



PROSPECTIVE COMPARATIVE STUDY OF SALMETEROL AND FLUTICASONE PROPIONATE POWDER VERSUS TIOTROPIUM BROMIDE AND FORMETEROL IN COPD PATIENTS

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ABSTRACT

Chronic obstructive pulmonary diseases (COPD) are a potentially fatal, The sign and symptoms are chronic cough, excessive mucus production, wheezing and shortness of breath after mild exertion. Many studies have now been published showing that the combination of the long-acting β_2 agonist with an Inhaled corticosteroids (ICS) provides greater improvement in lung function and symptoms control than at least doubling the dose of ICS. The objective of present study is to compare the effect of combinations of long- acting β_2 agonist with corticosteroids and long acting β_2 agonist with anticholinergic drug. In present work we use disease specific questionnaire to assess health status in COPD patients and are Clinical COPD Questionnaire (CCQ). St. Geroge Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT) to evaluate health status impairment and improvement in COPD patients.

KEYWORDS: COPD, CCQ, CAT, SGRQ, ICS, FEV1.

1. INTRODUCTION

Chronic obstructive pulmonary diseases (COPD) are a potentially fatal, slowly progressive respiratory disease in contrast to asthma. COPD is characterized by air flow obstruction that is not fully reversible. The sign and symptoms are chronic cough, excessive mucus production, wheezing and shortness of breath after mild exertion. In COPD conditions the chronic inflammation leads to structural changes referred to as airway remodeling. Bronchodilators play a central role in symptomatic relief of acute bronchoconstriction in both conditions and are the primary maintenance therapy for COPD patients. There is some epidemiologic evidence that mucus hypersecretion is accompanied by airflow obstruction of particularly peripheral airway, perhaps as a result of obstruction of particularly peripheral airway. The primary physiological abnormality in COPD is an accelerated decline in the forced expiratory volume in one second (FEV1) from the normal rate in patients over 40 years of age. The world health organization predicts that by 2020 COPD will rise from its current ranking as 12th most prevalent disease worldwide to the 5th and from the 6th most common cause of death to the 3rd.^[1]

However its severity is currently under appreciated.^[2] Existing oral medications for COPD have not been shown to modify the long-term decline in lung function that is the hallmark of this disease.^[3] Further treatment

guidelines recommend the use of inhaled long-acting bronchodilators to alleviate symptoms and reduce the risk of exacerbations in patients with moderate to very-severe chronic obstructive pulmonary of disease (COPD) but do not specify whether a long acting anticholinergic drug or a β_2 agonist is the preferred agent in preventing exacerbations of COPD.^[4] Many studies have now been published showing that the combination of the long-acting β_2 agonist with an Inhaled corticosteroids (ICS) provides greater improvement in lung function and symptoms control than at least doubling the dose of ICS.^[5] An inhaled long acting β_2 agonist may improve lung function and health status in symptomatic COPD, where as fluticasone propionate inhaled corticosteroids reduce the frequency of acute stage symptom exacerbations.

The objective of present study is to compare the effect of combinations of long- acting β_2 agonist with corticosteroids and long acting β_2 agonist with anticholinergic drug. Hence in present work combination of salmeterol with fluticasone and Tiotropium with Formeterol treated group are selected. The assessment of health related quality of life is an important tool for the determining the impact of disease (COPD) and monitoring there response to treatment.^[6] Understanding a chronic obstructive pulmonary disease (COPD) patient's health status is an integral part of overall

patient's management. International guidelines on the management of COPD recommend that both lung function and health status are monitored regularly to guide any change in treatment and both the European respiratory system and American thoracic society recommend that health status should be assessed as an outcome in clinical trials of new and existing pharmacological therapies for treatment of COPD.^[7] In present work we use disease specific questionnaire to assess health status in COPD patients and are Clinical COPD Questionnaire (CCQ), St.Geroge Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT) to evaluate health status impairment and improvement in COPD patients.

The CCQ is divided into 3 domains (Symptoms, Functional and mental status). The CCQ is correlates clinical status of airway, (e.g. airway obstruction and airway inflammation) it helps to identify not only the clinical status of airway but also activity limitation and emotional dysfunction in the patients.

