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The comparative analysis of salmeterol/fluticasone propionate combination and tiotropium bromide on lung function & health status changes, as well as prevention of exacerbations in patients with COPD.

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Abstract
COPD is the major cause of chronic morbidity & mortality throughout the world as well as Bangladesh. The varieties of treatment options are followed in order to improve lung function, health status changes and prevent exacerbations. These include long-acting inhaled bronchodilators, such as salmeterol and tiotropium, as well as inhaled corticosteroids (ICS) alone or combined with long-acting β_2-agonists.
Objective: *The present study is design to evaluate lung function, health status changes and prevention of exacerbations following treatment with twice daily salmeterol/fluticasone propionate combination (SFC) compare with once daily tiotropium bromide (Tio) in COPD patient.*
Material and Methods: *Initially 100 patients were included according to the inclusion and exclusion criteria of the study. A 2-weeks phase of run-in period was performed in order to evaluate with history and symptoms, examinations and certain baseline investigations, spirometry and SGRQ evaluation were done. During the run-in period all study patients were provided with any treatment with inhaled corticosteroids, short-acting bronchodilator, long-acting β_2-agonists, and anticholinergics that the patients may be using before was discontinued. After, randomization patients gave rotacap according to their code number. Than a baseline, at the end of the 2^{nd}& 12^{th} week follow-up was done to determine the improvement of symptoms by MRC dyspnoea scale, lung function by spirometry FEV1, health status changes by SGRQ evaluation, as well as status of exacerbation and need hospitalization. During the study period total 79 patients completed the procedure & came to the final follow-up.*
Results: *After analysis it was found that 38 patients were received SFC & 41 patients were received Tio. Patients who received SFC, the post-bronchodilator FEV1 improvement was 7.2±4.1 & who received Tio it was 2.9±1.4. Regarding health status changes, it was observed that significant improvement i.e. >4 unit changes of total score, activity scoresymptoms score,& impact score occur in the patients who received SFC than Tio. During study period 5.3% patients suffered from exacerbation & 2.6% patients required hospitalization in SFC group but in Tio group it was 9.8% & 4.9% respectively.*
Conclusion: *SFC group experienced higher improvement of symptoms, lung function, health status changes, fewer exacerbations & less required hospitalization during the clinical trial. Concerning about the exacerbation prevention of the relative risk reduction was 46%, absolute risk reduction was 4.5%, and NNT was 22. Regarding hospitalization prevention among the patients, the relative risk reduction was 47%, absolute risk reduction was 2.3%, and NNT was 43.*
Keywords: *COPD, Salmeterol,Tiotropium Bromide.*

Introduction

Chronic obstructive pulmonary disease is major cause of chronic morbidity & mortality throughout the world. Many people suffer from this disease for years & die prematurely from it or its complications. COPD is currently the fourth leading cause of death in the world & further increase in its prevalence and mortality, also a common health problem in Bangladesh & one of the common conditions seen by physicians. It is the burden for both the developed & developing countries. Although there is no prevalence study done in Bangladesh, the problem is increasing in this country like other parts of the world. Many patients with COPD experience periodic worsening of their symptoms, reflecting an acute deterioration in lung mechanics and airway inflammation secondary to viral and/or bacterial infection. These exacerbations contribute to impaired health status and increased hospitalization costs, and predict mortality.[1,2]

