https://doi.org/10.29309/TPMJ/2025.32.01.8354

The Professional Medical Journal
www.theprofesional.com
2025, Volume, 32 Issue, 01

ORIGINAL ARTICLE

A comparative study of efficacy and safety of combination of Indacaterol and Tiotropium versus Conventional Combination Formoterol Budesonide & Tiotropium in moderate to severe COPD.

Saif ur Rahman[1], Rubina Aman[2], Malik Istikhar Ali Sajjad[3], Usman Khalid[4], Muhammad Naveed Abbas[5]

Article Citation: Saif ur Rahman, Aman R, Sajjad MIA, Khalid U, Abbas MN. A comparative study of efficacy and safety of combination of Indacaterol and Tiotropium versus Conventional Combination Formoterol Budesonide & Tiotropium in moderate to severe COPD. Professional Med J 2025; 32(01):36-41. https://doi.org/10.29309/TPMJ/2025.32.01.8354

ABSTRACT… Objective: To compare the efficacy and safety of indacaterol with tiotropium versus conventional formoterol/budesonide with tiotropium combination in patients with moderate to severe chronic obstructive pulmonary disease. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Pulmonology, PIMS Hospital, Islamabad. **Period:** January to August 2019. **Methods:** This study has recruited 88 patients between the ages of 40 – 70 years with complaints of moderate to severe degrees of COPD. The population was randomized and divided into two groups. Group A patients were instructed to use indacaterol 150mcg and tiotropium 18mcg DPI once a day and Group B patients were instructed to use formoterol/budesonide (12/400) DPI twice daily along with tiotropium 18mcg DPI once daily. Patients were followed up for improvement in FEV 1 with spirometry at 4 weeks and 8 weeks. The efficacy of both treatments was ascertained by estimating percentage improvement in FEV1 from baseline at 4 and 8 weeks and compared in both groups. **Results:** In total, there were 88 participants divided into two equal groups. At 4 weeks after the initiation of therapy, the mean FEV1 in group A was 1.98 L ± 0.52 SD and it was 1.89 L ± 0.53 SD in group B (p=0.429). At 8 weeks after the initiation of therapy, the mean FEV1 in group A was 2.01 L ± 0.53 SD and it was 1.91 L ± 0.52 SD in group B (p=0.419). Among the age group 40- 55 years, at 4 weeks, the percentage improvement in FEV 1 from baseline was 16.65% ± 7.62 SD in group A and it was 6.04% ± 3.57 SD in group B (P=0.001). At 8 weeks, the percentage improvement in FEV 1 from baseline was 18.12% ± 7.56 SD in group A and it was 7.56% ± 3.47 SD in group B (P=0.001). Among the age group 56-70 years, at 4 weeks, the percentage improvement in FEV 1 from baseline was 15.56% ± 7.19 SD in group A and it was 7.25% ± 3.08 SD in group B (P=0.001). At 8 weeks, the percentage improvement in FEV 1 from baseline was 17.21% 7.13 SD in group A and it was 8.78% ± 3.17 SD in group B (P=0.001). **Conclusion:** The results indicate that the fixed dosage of indacaterol and tiotropium has provided a better prognosis in increasing FEV1 and improving lung function.

Key words: COPD, Comparison, Efficacy, Indacaterol, Tiotropium.

INTRODUCTION

Chronic obstructive lung disease (COPD) is one of the leading causes of death and morbidity in the United States and other countries, which is a persistently serious health and socioeconomic issue globally.[1-3] The periodic worsening of symptoms including cough, dyspnea, and sputum production is known as an exacerbation of COPD and profoundly affects the physiology of the lungs, quality of life, and hospitalizations.[4,5] It has been understood that the pathologic anomalies in the small airways that cause COPD are permanent and progressive, and are most frequently linked to alveolar loss. Although additional etiologic agents have been mentioned, smoking cigarettes is the primary and most common cause of this illness. According to reports, 11% of COPD sufferers had never smoked.[3,6,7]