St.Geroge Respiratory Questionnaire (SGRQ) is designed to measure the impact of chest disease on health related quality of life and well being. It can be used in COPD as well as in asthma. It has been shown to correlate well with established measures of symptoms level, disease activity and disability. The first part (symptoms) evaluates symptomatology, including frequency of cough, sputum production, wheeze, breathlessness and the duration of frequency of attacks of breathlessness or wheeze. The second part has two components activity and impact. The activity section addresses activities that cause breathlessness or are limited because of breathlessness. The impact sections covers a range of factors including influence on employment, being in control of health, panic, stigmatization, the need for medication, side effects of prescribed therapies, expectations for health and disturbance of daily life. The SGRQ consists of three sections and a total score: symptoms measuring the frequency and severity of respiratory symptoms; Activity measuring limitations of activities by breathlessness and activities that cause breathlessness; Impacts, measuring disturbance in social and psychological functioning due to airway disease; Total score summarizes the impact of the disease on overall health status.^[15]

CAT scores had already been categorized in to severity scores. Low impact (CAT score 1 to 10) Medium impact (11 to 20), High impact (31 to 40). In case of CAT is a short, simple questionnaire which is quick and easy for patients to complete. It provides a framework for discussions with COPD patients and should enable and them to gain a common understanding and grading of the impact of the disease on their life. It should help us to identify where COPD has the greatest effects on the patients health and daily life. The CAT provides a reliable measure of the impact of COPD on a patient's health status. The CAT dose not replaces COPD

treatment but help us monitor their effects. e.g. Recovery from exacerbations. CAT scores severity and to better understand the minimal clinically relevant change from one visit to the next. The CAT provides a reliable measure of the impact of COPD on patient's health status.^[16]

AIM AND OBJECTIVE

1. The primary objective of present study is to assess the efficacy of salmeterol and fluticasone propionate powder versus Tiotropium bromide and formeterol in COPD patients.
2. To assess quality of life (QOL) of patients with the study drug using (QOL) questionnaire and st.Geroge Respiratory Questionnaire (SGRQ) in COPD patients.

METHOD

Shwas lifeline centre sangli was selected for the study. Prospective Observational study was undertaken for our research purpose. Newly registered COPD Patients as well as regular follow up patients suffering from COPD were included in study according to inclusion and exclusion criteria. Data on demographic variables such as age, sex, Height, weight, Family history, and Patients behavior were collected from clinical record of patients. Prospective study was carried out from August 2015 to march 2016.

Study sites

a) Shwash lifeline center sangli. Shwash lifeline is a 40 bedded, tertiary care hospital providing inpatient as well as outpatient healthcare services in and around sangli district. Center is a well equipped with sophisticated laboratory equipments.

Ethics Committee Approval

The Study protocol was prepared and approved by Ethics Committee of our college and affilitied university.

Study design

Prospective, Comparative, Observational study.^[1]

Study duration

- 1) Data Collection: 6 month.
- 2) Data analysis, drafting and submission in 2 months.

Study period

August 2015 to March 2016.

Sample size

40 patients in each group.

The subjects were divided into two groups based on treatment viz.

Group I - Combination of salmeterol with Fluticasone

Group II - combination of tiotropium bromide with Formeterol. Dosage of both the combinations are given as DPI (dry powder inhaler).^[18]

Study Criteria

The patients were enrolled into the study as per the inclusion and exclusion criteria is given below.

Inclusion criteria

1. Patients in age group of 40-70.
2. Patients with the history of cough, productive sputum.
3. Patients must be willing to give written informed consent and able to adhere to dose and visit schedule.

Exclusion Criteria

Patients presenting with any of the following will not be included in this study.

1. Patients unwilling or unable to give informed consent.
2. Pregnant or lactating woman.
3. Patients with history of psychiatric illness or peripheral neuropathy.^[1]

Study procedure

Ethical clearance was obtained from institutional ethics committee (IEC) before initiation of study. Informed Consent form was developed in two different regional languages (English and Marathi). The informed consent form was signed by subjects in to the study. On cross checking with the Inclusion, Exclusion criteria subjects were given informed consent form to be a part of the study. The subjects were monitored from the day of enrolment to the day of Completion of study. All the details during this period were noted in the patients history form.