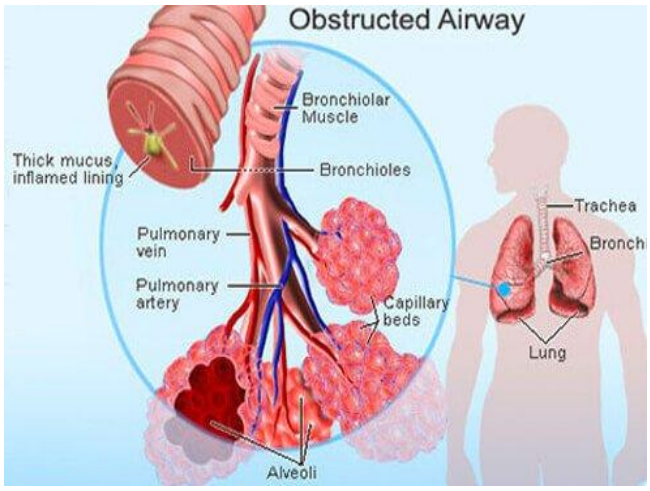

Figure 1: Chronic Obstructive Pulmonary Disease & Treatment

A variety of COPD treatments have been shown to prevent exacerbations. These include long-acting inhaled bronchodilators, such as salmeterol and tiotropium, as well as inhaled corticosteroids (ICS) alone or when combined with long-acting β_2-agonists (LABAs). The efficacy of an ICS/LABA combination or a long acting anticholinergic in preventing exacerbations has not been directly compared nor has the effect of these treatments on lung function or health status tested over an extended period. Inhaled long-acting β_2 agonists improve airflow obstruction, control of symptoms, and health status in patients with COPD over 3-4 months and have several potentially beneficial non-bronchodilator effects. The role of inhaled corticosteroids in COPD management is less certain. These drugs do not change the rate of decline in lung function, but can increase post-bronchodilator forced expiratory volume in 1 sec (FEV_1), reduce the number of exacerbation, and slow the rate of decline in health status.[3]

There are few studies regarding the combined of salmeterol/fluticasone propionate combination or tiotropium bromide & their comparison in the prevention of chronic obstructive pulmonary disease exacerbations. In Bangladesh no study has been carried out to date regarding the comparison of twice daily salmeterol/fluticasone propionate combination with once daily tiotropium bromide in patients with COPD. The present study is design to evaluate lung function, health status changes and prevention of exacerbations following treatment with twice daily salmeterol/fluticasone propionate combination compare with once daily tiotropium bromide in stable COPD patient.

Objectives

General objective

- To compare the effects of salmeterol/ fluticasone propionate combination and tiotropium bromide on lung function & health status changes, as well as prevention of exacerbations in patients with COPD.

Specific Objectives

- To find the efficacy of both drugs in a COPD patient,
- To make a comparative analysis of both drugs, and
- To search better standard therapy in patients with COPD.

Methodology

The study type was a double blind, prospective, and Randomized Controlled Clinical Trial (RCT). This study was carried out during the period from 1st January' 2018 to 30th November 2018, in the outpatients department (OPD) of Patuakhali 250 Bed Sadar Hospital, Patuakhali. Initially 100 patients were included according to inclusion and exclusion criteria, after taking informed consent. Amongst them 12 patients from group-I and 9 patients from group-II did not come for a follow-up at 12th week. So, 38 patients in group-I and 41 patients in group-II were included in the study. It was a consecutive random sampling. Patients were randomized in two groups where one group was givenrotacap containing salmeterol/fluticasone propionate combination with a cyclohaler device, and the other group was given rotacap containing tiotropium bromide and placebo with a cyclohaler device.

Inclusion Criteria
1. Clinical diagnosis of COPD, as defined by GOLD.
2. Age >40 years.
3. History of cigarette smoking >10 pack years.
4. Respiratory symptoms (Cough, shortness of breath and sputum production) for greater than 2 years.
5. Clinically stable airway obstruction.
6. A forced expiratory volume in first second (FEV_1) of <80% to >35% of predicted normal values and ratio of FEV_1 to forced vital capacity (FVC) of <70%
7. Participants, who gave consent and willing to comply with the study procedure, were included.

Exclusion Criteria
1. If the patient has acute exacerbation of COPD
2. Patient with a history of asthma, allergic rhinitis, atopy or increase total eosinophil counts
3. A significant disease other than COPD
4. A recent history of myocardial infarction (<1year), heart failure or cardiac arrhythmia required drug treatment
5. If the patient require regular day time supplemental oxygen or will on exceeding the equivalent of 10 mg prednisolone daily during the month prior to entering study
6. Patient has upper respiratory tract infection
7. Patient has known hypersensitivity to anticholinergic drug
8. Known symptomatic prostatic hypertrophy
9. Narrow angle glaucoma

Study Design

The study was hospital based clinical trial which comprised of **Run-in phase-** for confirmation of diagnosis and evaluation of eligibility with 12 weeks **Clinical and follow-up phase-** management of COPD treatment along with either

salmeterol/fluticasone combination or tiotropium bromide and placebo and to see the effect of the drugs.

Results

The mean (±SD) age was 54.3±9.9 yearsin group-I & in group-II the mean (±SD) age was 54.1±8.5 years as shown in table 1.

