



A COMPARATIVE STUDY ON THE COMBINATION USE OF INDACATEROL WITH GLYCOPYRRONIUM AND FORMOTEROL WITH TIOTROPIUM IN COPD PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: The objectives of the study is to assess the symptomatic improvement and frequency of exacerbation in COPD patients and thereby evaluating the effectiveness of both the combinations and to evaluate the quality of life of COPD patients. Also to assess the medication adherence and safety profile of these combinations in COPD patients.

Methods: This is a prospective observational study conducted in 70 patients diagnosed with COPD. The study population was divided into two groups. In each group, 35 patients were enrolled. One group included the patients who were taking Indacaterol with Glycopyrronium 110/50µg and the second group taking Formoterol with Tiotropium 6/9µg. The SGRQ score, QOL score, Medication adherence and adverse effects were measured at beginning and at the end of 4 weeks. **Results:** The Indacaterol with Glycopyrronium and Formoterol with Tiotropium are effective in COPD patients, but significantly more difference was seen with Indacaterol with Glycopyrronium. As it shows more improvement in the SGRQ score, QOL score, Medication adherence and lesser number of adverse effects was seen with Indacaterol with Glycopyrronium. p value is significant .(p<0.0001).

Conclusion: Both Indacaterol with Glycopyrronium and Formoterol with Tiotropium are effective in COPD patients. Both of them show improvement in SGRQ score and QOL score. Indacaterol with Glycopyrronium was found to be more effective in improving SGRQ score and QOL. Also the frequency of adverse effects was lesser with Indacaterol with Glycopyrronium. Thus this study throws light on the fact that Indacaterol with Glycopyrronium should be preferred over Formoterol with Tiotropium.

KEYWORDS: Chronic Obstructive Pulmonary Disease (COPD), Indacaterol with Glycopyrronium (Ind/Gly), Formoterol with Tiotropium (Form/Tio), St.George Respiratory questionnaire (SGRQ), Quality of life (QOL), Safety profile.

INTRODUCTION

According to WHO, Chronic Obstructive Pulmonary disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. It is a common preventable and treatable disease characterized by persistent limitation in airflow, leading to reduced ventilatory capacity and is associated with shortness of breath. It is usually progressive and associated with an enhanced chronic inflammatory response in airways and the lungs to noxious particles or gases.^[9,14] Emphysema and Chronic Bronchitis are the two most common conditions that contribute to COPD. Chronic bronchitis is the inflammation of the lining of the bronchial tubes, which carry air to and from the air sacs, of the lungs. It is characterized by daily cough and sputum production. Emphysema is a condition in which the air sacs at the

end of the smallest air passages of the lungs are destroyed as a result of damaging exposure.^[10] COPD is a complex syndrome comprised of airway inflammation, mucociliary dysfunction and consequent airway structural changes.^[11]

Airway Inflammation:- COPD is characterized by chronic inflammation of the airways, lung tissue and pulmonary blood vessels as a result of exposure to inhaled irritants such as tobacco smoke. The inhaled irritants cause inflammatory cells such as neutrophils, CD8+ T- lymphocytes B cells and macrophages to accumulate. When activated, these cells initiate an inflammatory cascade that triggers the release of inflammatory mediators such as tumour necrosis factor alpha (TNF-α), interferon gamma (INF-γ), matrix metalloproteinases (MMP-6, MMP-9), C-reactive

proteins (CRP), interleukins (IL-1, IL-6, IL-8) and fibrinogen.^[7]

Structural Changes:- Airway remodeling in COPD is a direct result of inflammatory response associated with COPD and leads to narrowing of the airways. Three main factors contribute to this: peribronchial fibrosis build up of scar tissue from damage to the airways and the over multiplication of the epithelial cells lining the airways.^[8]

Mucociliary Dysfunction:- Smoking and inflammation enlarge the mucous glands that line airway walls in the lungs causing goblet cell metaplasia and replacement of healthy cells by more mucus secreting cells.^[11] Additionally inflammation associated with COPD causes damage to the mucociliary transport system which is responsible for clearing mucus from the airways.^[12,15] Symptoms of COPD are Persistent Dyspnoea : progressive (worsens over time), worse with exercise, Chronic cough: May be intermittent or may be unproductive,