RESULT AND DISCUSSION

Chronic Obstructive Pulmonary disease is a potentially fatal, slowly progressive respiratory disease in contrast to asthma. The signs and symptoms are chronic cough, excessive mucus production, wheezing, shortness of breath. The World Health Organization predicts that by 2020 COPD will rise from its current ranking as 12th

most prevalent disease worldwide. However its severity is currently under appreciated. Existing oral medications for COPD have not shown to modify the lung function. That is hallmark of disease. But do not specify the whether a long acting anticholinergic drug or a β_2 agonist is the preferred agent in preventing exacerbations of COPD.^[1]

Many studies have now been published showing that the combination of the long acting β_2 agonist with an inhaled corticosteroids provides greater improvement in lung function and symptoms control than at least doubling the dose of ICS (Inhaled corticosteroids).^[5]

The primary objective of present study is to compare the effect of combinations of long acting β_2 agonist with corticosteroids and long acting β_2 agonist with anticholinergic drug. The assessment of health related quality of life is an important tool for the determining the impact of disease (COPD) and monitoring their response to treatment. Understanding a chronic obstructive pulmonary disease (COPD) patient's health status is an integral part of overall patient's management. International guidelines on the management of COPD recommend that both lung function and health status are monitored regularly to guide any change in treatment and both the European respiratory system and American thoracic society recommend that health status should be assessed as an outcome in clinical trials of new and existing pharmacological therapies for treatment of COPD. In present work we used disease specific questionnaire to assess health status in COPD patients are Clinical COPD Questionnaire (CCQ), St. George Respiratory Questionnaire (SGRQ) and COPD Assessment Test (CAT) used to evaluate health status impairment and improvement in COPD patients. Details are given below.

Questionnaire	Number of items	Number of domain	Domains score	Total score
CCQ	10	3	1.Symptoms 2.Functional 3. Mental	Total score
SGRQ	50	3	1.Symptoms 2. Activity 3. Impact	Total score
CAT	08	--	1. Cough 2. phlegm 3.Chest tightness 4.Breathlessness going uphill. 5.Activity limitation at home 6. Confidence while leaving home. 7.Sleep 8. Energy	Total score

In the present study, total of 120 patients were selected on the treatment basis, however 09 were lost to follow up, 23 did not meet inclusion and exclusion criteria and 08 were excluded due to insufficient information for analysis, leaving 80 eligible patients.

Finally study was carried out on 80 patients with COPD diagnosed and classified on the basis of treatment in two groups consist 40 patients in each group. Group I patients are salmeterol with fluticasone treated and group II are Tiotropium with formoterol treated drugs are given

in form of dry powder inhaler. In both groups patients demographic data was collected. In group I 27(67.5%) male, 13(32.5%) female patients, 29(72.5%) male, 11(27.5%) female patients were found respectively. In group I 25%, patients were housewife, 50% patients were farmer 7.5% patients were serviceman and worker. Finally 10% patients were businessman as well as in group II 42.5%, patients were housewife, 40% patients were farmer 2.5% patients were serviceman and 7.5%

patients were worker and businessman. Data based on socioeconomic status in 67.5% and 72.5% patients having moderate socioeconomic status of patients in group I and group II respectively. In group I and group II 30% and 27.5% patients having family history yes were found also factor related to patients are Age, Weight, Height (mean values) is in Group I are Age 54.12yrs, weight 52.65kg, Height 155.7cm and in group II Age 57.52 yrs, weight 57.65kg, Height 147cm respectively.