Table 1: Age distribution of the study patients

Age in years	Group-I (n=38)		Group-II (n=41)		Total	
	N	%	N	%	N	%
40-49	13	34.2	16	39.0	29	36.7
50-59	18	47.4	17	41.5	35	44.3
60-69	4	10.5	7	17.1	11	13.9
≥ 70	3	7.9	1	2.4	4	5.1
Mean±SD	54.3	±9.9	54.1	±8.5	54.3	±9.9
Range (min-max)	(40	- 77)	(41	- 75)	(40	- 75)

Figure 2 shows that male was predominant in both groups and male female ratio was almost 10.3:1.Maximum of the patients were smoker in both groups. Pack years were found 37 in group-I and 34 in group-II patients (Figure 3). However, mean pack years were 33.5±12.1 pack per year in group-I and 31.3±10.2 pack per year in group-II(Figure 3).

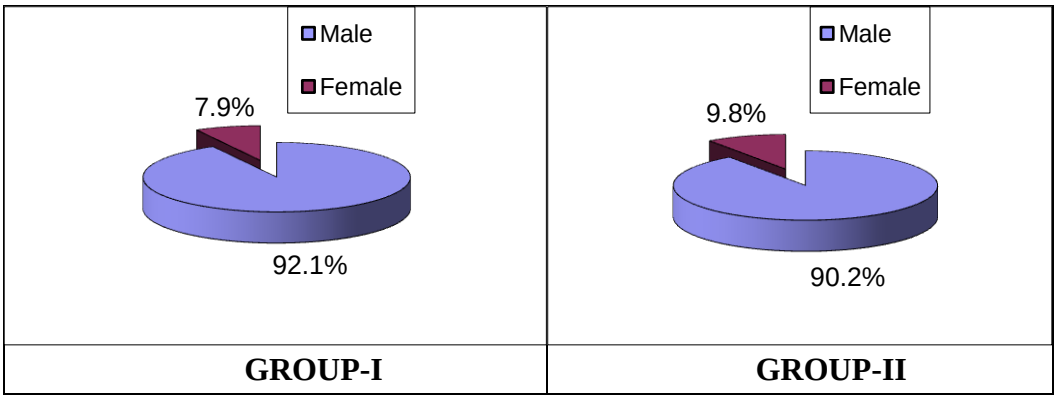

Figure 2: Pie diagram showing sex distribution

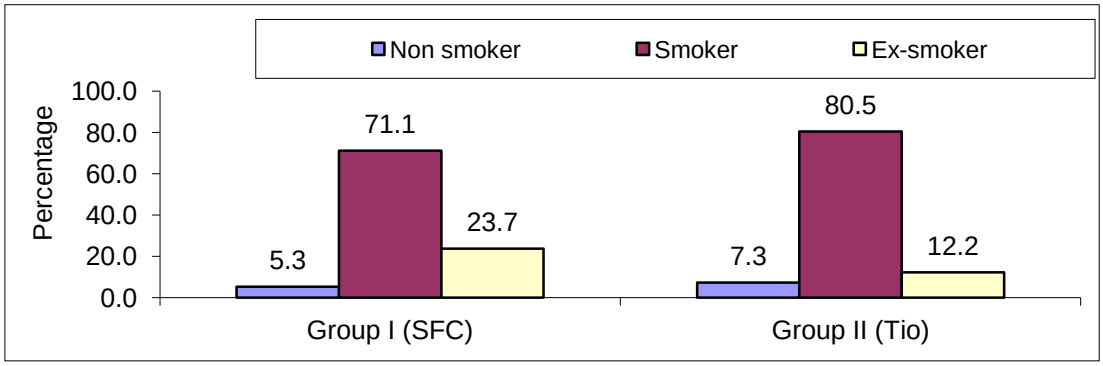

Figure 3: Bar diagram showing smoking history of the study patients

Mean (±SD) BMI was found 20.8±3.5 kg/m^2 and 19.9±3.3 kg/m^2 in group-I and group-II respectively as per table 2.

Table 2: BMI (kg/m^2) distribution of the study patients

BMI (kg/m^2)	Group-I (n=38)		Group-II (n=41)		P value
	N	%	N	%	
<18.5	11	28.9	14	34.1	
18.5-24.9	20	52.6	24	58.5	
25.0-29.9	7	18.4	3	7.3	
≥30.0	0	0.0	0	0.0	
Mean±SD	20.8	±3.5	19.9	±3.3	0.795^{ns}
Range (min-max)	(15.43	- 29.3)	(14.88	- 26.64)	

The mean (±SD) difference of MRC dyspnoea index at baseline and follow-up during 12th week was found 0.43±0.5 and 0.19±0.41 in group-I and group-II respectively, which was statistically significant (p<0.001).(Figure 4)