Atypical spirometry findings are the disease's distinguishing feature. According to the patient's age, the lower limit of normal or a lowered ratio of forced expiratory volume in one second/forced vital capacity (FEV1/FVC) of less than 0.7 are both considered to be symptoms.[8-10] An abnormal increase in the constant volume of

1. MBBS, MD (Pulmonology), Senior Registrar Pulmonology, Allied 2 Hospital, Faisalabad Medical University, Faisalabad.
2. MBBS, FCPS (Pulmonology), Professor and HOD Pulmonology, Pakistan Institute of Medical Sciences, Islamabad.
3. MBBS, FCPS (Pulmonology), Assistant Professor & HOD Pulmonology, Allied II Hospital, Faisalabad.
4. MBBS, Post Graduate Resident (FCPS Pulmonology), Pulmonology, Allied II Hospital, Faisalabad.
5. MBBS, Post Graduate Resident (FCPS Pulmonology), Pulmonology, Allied II Hospital, Faisalabad.

Correspondence Address:
Dr. Saif ur Rahman
Department of Pulmonology
Faisalabad Medical University.
drsaifurrehman90@gmail.com

Article received on: 04/09/2024
Accepted for publication: 14/11/2024

lungs or a quicker annual decline in FEV1 and FVC indicates that a patient's COPD is getting worse. The decline in shortness of breath, rising difficulty doing everyday tasks, an increase in the frequency and severity of exacerbations, and eventual premature mortality are indicators of deteriorating lung function.

National and global protocols provide recommendations based on evidence for the treatment of COPD.[11] There is currently no approved therapy for COPD.[12] Quitting smoking is the single most effective way to slow the course of COPD. Quitting smoking increases the likelihood of the patient surviving.[13] However, only a few effective pharmaceutical therapies have provided some relief and respite to people with this illness. The therapy of COPD involves the use of long-acting inhalational bronchodilators. These mainly consist of long-acting muscarinic antagonists (LAMAs) and long-acting beta 2 agonists (LABAs). For individuals who have recurrent exacerbations, a better therapeutic strategy that works best is a maintenance therapy of LABA with inhaled corticosteroids (ICS).[14] Several therapy plans have been researched in numerous trials, as well as numerous medication combinations.

It is now a fact that different doctors utilize different treatment regimens to treat COPD.[15] These regimens are developed based on the viability, the local population's response, and the doctor's clinical expertise. For the management of moderate to severe COPD in our community, there are no established guidelines. Indacaterol, a recently launched ultra-long-acting beta-2 agonist, will be compared to conventional regimens to assist us in evaluating how well it works for our local population. From there, we can help develop local guidelines for our patients. Tiotropium and indacaterol with one dose daily were compared to formoterol/budesonide, which was administered twice daily, and indacaterol, which was administered once daily. The goal of this study was to identify the best pharmacological combinations for managing COPD that could be used locally with excellent compliance and affordable treatment options. This study will assist us in providing better care for our patients while also enhancing their quality of life.

METHODS

This experimental study was conducted in the Department of Pulmonology, PIMS Hospital, Islamabad from January to August 2019. All patients from age 40 to 70 years, both genders, Post Bronchodilator FEV1/FVC Ratio <70%, post Bronchodilation FEV1>30% predicted and <80% predicted, post bronchodilation FEV1 reversibility < 12% were recruited for this study. The exclusion criteria were diagnosed case of asthma, women of child bearing age and COPD acute exacerbation in last 1 month. All patients with co-morbidities like ischemic heart disease and left ventricular failure, Benign prostate hypertrophy, malignancies, HIV, active pulmonary tuberculosis determined on history and medical record. The study was performed in accordance with the declaration of Helsinki. The ethical approval was obtained from PIMS (registration no: NO.F.2-11/SZABMU/AS&RB-62/2019).