Chronic sputum production: Any pattern of chronic sputum production may indicate COPD.^[1,6]

Indacaterol/Glycopyrronium is a fixed dose combination of two long acting bronchodilators. Indacaterol is long acting β_2 adrenergic agonist (LABA) and Glycopyrronium is long acting muscarinic antagonist (LAMA). Indacaterol/ glycopyrronium significantly reduced the rate of moderate or severe exacerbations, improvement in lung function (forced expired volume in 1 second [FEV₁]), dyspnoea, health status and use of rescue medication compared with glycopyrronium alone in people with severe or very severe COPD.^[2] Indacaterol is a long-acting β_2 adrenoceptor partial agonist with high intrinsic activity that stimulates intracellular adenylyl cyclase, which converts adenosine triphosphate to cAMP. The resulting increased intracellular cAMP levels lead to relaxation of bronchial smooth muscle.^[3]

Formoterol (beta (2)-agonist) and Tiotropium (anticholinergic) are long-acting bronchodilators. Formoterol has a fast onset and a bronchodilator effect of approximately 12 h, while Tiotropium has a 24-h bronchodilator effect. A combination of Tiotropium and Formoterol is more effective than single drugs alone in inducing bronchodilation and a bronchodilator-mediated symptom benefit in patients suffering from COPD.^[4] Formoterol is a potent, selective long acting beta agonist that acts locally in the lungs and work as a bronchodilator ,by relaxing the smooth muscle in the airway walls to widen the airways. Tiotropium is a long acting anticholinergic that acts on specific receptors (muscarinic receptors) in the bronchioles of the lung and inhibits the interaction of acetyl choline, with muscarinic receptors, which prevents spasm of the airway wall caused by the acetyl choline.^[5]

The effectiveness of both the drugs are compared using SGRQ-C questionnaire score.

The SGRQ-C provides a total score and also component scores for symptoms, activities and impacts each of which ranges from 0-100, with directionality such that higher scores reflect worse HRQOL. The questionnaire that we are using here for measuring the QOL is EQ-5D-5L questionnaire. In this questionnaire, Mobility, selfcare, ability to do the usual activities, pain/discomfort, anxiety/depression are measured.

MATERIALS AND METHODS

Study Design: Prospective Observational Study

Study Population: Patients diagnosed with COPD

Study Site: Study conducted at Pushpagiri Medical College, Thiruvalla

Study Period: 6 Months

Sample Size: 70 patients

The sample size is calculated by the following equation

$$N = \frac{(Z_{\alpha} + Z_{\beta})^2 [P_1(1-P_1) + P_2(1-P_2)]}{(P_1 - P_2)^2}$$

α = Type I error (fixed at 5% level)

β = Power (fixed at 80% level)

P₁ = Proportion having clinical response in Indacaterol with Glycopyrronium

P₂ = Proportion having clinical response in formoterol with tiotropium

Inclusion Criteria

- Both male and female
- Those who give consent voluntarily to participate in the study
- Patients receiving either Indacaterol with Glycopyrronium or Formoterol with Tiotropium
- Age group more than 35
- Both IP and OP patients

Exclusion Criteria

- Patients who are not willing to give the consent
- Patients who are pregnant and lactating

Study Procedure

This is a prospective observational study conducted in 70 patients diagnosed with Chronic Obstructive Pulmonary Disease who were in the Pulmonology department of Pushpagiri Medical College Hospital, Thiruvalla. The medications used in this study are Indacaterol with Tiotropium and Formoterol with Tiotropium. The study population was divided into two groups. In each group, 30 patients were enrolled. One group included the patients who were taking Indacaterol with Glycopyrronium 110/50 μ g and the second group taking Formoterol with Tiotropium 6/9 μ g. A patient documentation form was prepared on the parameters like date of admission. O.P no, age, gender, education and occupation ,social and medical history and ADR of the

respective study. The effectiveness of therapeutic strategy used in the patients was estimated by taking severity, frequency, symptom score, activity score, impact score and duration was taken into consideration. Effectiveness was assessed in the participants on the first day and at the follow up time by conducting a personnel or telephonic interview using St. George Respiratory questionnaire which include questions related to symptoms, impacts, and activity of COPD. Quality of life of COPD patients was measured by using EQ-5D-5L questionnaire. Medication adherence was calculated by using Morisky-8 medication adherence questionnaire during the period of study. Safety profile was calculated by the appearance of ADR using Naranjo algorithm. The follow up details were collected after 4 weeks.

