

# Effect of Inhaled Anti-Cholinergic by Pressurized Metered Dose Inhaler (PMDI) or Dry Powder Inhaler (DPI) on Eyes of Patients of Chronic Obstructive Pulmonary Diseases (COPD).

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## ABSTRACT

**Background:** COPD is characterized by persistent airflow limitation associated with an enhanced chronic inflammatory response to noxious particles or gases in airways and lungs. Anticholinergics are bronchodilators which lead to side-effects like dry mouth, worsening glaucoma, dry cough and blurred vision on administration. Glaucoma is frequently seen in patients with chronic bronchitis who require treatment with nebulized bronchodilator drugs. **Aims and objectives:** The present study was done to find out the efficacy and safety of inhaled anticholinergics on intraocular pressure (IOP) in eyes of COPD and potential glaucoma patients. **Methods:** Total 110 patients of suspected COPD aged between 40 to 80 years were observed in this study. The diagnosis was also confirmed by spirometry and patient condition was allocated into stages as per GOLD 2014. Level of IOP before and after inhalation of drug in both eyes of patients at 2nd hour, 8th day, 15th day, 22nd day and at 28th day was analyzed. Study group (N=70) received ipratropium 40µg eight hourly or tiotropium 18 µg once a day and formoterol 6 µg twice a day plus fluticasone 125 µg twice a day and control group (N=40) received formoterol 6 µg twice a day and fluticasone 125 µg twice a day except anticholinergics. Comparison of IOP was done by statistical analysis. **Results:** In the present study, patients of COPD with mean age of 59± 8.84 years were observed for IOP. In study group, mean change in IOP was more (3.3±2.3 mmHg) in stage 2 than in stage 3 (1.5±1.5 mmHg) and least in stage 4 (1.3±1.06 mmHg) (p=0.035). During distribution of angle at 28th day after inhaled anticholinergics, 4 patients with narrow angle and 3 with open angle developed IOP beyond normal range(>20mmHg), but all were normal on fundoscopic examination (ocular hypertension). At the end of 28th day, there were 4 patients with ocular symptoms in study group which disappeared after discontinuing tiotropium inhaler. **Conclusion:** Inhaled formoterol and fluticasone with anticholinergic drugs given by PMDI leads to ocular hypertension in COPD patients whose eyes were normal at initial clinical examination whereas formoterol and fluticasone without anticholinergics did not cause any significant change in IOP. Inhaled anticholinergics increased intraocular pressure in COPD patients.

**Keywords:** PMDI, DPI, COPD, anticholinergics, bronchodilators, glaucoma.

## INTRODUCTION

COPD is characterized by persistent airflow limitation associated with an enhanced chronic inflammatory response to noxious particles or gases in airways and lungs. The incidence and mortality of COPD are expected to increase in near future and assumed to become the third commonest cause of death and the fifth commonest cause of disability in the world by 2020.<sup>[1]</sup>

Anticholinergics are group of bronchodilators which affect the muscles around the bronchi (large airways). When lungs are irritated, these bands of muscles become tight making the bronchi narrower. Anticholinergics work by stopping the muscles from tightening; these drugs can be delivered by either an inhaler or a nebulizer.<sup>[2]</sup>

There are two kinds of anticholinergics (Short-acting and long-acting). Short-acting anticholinergics (ipratropium) work in about 15 minutes, last for 6-8 hours whereas, long-acting anticholinergics (tiotropium) lasts for 24 hours. Both take 20-30 minutes to have a good effect therefore not considered the ideal "reliever" medication.<sup>[3]</sup>

Anticholinergics also have some side-effects including dry mouth, worsening glaucoma, dry cough. Glaucoma is frequently seen in patients with chronic bronchitis treated with bronchodilator drugs.