Patients were enrolled from pulmonology unit of PIMS. At study entry baseline demographics, age and gender were recorded. A detailed history was taken along with the clinical examination and baseline post bronchodilation spirometry was done for all patients. Participants were randomly assigned to Group-A and Group-B. Group-A patients were instructed to use indacaterol 150mcg and tiotropium 18mcg DPI once a day and Group B patients were instructed to use formoterol / budesonide (12/400) DPI twice daily along with tiotropium 18mcg DPI once daily. Patients were followed up for improvement in FEV 1. Spirometry was done at each follow-up visit i.e 4 weeks and 8 weeks. All data was entered on pre-designed questionnaire. Both groups were given Short-Acting Beta Agonists (SABA) as rescue inhaler in case of acute episode of shortness of breath and frequency of usage of rescue inhaler were recorded in both groups. Confidentiality of data was ensured.

The sample size was estimated by using Open Epi software. The mean value of FEV1 at 4 weeks in Intervention group was 85.77 and anticipated population value, mean value of FEV1 at 4 weeks

in control group was 77.33 in previous literature. The estimated sample size was 44 patients in each group (88 patients in total) at significance level of 5% and 80% power.

The SPSS version 22 was used for data analysis. For the qualitative variables like gender and improvement in FEV 1, frequency/percentages were estimated. Mean ± SD were presented for quantitative variables like age, duration of disease and FEV 1 at follow up visits at 4 weeks and 8 weeks. Independent sample t-test was applied to compare efficacy in terms of percentage improvement FEV1 between both groups at 4 and 8 weeks. Paired sample t-test was applied to compare FEV1 at baseline with 4 weeks and 8 weeks in each group. Chi-square test was applied to compare safety in both groups taken P ≤0.05 as significant.

RESULTS

A total of 88 patients were enrolled with age between 40-80 years either gender who had COPD of moderate to severe degree (Post-bronchodilation FEV1>30% to <80% predicted). Patients were followed up for improvement in FEV 1 with spirometry at 4 weeks and 8 weeks. There were 65.9% males and 34.1% females in group A and 68.2% males and 31.8% females in group B. Group A patients had a mean age of 56.8 years ± 5.7 SD and mean age of patients in group B was 55.5 years ± 5.2 SD. In group A, there were 38.6% patients who were in age group 40-55 years and 61.4% were in age group 56-70 years. In group B, there were 47.7% patients who were in age group 40-55 years and 52.3% were in age group 56-70 years. In group A, there were 72.7% patients who had moderate COPD and 27.3% had severe disease. In group B, 75.0% patients had moderate COPD and 25.0% had severe disease.

Baseline FEV-1 was similar in both groups. Mean FEV1 at baseline in group A was 1.71 ± 0.44 liter and it was 1.77 ± 0.49 liter in group B (P = 0.509). At 4 weeks, after the initiation of therapy, mean FEV1 in group A was 1.98 ± 0.52 liter and it was 1.89± 0.53 liter in group B (P=0.429). At 8 weeks after the initiation of therapy, mean FEV1 in group A was 2.01 ± 0.53 liter and it was 1.91 ± 0.52 liter in group B (P=0.419) as presented in Table-I.

Efficacy of both the treatments was ascertained by estimating percentage improvement in FEV1 from baseline at 4 and 8 weeks and compared in both groups. At 4 weeks, percentage improvement in FEV 1 from baseline was 15.98% ± 7.29 liter in group A and it was 6.67% ± 3.34 liter in group B (P > 0.001). At 8 weeks, percentage improvement in FEV 1 from baseline was 17.56% ± 7.22 liter in group A and it was 8.21% ± 3.24 liter in group B (P=0.001). Improvement in FEV 1 was significantly better in patients who received 150mcg and tiotropium 18mcg DPI once a day (group A) as compared to patients who received formoterol/budesonide (12/400) DPI twice daily along with tiotropium 18mcg DPI once daily (group B) at 4 weeks, which was maintained at 8 weeks with P value <0.001.