Statistical methods

The data was analyzed using Microsoft Excel worksheet and SPSS 17.0 software. Results were analyzed using paired *chi square* test to compare the baseline and discharge readings within each group. A *P* value of < 0.0001 was considered significant.

RESULTS

1. Gender Categorization

Table 2: Distribution of patients based on the gender.

Gender	Indacaterol/ Glycopyrronium (%)	Formoterol/ Tiotropium (%)
Male	80	74.2
Female	20	25.7

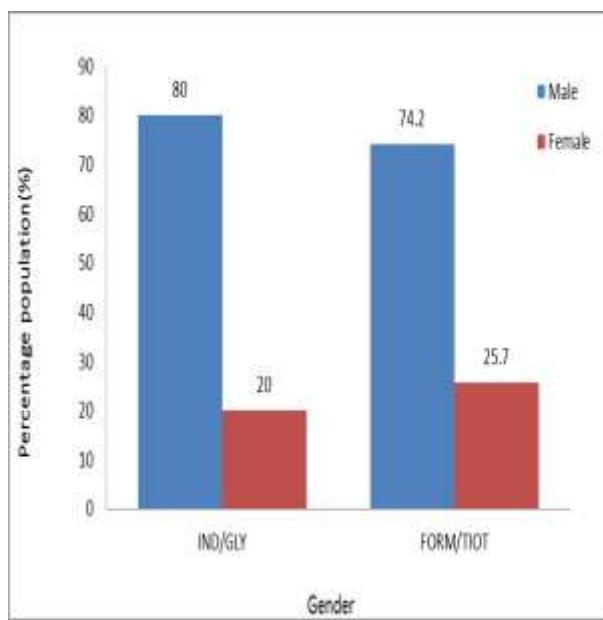


Figure 1: Distribution of patients based on gender

Table 1 and Figure 1 show that, majority of the study population was found to be male

2. Age Categorization

Table 2: Distribution of patients based on the age.

Age	Indacaterol/ Glycopyrronium (%)	Formoterol/ Tiotropium (%)
35-50	2.8	5.7
50-65	40.1	65.8
65-80	51.4	22.8
>80	5.7	5.7

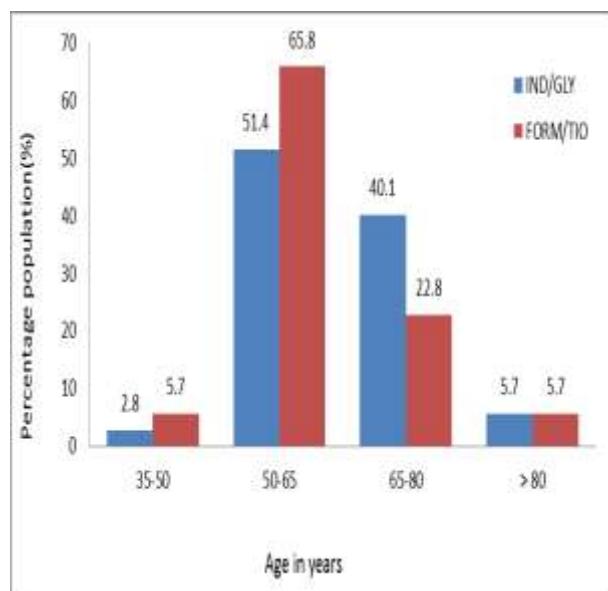


Figure 2: Distribution of patients based on the age.

Table 2 and Figure 2 show that, majority of the study population was in the 50-65 age group. The mean age was found to be 64.8(± 10.68) years

3. Social History

Table 3: Distribution of patients based on the Social History.