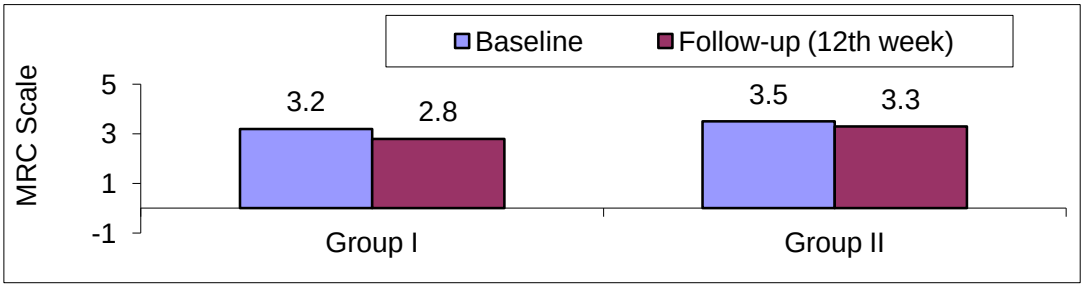

Figure 4: Bar diagram showing Mean distribution of MRC dyspnoea index

In group-I, the mean (±SD) post-bronchodilator FEV_1 (% predicted) during baseline was 56.9±10 and follow-up during 12th week was 64.1±10.9. In group-II, the mean (±SD) post-bronchodilator FEV_1 (% predicted) at baseline was 56.6±11.7 and follow-up during 12th week was 59.7±11.4. The mean (±SD) difference was found 7.2±4.1 and 2.9±1.4 in group-I and group-II respectively, which was statistically significant (p<0.001). (Table 3)

Table 3: Mean distribution of post-bronchodilator FEV_1 (% predicted)

Post-bronchodilator FEV_1 (% predicted)	Group-I (n=38)		Group-II (n=41)		P value
	Mean	±SD	Mean	±SD	
Baseline	56.9	±10	56.6	±11.7	0.920^{ns}
Range (min-max)	(38.2	- 78.7)	(35.5	- 79.9)	
Follow-up (12th week)	64.1	±10.9	59.7	±11.4	0.092^{ns}
Range (min-max)	(35.5	-87.4)	(39.5	-81.5)	
Difference	7.2	±4.1	2.9	±1.4	0.001^{s}
^{a}P value	0.001^{s}		0.001^{s}		

The mean distribution of total score, symptoms score, activity score and impacts score is detailed in the table 4, 5, 6, and 7 below.

Table 4: Mean distribution of total score

Total score	**Group-I (n=38)**		**Group-II (n=41)**		**P value**
	Mean	**±SD**	**Mean**	**±SD**	
Baseline	54	±3.6	53.7	±3.8	0.684^{ns}
Range (min-max)	(48.5	- 60.8)	(49.7	- 61.7)	
Follow-up (12th week)	47.9	±3.7	50.1	±3.9	0.022^{s}
Range (min-max)	(41.6	- 54.9)	(44.6	- 58.1)	
Difference	6.0	±0.65	3.6	±0.6	0.001^{s}
^{a}P value	0.001^{s}		0.001^{s}		

Table 5: Mean distribution of symptoms score

Symptoms score	Group-I (n=38)		Group-II (n=41)		P value
	Mean	**±SD**	**Mean**	**±SD**	
Baseline	52.9	±3	47.1	±3.2	0.001[s]
Range (min-max)	(48.7	- 58.2)	(43.4	- 51.1)	
Follow-up (12th week)	46.1	±2.9	44.1	±3.3	0.007[s]
Range (min-max)	(41.0	- 52.8)	(39.0	- 48.3)	
Difference	6.8	±1.8	2.9	±1.0	0.001[s]
[a]P value	0.001[s]		0.001[s]		

Table 6: Mean distribution of activity score

Activity score	Group-I (n=38)		Group-II (n=41)		P value
	Mean	±SD	Mean	±SD	
Baseline	65.4	±5.4	64.3	±4.9	0.324[ns]
Range (min-max)	(53.2	- 73.5)	(56.2	- 75.5)	
Follow-up (12th week)	58.9	±5.7	61.1	±4.8	0.068[ns]
Range (min-max)	(43.2	- 66.5)	(49.5	- 70.9)	
Difference	6.56	±1.8	3.1	±1.2	0.001[s]
[a]P value	0.001[s]		0.001[s]		