Safety of both the treatments was ascertained by observing adverse events in terms of worsening of COPD (use of rescue inhaler), tachycardia and number of hospital admissions during 8 weeks. The major adverse event reported in both the groups was worsening of COPD as ascertained by use of rescue inhaler. It was observed in 22.7% (n=10) in group A patients and it was reported in 25.0% (n=11) in group B patients (P=0.803). Tachycardia was reported in 9.1% (n=4) in group A patients and it was reported in 6.8% (n=3) in group B patients (P=0.694). Hospital admissions during 8 weeks of follow-up were reported in 13.6% (n=6) group A patients and 15.9% (n=7) in group B patients (P=0.764). Both treatments were found safe and there was no statistically significant difference noted in adverse events observed during 8 weeks of follow-up in both the treatment groups.

At 4 weeks, the percentage change in FEV 1 from baseline was 16.65% ± 7.62 in group A and 6.04% 3.57 SD in group B for the age range of 40-55 years (p-value <0.001). After 8 weeks, Group A saw an elevation in FEV 1 of 18.12% ± 7.56 from the baseline and in group B, it was 7.56% ± 3.47 (p-value <0.001).

Variables	Groups	Mean (SD)	P-Values
FEV1 (Liters)	Indacterol+ tiotropium	1.71 (0.44)	0.509
	Formoterol/budesonide+ tiotropium	1.77 (0.49)	
FEV1 (liters) 4 weeks	Indacterol+ tiotropium	1.98 (0.52)	0.429
	Formoterol/budesonide+ tiotropium	1.89 (0.53)	
FEV1 (liters) 8 weeks	Indacterol+ tiotropium	2.01 (0.53)	0.419
	Formoterol/budesonide+ tiotropium	1.91 (0.52)	

Table-I. Comparison of FEV1 (in liters) from baseline to 4- and 8-weeks follow-up between two groups

Age groups	Variables	Groups	Mean (SD)	P-Value
40-55 years	Percentage improvement in FEV 1 at 4 weeks (%)	Indacterol+ tiotropium	16.65 (7.62)	0.001
		Formoterol/ budesonide+tiotropium	6.04 (3.57)	
56-70 years	Percentage improvement in FEV 1 at 4 weeks (%)	Indacterol+ tiotropium	15.56 (7.19)	0.001
		Formoterol/ budesonide+tiotropium	7.25 (3.08)	
40-55 years	Percentage improvement in FEV 1 at 8 weeks (%)	Indacterol+ tiotropium	18.12 (7.56)	0.001
		Formoterol/ budesonide+tiotropium	7.56 (3.47)	
56-70 years	Percentage improvement in FEV 1 at 8 weeks (%)	Indacterol+ tiotropium	17.21 (7.13)	0.001
		Formoterol/ budesonide+tiotropium	8.78 (3.17)	

Table-II. Comparison of FEV 1 among groups after stratification into age groups

Within the ages 56 - 70 years, proportion change in FEV 1 in the at 4 weeks from baseline was 15.56% ± 7.19 in group A and 7.25 % ± 3.08 in group B (p-value <0.001) as shown in table.2. The percentage elevation after 8 weeks in group A, the FEV 1 from baseline was 17.21%, 7.13 SD, and it was 8.78% ± 3.17 in group B (p-value <0.001).

DISCUSSION

Chronic obstructive pulmonary disease (COPD is a debilitating disease which affects quality of life.[16] There are various treatments used in management of COPD.[12] In our study we compared ultra-long acting beta agonist along with Tiotropium versus conventional treatment. According to results, after administration of Tiotropium along with Indacterol has elevated the FEV 1 to three times of the baseline value and was more potent than conventional treatment comprised of Formoterol/ budesonide and Tiotropium. Additionally, it has also been observed that among the two age groups of 40 – 55 and 56 – 70 years, the effectiveness of the new regimen was high.