Social history	Indacaterol/ Glycopyrronium (%)	Formoterol/ Tiotropium (%)
Smokers	71.4	62.8
Non smokers	11.4	22.8
Alcoholics	8.6	8.6
Alcoholics & Smokers	8.6	5.8

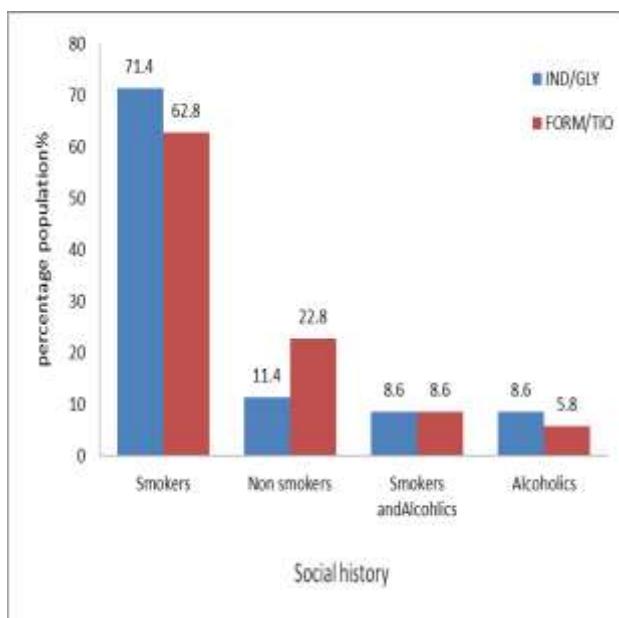


Figure 3: Distribution of patients based on the social history.

Table 3: and Figure 3 shows that majority of the study population were smokers.

4. Co-Morbidities

Table 4: Distribution of patients based on co-morbidities.

Co morbidities	Indacaterol/ Glycopyrronium (%)	Formoterol/ Tiotropium (%)
Hyperlipidaemia	14.2	20
CAD	8.5	5.7
Diabetes Mellitus	16	28.5
Migraine	2.8	5.7
Hypertension	40	37.1

Table 5: Effectiveness of medication based on the symptom score of COPD patients.

DRUG	Visits	Mean of Symptom score	SD	Mean difference	p value
IND/GLY	Visit 1	66.22	±13.68	36.13	<0.0001
	Visit 2	30.09	±8.70		
FORM/TIO	Visit 1	71.36	±8.90	18.61	<0.0001
	Visit 2	52.75	±8.64		

Asthma	11.4	14.2
CKD	2.8	5.7
Nil	5.7	5.7

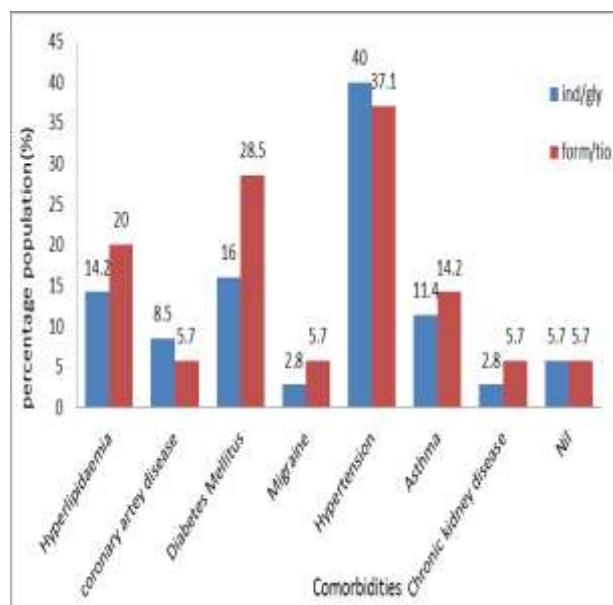


Figure 4: Distribution of patients based on comorbidities.

From the table 4 and figure 4, it is clear that most significant comorbidity associated with COPD is hypertension, although majority of population reported the presence of diabetes.

