipratropium matched placebo four times daily and the rest were treated by tiotropium matched placebo once daily + ipratropium 40 μg four times daily in group B.

Ten patients withdrew from the study before its completion, 2 for no contact, 1 for lack of efficacy, 1 for adverse event, one for protocol violation in group A and 2 for no contact, 1 for adverse event, 1 for protocol violation and 1 for other reason. The withdrawal rates were similar in the two treatment groups, 5 in each group (11.1%).

The prospective study was conducted in outpatient department of the National Institute of Disease of the Chest & Hospital, Dhaka, for a period of two years, starting from January 2005 to December 2006.

The mean age difference was not statistically significant though the mean age of the group A was a little bit higher than the group B patients.

Van et. al, 2000 on behalf of the Dutch Tiotropium Study Group showed age of Tiotropium group was 64 ± 8 and Ipratropium 65±8. It is consistent with my study.

It indicates that most patient with COPD seek medical attention when they are between 50-69 year.

Regarding sex, in both groups, the highest percentage were male (95.6%) and (97.8%) respectively and only 4.4% and 2.2% were female respectively. No statistically significant sex difference was found between two groups of patients.

The high male predominance which also found in other studies done in Bangladesh on COPD patients (1, 2) may be due to increased smoking habits among males, also male are more exposed to external environment. Atmospheric pollution and smoking are two principal predisposing factors for COPD. Females were found least affected in the study probably due to

- Few females smokers in this country
- Most were housewives
- Had a sheltered mode of life and
- Less exposure to occupational dust and fumes.

But in western world, male female difference in cigarette consumption is narrow, thereby existing sex differences in the prevalence of COPD is expected in our society due to lack of smoking habit in female in our society.

No statistically significant difference in mean body mass index was found between two groups of patients. Regarding height and weight there is also not significant difference between the two groups.

Though the mean weight and height were lower than Van et al 2000 but it is consistent with other studies done in Bangladesh[2].

Peoples who suffer from cough don't give importance to the disease and usually don't come to a doctor or take medicine from pharmacy to suppress the cough. They usually don't recognize the symptom as a disease unless it becomes severe or becomes associated with breathlessness. This attitude come out in our study with the mean duration of symptom before coming to a chest physician or Chest institute. The mean duration of symptom were measured. The mean duration of illness was a little bit higher in group A as compared to group B. The difference was not statistically significant. It could be due to ignorance of patients regarding the disease. They also tried to get treatment from local doctors.

Van et. al, 2000 on behalf of the Dutch Tiotropium Study Group showed mean history of smoking of Tiotropium group was 33±16 pack year and Ipratropium 35±19 pack year. It is consistent with our study.

As this is well recognized fact that smoking is the principal risk factor for the development of COPD, we also tried to find out the smoking history—its duration as well as number of stick consumed expressed in pack year. The mean smoking history of patients in group A was 29.27±8.4 and for group B was 26.32±7.23. Though it is a little lower in our study groups but analysis revealed no statistically significant difference in smoking history, though the mean smoking history was a little bit higher in group A compared to group B.

It is clear that COPD does not have a single cause and that multiple factors must act in combination for the disorder to become clinically evident. Cigarette smoking is the principal identified risk factor in the causation of COPD, yet only a minority of persons who smoke develop COPD while an occasional lifelong nonsmoker may develop severe disease. Other factors are clearly operative, but their identity remains largely unknown. There is widespread concern that noxious fumes, dust and smoke encountered in the workplace may permanently impair ventilatory function and contribute to the development of COPD.

For most occupational exposures, the risk of developing COPD appears to be more pronounced in those workers who also smoke cigarette. In general, the magnitude of the occupational effect is substantially less important that the smoking effect and occupation alone would rarely lead to the development of clinically apparent COPD[3].

Analysis found no statistically significant difference of occupation between two groups of patients. Educational background is important on giving information to the patients. Though there is less percentage of patients from less educated group but the awareness of the disease and tendency for

seeking medical help among relatively less educated group was not far behind than the relatively well educated people which are consistent with[2].

During questioning we found before coming to a chest hospital or chest physician the patients tried different medication from various advice—from local village doctor and also qualified doctor. But treatment regimen was very much faulty. Those with lack of knowledge of latest guidelines and also fear of using inhaler was obvious from the previous treatment history.

It was found that all the patients (both the groups) had history of taking various types of bronchodilator drugs prior to attending the hospital but the difference was not statistically significant. And about Long acting beta agonist, both the group had history of taking this drug, the difference was not statistically significant. Patients also had history of taking anticholinergic drugs, the difference was not statistically significant. Regarding oral theophyline use the difference was not statistically significant. Regarding the use of oral steroid, only 17.8% in group A patients and 24.4% in group B patients had previous history of taking oral steroid. And about inhaled steroid 37.8% in group A had history of taking the medicine while 46.7% in the group B had the same, the difference is not statistically significant. They took drugs irregularly and inhaler technique was mostly incorrect. It also indicates that the disease is progressive and irreversible.

The peak expiratory flow, forced vital capacity and forced expiratory volume in one second before bronchodilator were recorded before day 1 of the study as baseline measure. The parameters were also measured after bronchodilation with short acting beta 2 agonist.