Dahl R et al. conducted a study over a period of one year compared indacaterol with LABA formoterol (BD dose) and placebo in terms of their safety and efficacy profile. Patients having moderate to severe COPD were randomized into one of the three groups. The first group received indacateral 300 mcg once a day (437 patients) or 600 mcg once daily (428 patients), the second group received formoterol 12 mcg twice a day (435 patients), and the third group received placebo (432 patients) for a total of fifty-two weeks. Their primary endpoint measure was FEV 1 at 12 weeks. Their results showed that indacaterol raised the 24 h post dose FEV 1 at 12 weeks by 100 ml when compared to formoterol and by 170 ml when compared to placebo. After 52 weeks these differences were significantly maintained. They further demonstrated that indacaterol had a good safety profile and was well tolerated by the patients. Authors concluded that in patients with moderate to severe COPD, indacaterol once a day is a more effective 24 hour bronchodilator that improves the clinical condition and health status of the patient when compared with a 12 hour LABA given twice daily.[14] In another study conducted by McKeage K et al., the tolerance level and clinical efficacy of indacaterol in adult patients with moderate to severe COPD was observed. They reported that indacaterol showed significantly better results as compared to placebo. Even in larger and longer trilas that lasted from 12 weeks to 1 year, 150 or 300 mcg of indaceterol once daily was significantly better than placebo. They further demonstrated that indacaterol and tiotropium together enhanced

lung function, improved shortness of breath, use of rescue medication and general health status significantly more than tiotropium bromide alone. The most commonly occurring unfavourable event in clinical studies was worsening of the COPD.[17]

A review analysis conducted by Incorvaia C et al., Increased efficacy of indacaterol in comparison to placebo has been demostrated. The trials that followed evaluated the performance of indacaterol versus other bronchodilators including tiotropium bromide, salmeterol and formoterol. Indacaterol had comparable efficacy with tiotropium in terms of raised FEV1, better quality of life and other patient reported outcomes (PROs), and had a slightly higher efficacy when compared to salmeterol and formoterol. The drug was found safe and well tolerable in these trials.[18]

A systematic review was conducted by Gong Y et al., suggested after reviewing 22 studies involving 16,486 participants that the efficacy of indacaterol was less than vilanterol/umeclidinium, as its fixed dose combinations has the highest degree of efficiency in LABA/LAMA.[19] In a randomized trial, Lee SH., et al had directly switched the patient's regime from once-daily tiotropium (TIO) 18 µg to indacaterol/glycopyrronium (IND/GLY) 110/50 µg once daily in COPD patients in Korea. It was observed than the direct switch from tiotropium to indacaterol/glycopyrronium caused improvements in lung's physiology and related patient's results along with a good safety limit in mild-to-moderate air flow.[20]

CONCLUSION

The present study has summarized that the efficacy of indacaterol and tiotropium is more than formoterol/budesonide. Although, both of the regimens were found safe and there was no adverse effect recorded. Additionally, the fixed combination of indacaterol and tiotropium is easier to use daily as compare to twice daily dose of formoterol/budesonide with tiotropium.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Copyright© 14 Nov, 2024.

REFERENCES

1. Varmaghani M, Dehghani M, Heidari E, Sharifi F, Moghaddam SS, Farzadfar F. **Global prevalence of chronic obstructive pulmonary disease: Systematic review and meta-analysis.** East Mediterr Health J. 2019; 25(1):47-57.

2. Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, et al. **Towards the elimination of chronic obstructive pulmonary disease: A Lancet Commission.** The Lancet. 2022; 400(10356):921-72.

3. Yang IA, Jenkins CR, Salvi SS. **Chronic obstructive pulmonary disease in never-smokers: Risk factors, pathogenesis, and implications for prevention and treatment.** The Lancet Respiratory Medicine. 2022; 10(5):497-511.

4. Vogelmeier CF, Roman-Rodriguez M, Singh D, Han MK, Rodriguez-Roisin R, Ferguson GT. **Goals of COPD treatment: Focus on symptoms and exacerbations.** Respiratory Medicine. 2020; 166:105938.

5. Jones S. **COPD-Pathology, Diagnosis, Treatment, and Future Directions: Pathology, Diagnosis, Treatment, and Future Directions: BoD–Books on Demand; 2024.**

6. PRASAD B. **Chronic obstructive pulmonary disease (COPD).** International Journal of Pharmacy Research & Technology (IJPRT). 2020; 10(1):67-71.