5. Effectiveness Of Medications Based On Symptom, Activity Impact & Total Score Of Copd Patients.

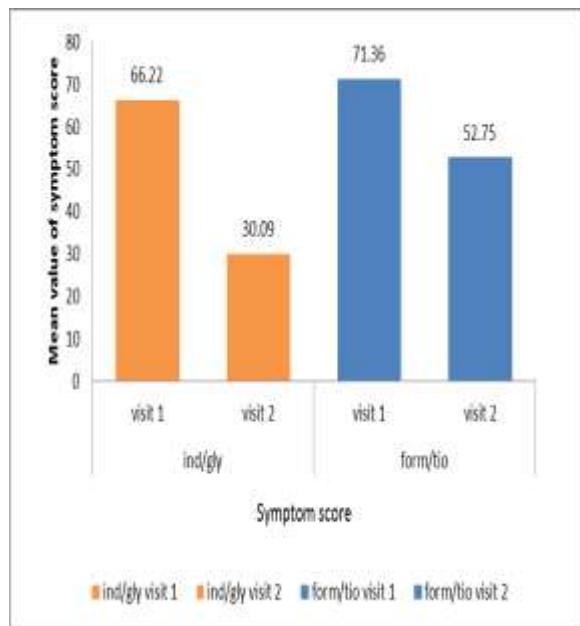


Figure 5: Effectiveness of medication based on symptoms of COPD patients.

Table 6: Effectiveness of medications based on the activity score of COPD patients.

DRUG	Visits	Mean value of Activity score	SD	Mean difference	p value
IND/GLY	Visit 1	41.22	±4.1	10.18	<0.0001
	Visit 2	31.04	±3.09		
FORM/TIO	Visit 1	41.3	±8.2	3.8	<0.0001
	Visit 2	37.5	±7.2		

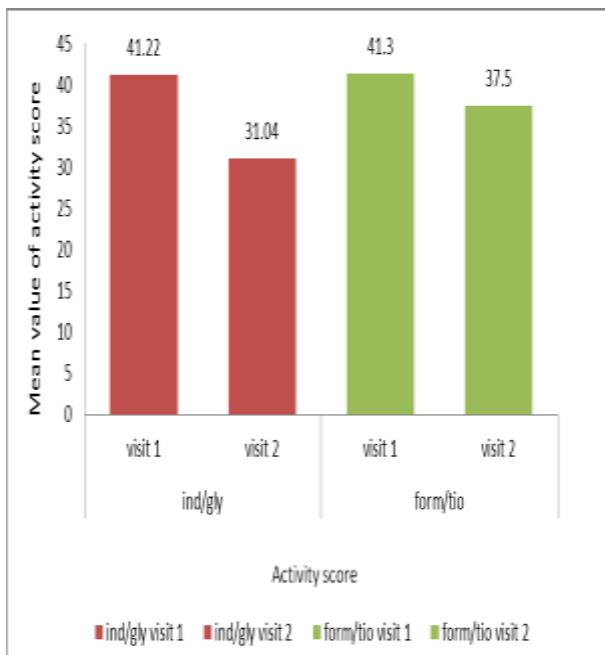


Figure 6: Effectiveness of medication based on activity score of COPD patients.

Table 6 and Figure 6 shows that the average activity score of the patients with Ind/Gly decreased from 41.22

to 31.04 and patients with Form/Tio decreased from 41.3 to 37.5 indicating the effectiveness of Ind/Gly on the activity of COPD patients. Here the p value was found to be <0.0001 indicating that the effectiveness of medication on the activity of COPD patients was significant.

Table 7: Effectiveness of medications based on the impact score of COPD Patients.

DRUG	Visits	Mean value of impacts score	SD	Mean difference	p value
IND/GLY	Visit 1	39.5	±5.8	19.1	<0.0001
	Visit 2	20.4	±2.7		
FORM/TIO	Visit 1	42.2	±6.8	6.4	<0.0001
	Visit 2	35.8	±5.7		