The analysis of CCQ scores

Group I (Salmeterol +Fluticasone)					Group II (Tiotropium bromide + formeterol)			
Sr.no	Symptom state	Functional State	Mental state	Total score	Symptom state	Functional state	Mental state	Total score
Initial score	3 (±1.89)	1.17 (±0.74)	2.90 (±1.85)	3 (±1.10)	3 (±1.78)	1.30 (±0.48)	2.87 (±0.98)	2.75 (±0.97)
4 th week	2.89 (±1.90)	1.52 (±1.79)	1.45 (±1.98)	2.83 (±1.89)	2.83 (±1.89)	1.80 (±1.89)	1.24 (±1.78)	2.65 (±1.82)
8 th week	1.19 (±1.35)	1.90 (±1.76)	1.69 (±1.32)	1.96 (±1.57)	1.78 (±1.90)	1.94 (±1.65)	1.57 (±1.34)	1.66 (±1.22)
12 th week	0.82 (±0.24)	2.10 (±1.41)	0.22 (0.20)	0.22 (±0.10)	0.83 (±0.76)	3 (±1.70)	0.10 (±0.26)	1.41 (±1.09)

Values are expressed in mean and S.D

The method used to develop clinical COPD Questionnaire (CCQ) was adapted from those used to develop both Quality of life Questionnaire and clinical status questionnaire. The CCQ is a self administered Questionnaire specially developed to measure clinical control in COPD. The CCQ consist of 10 items with an overall score and 3 domains: symptoms (4 items), functional state (4 items) and mental state (2 items). It Identified that the Questionnaire should not only contains the symptoms for estimating clinical status of the airways but also the functional impairment that are most important to patients (physical and emotional). All score range from 0 to 6; (0= no impairment, 6= severe impairment).

In the present study outcome of CCQ is represented as less than 50% (score 0, 1, 2,) mild symptoms, less improvement in functional state and good mental state while more than 50% - (score 3,4,5,6) moderate to severe symptoms, more improvement in functional status and poor mental state. In group I (SAL+FLU) there is no any improvement in symptoms state found till 8th weeks of treatment. However from group II (TIO+ FOR) the improvement of symptoms state observed in 10 patients (25%) after 4th weeks. The results of 12th weeks treatment indicates improvement in health status of patients from group I and group II were 27.5% and 62.5% respectively. It reveals that rate of decrease in severity of symptoms is more in group II than group I. As per the result of evaluation of functional state in group I (SAL+FLU) and group II (TIO+FOR), there is no any improvement till 4th weeks of treatment. However percentage improvement in functional state after 8th weeks in group 1 and group II are 32.5% and 75%

respectively which is continuously improved till 12th weeks of treatment. The result of mental state assessment indicates that there is no any significant improvement in mental status of patients till the 4th weeks of treatment. While it is progressively increased and percentage increase in mental status after 12th weeks are 65% and 100% in group I and group II respectively. Hence from the result of three domains of CCQ, Tiotropium bromide with formeterol treatment is more effective than salmeterol with fluticasone.

CCQ score in group I and group II, at baseline level for symptom state is 3 in both the groups, functional state are 1.17&1.30, while mental state are 2.9&1.87 respectively.

Improvement of COPD patients are observed in all three domains during the treatment. After 12th weeks, symptoms state score are 0.82 and 0.83 for group I and II respectively which indicates no difference in result of symptoms state score among the groups. However there is significant difference in improvement in functional state in both the groups, and better result observed in group II. After 12th weeks treatment, group I and II showed good mental state score which indicate diminution in concern and depression due to disease. Group II score illustrate more improvement in mean mental score (0.10) as compare to Group II (0.22).

Analysis of SGRQ score

Analysis of change in total scores of St.Geroge respiratory Questionnaire (SGRQ) in Group I and Group II during three months treatments.

Group I (Salmeterol+ Fluticasone)					Group II (Tiotropium+ Formeterol)			
Visit	Symptoms score	Activity score	Impact state	Total score	Symptoms score	Activity score	Impact score	Total score
Initial score	71 (±6.30)	68 (±5.36)	70 (±6.10)	209	70 (±5.59)	65 (±4.60)	72 (±6.57)	207
4 th week	59.57 (±4.90)	54 (±4.80)	56.60 (±5.44)	170	52.20 (±6.10)	51.07 (±5.10)	55 (±4.10)	158.27
8 th week	57.52 (±5.60)	52.65 (±5.10)	46.60 (±4.25)	156.7	46.40 (±3.90)	44.37 (±4.90)	41.42 (±4.10)	132.19
12 th week	47.07 (±4.60)	43.25 (±4.70)	42.0 (±3.10)	132.3 2	38.04 (±3.90)	35.52 (±3.90)	32.40 (±3.40)	105.96