7. Pando□Sandoval A, Ruano□Ravina A, Candal□Pedreira C, Rodríguez□García C, Represas□Represas C, Golpe R, et al. **Risk factors for chronic obstructive pulmonary disease in never□smokers: A systematic review.** The Clinical Respiratory Journal. 2022; 16(4):261-75.

8. Ben Porath LY. **Clinical, functional and biomarkers criteria for the diagnosis of asthma-chronic obstructive pulmonary diseases overlap (ACO).** 2021.

9. Abdrabo MM, SAMRA S, Hassan Habib MF, Alsadik ME. **Role of different physical performance tests in predicting severity of chronic obstructive pulmonary diseases exacerbation.** Zagazig University Medical Journal. 2024; 30(1.5):2083-94.

10. Scanlon PD. **Hyatt's interpretation of pulmonary function tests:** Lippincott Williams & Wilkins; 2019.

11. Hurst JR, Buist AS, Gaga M, Gianella GE, Kirenga B, Khoo EM, et al. **Challenges in the implementation of chronic obstructive pulmonary disease guidelines in low-and middle-income countries: An official American Thoracic Society workshop report.** Annals of the American Thoracic Society. 2021; 18(8):1269-77.

12. Matera MG, Cazzola M, Page C. **Prospects for COPD treatment.** Current Opinion in Pharmacology. 2021; 56:74-84.

13. Caini S, Del Riccio M, Vettori V, Scotti V, Martinoli C, Raimondi S, et al. **Quitting smoking at or around diagnosis improves the overall survival of lung cancer patients: A systematic review and meta-analysis.** Journal of Thoracic Oncology. 2022; 17(5):623-36.

14. Domingo C, Rello J, Sogo A. **As-needed ICS-LABA in mild asthma: what does the evidence say?** Drugs. 2019; 79(16):1729-37.

15. Baha A, Kokturk N. **Physician's attitude against COPD guidelines and the choice of first-line treatment for COPD.** Respiratory Medicine. 2021; 176:106273.

16. Szymanska-Chabowska A, Juzwiszyn J, Tański W, Świątkowski F, Kobecki J, Chabowski M. **The fatigue and quality of life in patients with chronic pulmonary diseases.** Science Progress. 2021; 104(3):00368504211044034.

17. González-Morales LD, Moreno-Rodríguez A, Vázquez-Jiménez LK, Delgado-Maldonado T, Juárez-Saldivar A, Ortiz-Pérez E, et al. **Triose Phosphate Isomerase Structure-based virtual screening and in vitro biological activity of natural products as Leishmania Mexicana inhibitors.** Pharmaceutics. 2023; 15(8):2046.

18. Tejera E, Munteanu CR, López-Cortés A, Cabrera-Andrade A, Pérez-Castillo Y. **Drugs repurposing using QSAR, docking and molecular dynamics for possible inhibitors of the SARS-CoV-2 Mpro protease.** Molecules. 2020; 25(21):5172.

19. Gong Y, Lv Y, Liu H, Zheng Q, Li L. **Quantitative analysis of efficacy and safety of LABA/LAMA fixed-dose combinations in the treatment of stable COPD.** Therapeutic Advances in Respiratory Disease. 2022; 16:17534666211066068.

20. Rogliani P, Ritondo BL, Gabriele M, Cazzola M, Calzetta L. **Optimizing de-escalation of inhaled corticosteroids in COPD: A systematic review of real-world findings.** Expert Review of Clinical Pharmacology. 2020; 13(9):977-90.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Saif ur Rahman	Primary Author, Assessment of patient for inclusion and exclusion, Prescribing dose and follow up assessment, Data entry and analysis and making up results.	
2	Rubina Aman	Supervisor and advisor in assessing the patient and Prescribing the recommended dosages and follow up assessment. Analyzing the data and critical review of results.	
3	Malik Istikhar Ali Sajjad	Data cimpilation and analysis, Making results and conclusion and critical review.	
4	Usman Khalid	Assessment of data, Patients for inclusion and exclusion, data compilation and follow up assessment.	
5	Muhammad Naveed Abbas	Assessment of patient for inclusion and exclusion, prescribing dose, data compilation and follow up assessment.