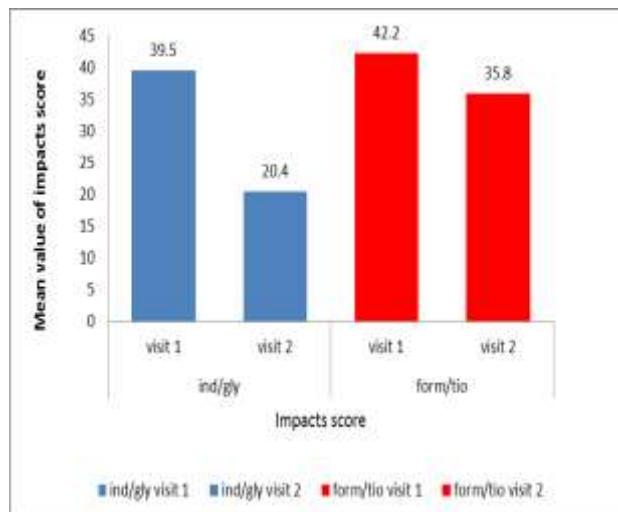
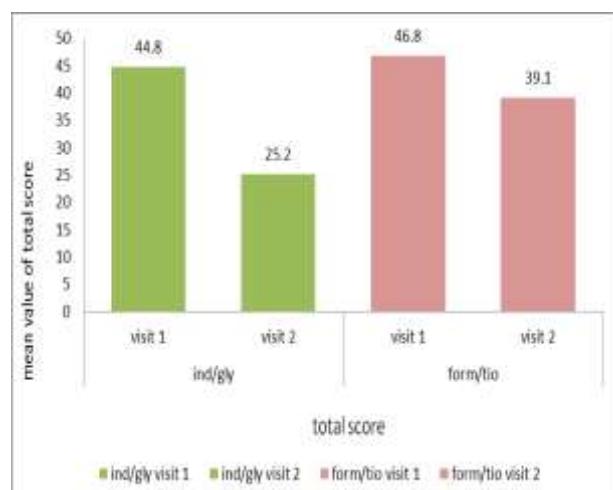
**Figure 7: Effectiveness of medication based on impact score of COPD patients.**

Table 7: and Figure 7 shows that the average impact score of the patients with Ind/Gly decreased from 39.5 to 20.4 and patients with Form/Tio decreased from 42.2 to 35.8 indicating the effectiveness of Ind/Gly on the activity of COPD patients. Here the p value was found to be <0.0001 indicating that the effectiveness of medication on the impacts of COPD patients was significant.

Table 8: Effectiveness of medication based on total score of COPD patients.

Drug	Visits	Mean value of total QOL	SD	Mean difference	p value
IND/GLY	Visit 1	44.8	±4.2	19.6	<0.0001
	Visit 2	25.2	±2.4		
FORM/TIO	Visit 1	46.8	±5.2	7.7	<0.0001
	Visit 2	39.1	±4.8		

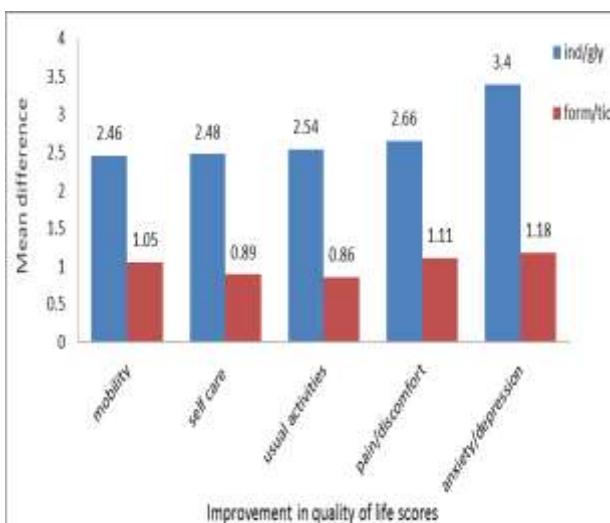
**Figure 8: Effectiveness of medication based on total quality of life of COPD patients.**

and patients with Form/Tio decreased from 46.8 to 39.1 indicating the effectiveness of Ind/Gly on the total quality of life of COPD patients. Here the p value was found to be <0.0001 indicating that the effectiveness of medication on the total quality of life of COPD patients was significant.

Table 8 and Figure 8 shows that the average total score of the patients with Ind/Gly decreased from 44.8 to 25.2

Table 9: Improvement in Quality of Life on Therapy.

Quality of life Scores	Indacaterol/ Glycopyrronium		Formoterol/ Tiotropium		p value
	Mean Difference	Std Deviation	Mean Difference	Std Deviation	
Mobility	2.46	±0.07	1.05	±0.03	<0.0001
Self care	2.48	±0.29	0.29	±0.04	<0.0001
Usual activities	2.54	±0.78	0.78	±0.00	<0.0001
Pain /Discomfort	2.66	±0.29	0.29	±0.08	<0.0001
Anxiety/Depression	3.4	±0.63	0.63	±0.12	<0.0001

**Figure 9: Distribution of adherence based on adherence.**

From the table 9 and figure 9 it is evident that there is significant rise in the quality of life of the patients taking Indacaterol with Glycopyrronium.