Table 7: Mean distribution of impacts score

Impacts score	Group-I (n=38)		Group-II (n=41)		P value
	Mean	±SD	Mean	±SD	
Baseline	48.2	±6	50.3	±5.9	0.136[ns]
Range (min-max)	(42.3	- 56.9)	(42.4	- 58.5)	
Follow-up (12th week)	42.8	±5.8)	45.9	±6.2	0.030[s]
Range (min-max)	(38.6	- 50.8)	(37.4	- 54.8)	
Difference	5.3	±1.5	4.4	±1.4	0.008[s]
[a]P value	0.001[s]		0.001[s]		

S=Significant, NS= Not significant, P value reached from unpaired t-test, [a]P value reached from paired t-test

During the study period 2(5.3%) patients in group-I and 4(9.8%) patients in group-II suffered from COPD exacerbation and 1(2.6%) exacerbation patients in group-I and 2(4.9%) exacerbation patients in group-II required hospitalization. No significant ($p>0.05$) difference was found between two groups in Chi square test. (Table 8)

Table 8: Distribution according to status of COPD exacerbation and number of patients required hospitalization

	Group-I (n=38)		Group-II (n=41)		Total		P Value
	N	**%**	**N**	**%**	**N**	**%**	
Status of COPD exacerbation							
Yes	2	5.3	4	9.8	6	7.6	0.451[ns]
No	36	94.7	37	90.2	73	92.4	
No. of pts. required hospitalization							
Yes	1	2.6	2	4.9	3	3.8	0.601[ns]
No	37	97.4	39	95.1	76	96.2	

NS= Not significant, P value reached from Chi square test

Exacerbation event rate was found in 9.8% of the patients who received Tiotropium bromide (Tio) and 5.3% of the patients who received Salmeterol/fluticasone propionate combination (SFC). Relative risk reduction was 45.9%, absolute risk reduction 4.5% and number needed to treat 22. Hospitalization event rate was observed in 4.9% of the patients who received Tiotropium bromide (Tio) and 2.6% of the patients who received Salmeterol/fluticasone propionate combination (SFC). Relative risk reduction was 46.9%, absolute risk reduction 2.3% and number needed to treat 43. (Table 9)

Table 9: Interpretation of results

	Event rate (%)		RRR (%)	ARR (%)	NNT
	Tio	SFC			
Exacerbation	9.8	5.3	45.9	4.5	22
Hospitalization	4.9	2.6	46.9	2.3	43

RRR= Relative risk reduction, ARR= Absolute risk reduction, NNT= Number needed to treat

Discussion

In the study, 12 patients (24%) from group-I and 9 patients (18%) from group-II were drop out. The main reason for withdrawal was the presence of adverse events of drugs during the treatment period, an increased frequency of oropharyngeal candidosis, worsening dyspnoea, experiencing an exacerbation, non-compliance, and failure to return. INSPIRE is the large-scale trial to evaluate the impact of two different treatment approaches- bronchodilatation with a long-acting inhaled anticholinergic agent or the combination of bronchodilatation using a LABA and anti-inflammatory therapy with an ICS- on COPD exacerbations over a 2-year period.

In this current study, the mean age was 54.3±9.9 years in group-I and 54.1±8.5 years in group-II. Most (47.4% Vs 41.5%) of the patients belonged to 50-59 in both age group. The mean age was more than 60 years observed by another study, which were higher than the current study. It is stated that the higher age range may be due to increased life expectancy in their study patients. Male was predominant in both groups, and the male-female ratio was almost 10.3:1, which closely resembles with other authors. It was observed that 71.1% and 80.5% patients smoker in group-I and group-II respectively. Ex-smoker was found 23.7% in group-I and 12.2% in group-II. Smoking history was almost similar between the two groups. However, mean pack-years were 33.5±12.1 in group-I and 31.3±10.2 in group-II. In group-I patients mean (±SD) difference of MRC dyspnoea index at baseline and follow-up during 12th week was 0.43±0.5, which was statistically significant ($p<0.05$). In group-II, the mean (±SD) difference of MRC dyspnoea index was 0.19±0.41, which was significantly ($p<0.05$) higher in group-I.

Mean (±SD) BMI was 20.8±3.5 kg/m2 in group-I and 19.9±3.3 kg/m2 in group-II which was almost similar in both groups. Higher body mass index observed by another study may be due to a higher body surface area of their study patients.