The mean baseline peak expiratory flow, forced vital capacity and forced expiratory volume in one second were measured in both the groups of patients. Analysis found no statistically significant mean differences between two groups of patients.

The percentage of FVC, percentage of FEV1 of predicted and FEV1/FVC were measured in both the groups of patients. The differences are not statistically significant.

The mean post bronchodilator peak expiratory flow, forced vital capacity and forced expiratory volume in one second were measured in both the groups. Analysis found no statistically significant mean differences between two groups of patients.

The percentage of change of FEV1 was 6.88±2.3 and 6.64±1.7 in group A and in group B respectively which is less than 12%.

In the present study, the pulmonary functions were evaluated by measuring the PEFR in L/min, FEV1 in L, FVC in L.

The mean difference of Trough FVC, FEV1 and PEFR from baseline which was our primary end point was measured at day 8, day 21 and day 42.

The difference of trough FVC, FEV1 and PRFR from baseline were better and statistically significant in group A

There is a small increase in all parameter which is consistent with (4).

18 μg tiotropium once daily via metered dose inhaler achieved a significantly greater improvement in trough values of FEV1, FVC and PEFR than 40 μg ipratropium four times daily at the end of day 8, 21 and 42.

These data confirm the results of previous single dose studies (5) that tiotropium has a bronchodilating effect of at least 24 hours.

During the maintenance therapy with tiotropium the values of FEV1 and FVC never returned to baseline values. There was still an improvement in trough FEV1 and FVC response 24 hours after the previous dose. Measurements after the first doses of both compounds showed that ipratropium had a more rapid onset of action than tiotropium. However, during maintenance therapy this difference was no longer of importance, as the "acute on chronic" effect of tiotropium achieved almost equal bronchodilation to ipratropium. The effect also observed by Van et al[4].

Furthermore, after both tiotropium and ipratropium the improvements in FVC were similar to those in FEV1. It is generally thought that anticholinergic agents produce their bronchodilating effect mainly in the central airways. Nevertheless, this increase in FVC might be interpreted as a diminution of air trapping and of closure of the small airways.

It is known that in COPD the relationship between PEF and FEV1 is poor and PEF may underestimate the degree of airways obstruction because of the airway collapsibility present in this disorder.

However, serial PEF measurements are of value in assessing treatment response. Using weekly means of PEF recordings in the tiotropium group steady state was reached after three weeks and sustained during the treatment period, whereas in the ipratropium group PEF showed a significant difference in between morning and evening PEF during the 6 week.

In keeping with the results of the clinical lung function, improvement in morning and evening PEF monitored at home and the difference between evening and morning (trough) PEF calculated.

Patients were given Peak flow meter to monitor morning (before taking drug) and evening (before taking drug) himself regularly. This was designed to find the duration of bronchodilating effect of both drug.

The effect of tiotropium remains for 24-36hr. As a result it elevates the value of PEFR during evening as well as next days trough PEFR values. But as the duration of effect for ipratropium is 6-8hr and taking it 6 hourly becomes prblematic for the patient we found the following observation.

The mean difference between trough and evening PEFR gradually decreased from day 8 to day 42 as the evening PEFR gradually increased through this period as compared to trough PEFR in group A. But in group B the difference remained the same throughout the study as the trough as well as evening PEFR remained almost static during this period. The difference of the mean was statistically significant. The results are consistent with study of [5].

However, we are aware that, in addition to spirometric indices there are outcome parameters. In addition to pulmonary function COPD affects the physical, social and emotional aspects of patients lives. Each patient evaluated by 7 scale questionnaire for COPD—"Mini COPD health score". The difference in score is statistically significant and better in Tiotropium group.

Concomitant use of rescue salbutamol is regarded as an indicator of disease control. So, we decieded to study the use of concomitant salbutamol. It is found that the concomitant use of â2 agonist use was a little high in group A than group B. But the difference of which is not statistically significant and consistent with[5] study.

At present the official GOLD guideline (6) recommend regular use of anticholinergics as first line treatment in patients with COPD suffering from continuing symptoms. The present study shows that tiotropium has important and significant advantages over ipratropium. Tiotropium is more potent, has a longer duration of action, and is able to produce a permanent improvement in baseline lung function. It allows once daily dosing which is convenient for patients with COPD and may enhance compliance with treatment.

Limitations

One limitation of the present study is that study population is limited in number. More the number of patients, more convincing will be the result. Another limitation of the present study is the absence of a placebo group. This procedure involves expensive apparatus like spirometry which requires external source of energy (i.e. Electricity)

Strength of the study

The study was double blind, double dummy and parallel group study. The study period was 6 week by which time the effect of tiotropium reaches steady state. Both subjective and objective improvement of patient was measured.

In conclusion, 18 µg tiotropium once daily was significantly more effective than 40 µg ipratropium four times daily in improving trough and peak lung function over the 6 week treatment period. These data support the use of tiotropium as first line treatment for the long term maintenance treatment of patients with airflow obstruction due to COPD.

Conclusion

So, in conclusion Tiotropium in a dose of 18 µg inhaled once daily MDI was significantly more effective than 40 µg ipratropium four times daily in improving trough PEFR, FEV1 and FVC as well as Mini COPD health score over 6 weeks period. These data support the use of tiotropium as first line treatment for the long term maintenance

treatment of patients with airflow obstruction due to COPD.

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