Table 10: Medication Adherence Among Patients With Copd Distribution of patients based on adherence.

Medication Adherence	1 st visit (%)	2 nd visit (%)
Indacaterol/ Glycopyrronium	37.1	91.4
Formoterol/ Tiotropium	31.4	88.5

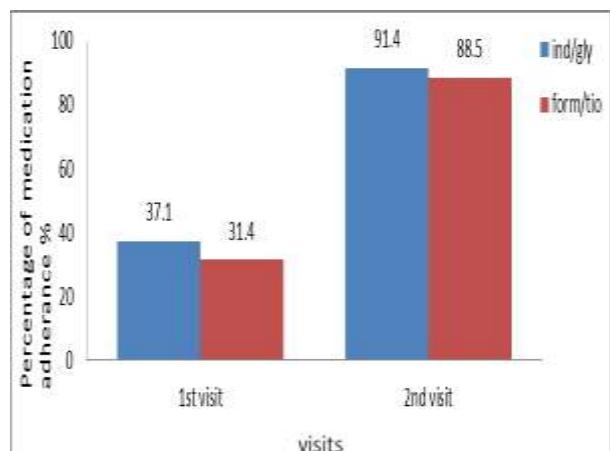
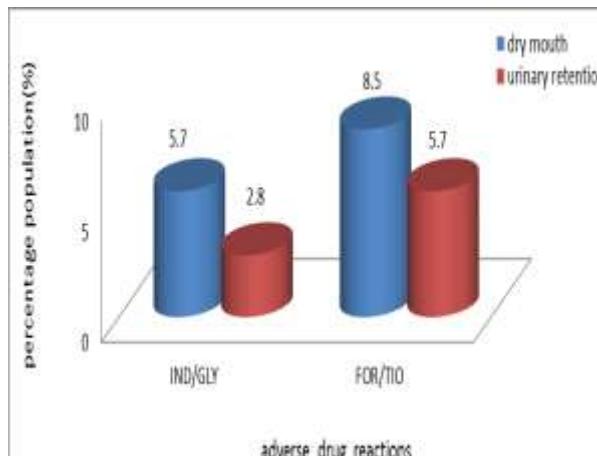
**Figure 10: Distribution of adherence based on adherence.**

Table 10 and Figure 10 shows that, the patients showed good adherence during their follow up. A significant change in adherence was found when compared to the patients previous visits

11. Safety Profile

Table 11: Distribution of patients based on the occurrence of ADR.

ADR	Indacaterol/ Glycopyrronium (%)	Formoterol/ Tiotropium (%)
Dry mouth	5.7	8.5
Urinary Retention	2.8	5.7

**Figure 11: Distribution of patients based on the occurrence of ADR.**

Out of 70 patients, the commonly occurred ADRs were dry mouth (5.7%) and urinary retention (2.8%) with the use of Ind/Gly and for Form/Tio, dry mouth (8.5%) and urinary retention (5.7%) were also observed. By Naranjo algorithm, 88.6 % had doubtful ADR, and 11.4% had possible incidence of ADR. From this study, it is clear that, the frequency of ADR is more with Formoterol with Tiotropium.

DISCUSSION

During the study, it is evident that, males are more frequently affected with COPD as 77.1% of the study population were males. It is because of smoking. From the study, it has been found that majority of the patients belongs to the age group of 50-65 years. That is, 51.4%

with ind/gly group and 65.8% with form/tio group. As it is a chronic condition, it may take several years to develop after smoking starts. That is the reason for the occurrence of COPD in older adults. 71.4% of population under Ind/Gly and 62.8% under Form/Tio have the social history of smoking. 18.6% of Ind/Gly and 8.6% of Form/Tio have an alcoholic history and 8.6% of Ind/Gly and 5.8% of Form/Tio have both alcoholic and smoking history. It is evident that the incidence of COPD is more in smokers. Majority of the study population have comorbidities of hypertension (38.5%) followed by diabetes mellitus (34.2%).