The best-known and most frequently used disease specific HRQL questionnaire for respiratory disease is the St. George respiratory questionnaire (SGRQ). It is a standardized, self-administered questionnaire for measuring impaired health status and perceived HRQL in airways disease. It contains 50 items, divided into three domains: symptoms, activity, and impact. The symptom domains measuring the frequency and severity respiratory symptoms. Activity domain measuring limitation of activities by breathlessness and activities that cause breathlessness. Impacts domains measuring disturbance in social and psychological functioning due to airways disease. Total score summarizes the impact of disease on overall health status. The result of our SGRQ study indicates that there is greater SGRQ scores initially due to decreased quality of life in all the patients. The improvement in quality of life is evaluated between the two groups.

The initial percentage symptoms score, activity score and Impact score of group I were 71, 68, 70 respectively. While the initial percentage symptoms score, activity score and Impact score of group II were 70, 65 and 72 respectively. There is no difference observed between the two groups in quality of life score initially. Further there was significant decrease in a SGRQ scores during the follow ups in both the treatment groups showing improvement in quality of life. The result of 12th weeks treatments in percentage symptoms score, activity score and Impact score of group I were 47.07, 43.25 and 42 respectively and for group II were 38.04, 35.52 and 32.40 respectively. Although the improvement was seen in both treatment groups, it was observed that improvement seen with Tiotropium with formeterol group was greater than that of salmeterol with fluticasone treatment groups.

Analysis of Forced expiratory volume FEV1

Visit	Group I (n=40) (Salmeterol + Fluticasone)	Group II (n=40) (Tiotropium + Formeterol)
Initial	38 L	42L
4 th week	53 L	65 L
8 th week	59L	69L
12 th week	70L	73L

FEV 1 Values are expressed in mean (Liter).

Of the diagnostic arsenal of internal medicine, dynamic lung volumes, in particular forced vital capacity and Forced expiratory volume in the first second (FEV1), are considered essential parameters. Forced expiration not only delivers important information about an existing pulmonary obstruction in the sense of reduced airway diameter but may also indicate a loss in lung retraction, parallel to diminished lung elasticity and enhanced airway instability. Significant decline in lung function is the hallmark of COPD. Similarly in our study the initial predicted mean FEV1 for group I was 38 L and group II was 42 L. There were significant changes in predicted

FEV1 in group I and group II, before and after treatment. Improvement in FEV1 values were found after 4th, 8th, 12th weeks in both the groups. After 12 week treatment the predicted mean FEV1 values for group I was 70L and group II was 73L. There is no significant difference in improvement of predicted mean FEV1 value in group I and II after 12th week.

Analysis CAT score

Analysis of Changes in total scores of COPD assessment test (CAT) during three months treatment.