In this study it was found during 12th-week follow-up, the mean (±SD) difference of post-bronchodilator FEV1 (% predicted) from baseline was 7.2±4.1 and 2.9±1.4 in group-I and group-II respectively, it was higher in group-I. So, lung function was better improved with salmeterol/fluticasone propionate than tiotropium bromide. In INSPIRE study, both treatment largely maintained the improvement in FEV1 achieved, a small statistically significant difference between salmeterol/ fluticasone propionate than tiotropium bromide. In the TORCH study, treatment effects on post-bronchodilator FEV1 followed better improvement with salmeterol/fluticasone propionate across all GOLD Stages. Also in the ISOLDE trial, the effect was greater in patients who received inhaled corticosteroids. There was also evidence that triple therapy caused a greater reduction in hyperinflation compared with treatment with SFC or Tio alone. The superiority of triple therapy demonstrated by this range of pulmonary function measurements, symptom scores and rescue medication use, particularly compared with Tio used alone.

In this study shows that a significant number of patients receiving SFC had greater than 4 point change from baseline than patients receiving tiotropium. The improvement in the total score in the SFC treatment group was largely driven by changes in the symptom and activities score. The mean (±SD) difference of total score at follow-up was 6.0±0.65 in group-I and 3.6±0.6 in group-II, Mean (±SD) difference of symptoms score at follow-up was 6.8±1.8 in group-I and 2.9±1.0 in group-II, Mean (±SD) difference of activity score at follow-up was 6.56±1.8 in group-I and 3.1±1.2 in group-II, Mean (±SD) difference of impacts score at follow-up was 5.3±1.5 in group-I and 4.4±1.4 in group-II, was significantly ($p<0.05$) higher in group I.

Wedzicha et al., (2007) found mean difference SGRQ total score significantly changed in the SFC group than in the tiotropium group. Similarly, Calverley et al., (2003) in INSPIRE study showed mean SGRQ total score were 49.7 in group-I and 50.5 in group-II. The improvement in total score was reflected by improvements in impacts domain with an adjusted mean treatment difference for SFC group versus tiotropium group of 3.2 units. In ISOLDE trial showed that fluticasone propionate significantly reduced the rate of decline in health status.[4,5] In the TORCH study, the greatest improvement relative to placebo was observed in those patients with the more severe disease treated with SFC. The difference in adjusted mean change in SGRQ for SFC versus placebo was 2.3 in GOLD stage-II, 3.3 in GOLD stage-III, 5.9 in GOLD stage-IV. Calverley et al., (2007) showed the combination regimen reduced exacerbations significantly, as compared with placebo, including those exacerbations requiring hospitalization, benefits were accompanied by sustained improvements in health status and FEV1. The rate of exacerbations falls by 25% in the combination group ($p<0·0001$) and 19% ($p=0·0033$) with placebo.[6] Jenkins et al., (2009), observed that SFC reduced the annual rate of exacerbations by 31.0% in patients with GOLD stage II COPD, also experienced a reduction in GOLD stage III by 26.0% and GOLD stage IV COPD by 14.0% per year versus placebo. Ferguson et al., (2008) found patients treated with SFC lowered the risk of experiencing recurrent exacerbations by 25% compared with salmeterol ($p<0.001$). Aaron et al., (2007) found the absolute risk reduction was 2.8 percentage points for tiotropium plus fluticasone/salmeterol versus tiotropium plus placebo ($p=0.62$). The risk for exacerbation was 0.85, lower rates of severe exacerbations of COPD requiring hospitalization; the incidence rate ratio was 0.53.[7-9] Calverley et al.,(2007), found the annual rate of exacerbations was 0.85 in the combination-therapy group and 1.13 in the placebo group, which is a reduction of 25% and corresponds to a number needed to treat of four to prevent one exacerbation in 1 year. Annual admission rates were 17% lower in the combination-therapy than in the placebo group, corresponding to a number needed to treat of 32 to prevent one hospitalization in 1 year.[6]

Despite powering issues, it was reported that improvement in lung function, health status, prevention of exacerbation of COPD & hospitalization rates were more of patients randomized to the salmeterol/fluticasone propionate combination arm.

Conclusion

Stable COPD patients who start salmeterol/fluticasone propionate combination therapy experience better lung function and symptomatic improvement than tiotropium brodemide, statistically significant beneficial effect was found on health status changes, fewer exacerbations rate and less required hospitalization. These improvements in clinical outcomes support the use of this treatment in patients with chronic obstructive pulmonary disease.

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