This study was done to compare the effectiveness of Indacaterol with Glycopyrronium and Formoterol with Tiotropium in COPD patients. In the present study, the study subjects were COPD patients. The criteria for evaluation were SGRQ score, QOL, medication adherence, and safety profile. The present study shows that both Indacaterol with Glycopyrronium and Formoterol with Tiotropium have significant effect on COPD patients. Clinical resolution of the symptoms occurred significantly more quickly with Ind/Gly than with Form/Tio. In the study population the average symptom score of the patients with Ind/Gly decreased from 66.2 to 30.09 and patients with Form/Tio decreased from 71.36 to 52.75 indicating the effectiveness of Ind/Gly on the symptoms of COPD patients. The average activity score of the patients with Ind/Gly decreased from 41.22 to 31.04 and patients with Form/Tio decreased from 41.3 to 37.5 indicating the effectiveness of Ind/Gly on the activity of COPD patients. The average impact score of the patients with Ind/Gly decreased from 39.5 to 20.4 and patients with Form/Tio decreased from 42.2 to 35.8 indicating the effectiveness of Ind/Gly on the activity of COPD patients. The average total score of the patients with Ind/Gly decreased from 44.8 to 25.2 and patients with Form/Tio decreased from 46.8 to 39.1 indicating the effectiveness of Ind/Gly on the total quality of life of COPD patients. The p value was found to be <0.0001 indicating that the effectiveness of medication on the total score of COPD patients was significant. The COPD patients have improvement in the symptom score, activity score, impact score and total score with the course of treatment with a decrease in SGRQ-C scores.

QOL is based on the patient's mobility, self care, capability to carry out usual activities, discomforts, anxieties and depression were assessed. QOL is assessed using EQ-5D-5L descriptive system. These scores are found to be increased before treatment and reduced after treatment. That is, greater score indicate reduction in the quality of life. There is significant increase in quality of life for both groups, significantly greater difference was seen with Ind/Gly group.

In this study, medication adherence was found to significantly increase after patient counseling for both drugs. Medication adherence was assessed by Morisky-8

questionnaire. Medication adherence of the patient during the first and second visits were assessed and compared. In the first visit 34.2% patients were adhered to the medication prescribed. After effective patient counseling, patient's attitude towards the therapy had changed. Medication adherence were improved after counseling, 90% patients were adherent during the follow up. This showed that there was significant improvement in the medication adherence after the pharmacist intervention.

Out of 70 patients, the commonly occurred ADR was dry mouth (5.7%) and urinary retention (2.8%) associated by the use of Ind/Gly and for Form/Tio, dry mouth (8.5%) and urinary retention (5.7%). By Naranjo algorithm, 88.6 % were doubtful ADR, and 11.4% is possible chance of ADR. Majority of patients have no side effects

CONCLUSION

This study ended with the conclusion that Indacaterol with Glycopyrronium and Formoterol with Tiotropium have a significant effect. Indacaterol with Glycopyrronium was found to be more efficacious in COPD patients in this study. Indacaterol/ glycopyrronium significantly reduced the rate of moderate or severe exacerbations, makes improvement in lung function, health status and reduces use of rescue medication. It provides the quick 24-hour bronchodilation effect, with the once-daily administration. It was assessed using SGRQ-C questionnaire. The COPD patients have improvement in the symptom score, activity score, impact score and total score with the course of treatment with a decrease in SGRQ-C scores.

Health related quality of life is assessed using EQ-5D-5L questionnaire. Mobility, Self care, usual activities, discomfort/pain, anxiety/depression was assessed. There is significant increase in quality of life for both groups, significantly greater difference was seen with Ind/Gly group.

Patients medication adherence had improved after effective patient counseling. Patient knowledge about the disease and medication had been increased.

Adverse reactions like dry mouth and urinary retention had reported during the study. But the incidence of occurrence of ADR is more with Formoterol/Tiotropium compared to Indacaterol/ Glycopyrronium. This study emphasize on the fact that Indacaterol with Glycopyrronium should be preferred over Formoterol with Tiotropium in patients with COPD.

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