Clinical variables	Initial	4th week	8th week	12th week	Initial	4th week	8th week	12th week
1) Cough	2.90 (± 0.480)	2.77 (± 0.422)	2.30 (± 0.572)	0.67 (± 0.693)	2.70 (± 0.595)	2.47 (± 0.640)	2.2 (± 0.60)	0.61 (± 0.673)
2) Phlegm	3 (± 0.610)	2.30 (± 0.516)	2 (± 0.627)	0.51 (± 0.637)	2.60 (± 0.45)	2.15 (± 0.735)	1.75 (± 0.67)	0.55 (± 0.507)
3) Chest tightness	2.80 (± 0.610)	2.40 (± 0.491)	1.62 (± 0.667)	0.41 (± 0.86)	2.69 (± 0.49)	2.015 (± 0.65)	1.82 (± 0.71)	0.230 (± 0.652)
4) Breathlessness going uphill.	2.90 (± 0.560)	2.50 (± 0.598)	2 (± 0.415)	0.57 (± 0.849)	2.55 (± 0.370)	2.25 (± 0.70)	2.02 (± 0.57)	0.260 (± 0.497)
5) Activity limitation at home.	2.70 (± 0.646)	2.52 (± 0.598)	2.10 (± 0.588)	0.27 (± 0.99)	2.70 (± 0.516)	2.15 (± 0.76)	1.92 (± 0.72)	0.120 (± 0.422)
6) Confidence while leaving home.	2.65 (± 0.458)	2.55 (± 0.550)	2.50 (± 0.516)	0.30 (± 0.142)	2.65 (± 0.41)	2.27 (± 0.67)	1.95 (± 0.63)	0.150 (± 0.504)
7) sleep	2.70 (± 0.425)	2.47 (± 0.591)	2.05 (± 0.516)	0.22 (± 0.424)	2.50 (± 0.420)	2.075 (± 0.615)	1.82 (± 0.67)	0.180 (± 0.483)
8) Energy	2.75 (± 0.460)	2.52 (± 0.590)	2.10 (± 0.533)	0.512 (± 0.506)	2.60 (± 0.37)	2.15 (± 0.73)	1.97 (± 0.163)	0.150 (± 0.503)
Total	22.4	20.03	16.67	3.46	20.99	17.5	15.4	2.25

Values are expressed in mean and standard deviation.

COPD assessment test (CAT) is short (8 items) and simple, patients completed questionnaire, where score had already been categorized in to severity bands as described in the CAT users guide low impact (CAT score 1 to 10), medium impact (11 to 20), High impact (21 to 30), very high impact (31 to 40). This analysis has used objective scientific methods to create clinical scenarios that are associated with different scores obtained with new measure of impaired health status for COPD. The approach enabled us to provide scenarios that describe patients exhibiting CAT scores ranging from the very mild to the severe. CAT score are scored on scale of 0 to 5 for a total possible score ranging from 0 to 40 with highest score represents greatest impact on health status. The 8 questions relate to cough, phlegm, chest tightness, breathlessness on exertion, activity limitation, impact of lung condition in sleep and energy levels. In the present study changes of total score and individuals questions COPD assessment test (CAT) expressed in mean and deviation. The total CAT scores of our study indicates that during treatment of 12th weeks the total CAT score of both the groups are progressively decreased further total CAT scores after 12th weeks are 3.46 and 2.25 for group I and group II respectively. When comparing in detail, scores for all individuals questions also decreased significantly.

The scientific method that are associated with different scores obtained with a new measures of impaired health status for COPD is used to focus attention on the true impact of COPD on a patients life. Thus COPD severity ladder is presented as an alternative approach to scenarios for providing clinicians with a picture of the life and health of a COPD patients with any given CAT score, which has scoring range 0 to 40. The implication of CAT scores needs to be considered in relation to an individual's disease severity.

As per COPD severity ladder 60% and 75% patients have high impact level of COPD at the time of patients'

enrollment in group I and group II respectively. While there was no significant change in impact level of COPD after 4th weeks treatment. Further during 8th week's treatment there was gradually decrease in impact level of COPD in both the group (10-20 medium to < 10 Low). However the results of 12th weeks treatment reveals that 55% patients have low impact of COPD and 45% patients recovered from the COPD symptom in group I and 17.5% patients have low impact of COPD and 82.5% patients recovered from the COPD symptom in group II. Hence it further reveals that Tiotropium with formoterol combination is more effective than salmeterol with fluticasone combination.

CONCLUSION

Finding of our study concluded that both the combinations Salmeterol with formoterol and Tiotropium with formoterol were effective for improving lung function, exertional and overall dyspnea, reduction in severity of exacerbations and improvement in health status and quality of life in COPD patients, Since FEV1 values were improved in both the treatment groups.

However results of Clinical COPD Questionnaire (CCQ) Saint George respiratory questionnaire (SGRQ), COPD assessment test (CAT) questionnaire and predicted FEV1 values reveals that dry powder inhaler of Tiotropium with formoterol was more effective than salmeterol with fluticasone combination.

Further it will be important to perform comparative studies with large sample in multicentric trial to document comparative efficacy of these formulation in COPD patients.

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