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Acute angle closure glaucoma is caused by closure of the anterior chamber drainage angles by contact between the peripheral iris and the posterior surface of the cornea.<sup>[4]</sup>

Tiotropium bromide is a long acting anticholinergic that reduce symptoms and exacerbations as well as improve lung function and quality of life with once-daily dosing, generally well tolerated with dry mouth being the main adverse effect. Tiotropium recipients experienced fewer exacerbations and COPD-related hospitalizations than placebo, salmeterol or ipratropium recipients.<sup>[5]</sup>

The present study was conducted to find out the effect and safety of inhaled anticholinergics on IOP in COPD patients and potential glaucoma patients.

## MATERIALS AND METHODS

The present study was conducted on 138 patients from January 2014 to October 2015 in the Department of Medicine, Government Medical College and Associated Hospital, Kannauj. Twenty eight patients were excluded from the study as 18 patients were not fulfilling the inclusion criteria and 10 were not co-operating with the study protocol. Remaining 110 patients were included and divided into study group (70) and control group (40). Study protocol approved by the board of faculty of medicine was followed.

COPD patients of either sex aged between 40 to 80 years were diagnosed according to criteria adopted and recommended by global initiative for chronic obstructive lung disease (GOLD) 2014. Clinical diagnosis considered if symptoms of chronic cough, chronic sputum production and progressive breathlessness was observed. All patients evaluated were subjected to detailed history, physical examination (anthropometry, general eye examination, measurement of IOP and assessment of angle of chamber), clinico physiological tests (pulse rate, blood pressure, respiratory rate, oxygen saturation, hemoglobin, total and differential leukocyte count, blood sugar, liver function test, renal function test, sputum for acid fast bacilli) and chest X- ray PA view to confirm the diagnosis. The diagnosis was also confirmed by spirometry and patient condition was allocated into stages as per criteria adopted and standardized by GOLD 2014.6 Bronchodilator reversibility testing was also performed by inhaled salbutamol 200µg using metered dose inhaler via spacer, after withholding inhaled short acting bronchodilator for 6 hrs, long acting  $\beta_2$  agonists for 12 hrs and sustained release theophyllines for 24 hrs. Lung functions were again measured after 10-15 minutes of inhaled bronchodilator.

Before ophthalmological examination of the patient, food and water intake of last 24 hours was recorded. Study group received ipratropium 40µg eight hourly or tiotropium 18 µg once a day and formoterol 6 µg

twice a day plus fluticasone 125 µg twice a day while, control group received above medicines except ipratropium or tiotropium, all the inhalers were given as PMDI.

Ophthalmic examination and gonioscopy were done as pre-treatment. IOP measurements were done by applanation tonometer before starting treatment, 2 hours after first dose and thereafter weekly for 4 weeks at 2.00pm every day. Level of IOP of both eyes of patients before and after inhalation of drug in study and control group at 2nd hour, 8th day, 15th day, 22nd day and at 28th day was analyzed. Comparison of IOP was done by ANOVA and independent t tests using statistical package for social science (SPSS) software (window version 22) and  $p < 0.05$  was considered as significant.

## RESULTS

In the present study, mean age of patients was  $59 \pm 8.84$  years. Maximum patients (32.8%) in study group had age group between 1-60 years. However in control group, maximum patients were in age group of 61-70 years.

Distribution of stage of COPD as per GOLD 2014 showed that most of the Patients (60%) belong to stage 3 followed by stage 4 (40%). None of the patient was in either stage 1 or 2. Stage wise, most of the patients were well distributed between the groups ( $p=0.045$ ).

While in distribution of angle of anterior chamber, maximum patients (60%) belong to stage 3 followed by stage 4 (40%). None of the patient was in either stage 1 or 2. Stage wise, most of the patients were well distributed between the groups.

Comparison of IOP in COPD patients after anti-cholinergic treatment is given in table 1. In study group maximum change observed in IOP at 28th day was +7.4 mmHg and +7.0 mmHg in left and right eye respectively in one patient. In control group maximum change in IOP was 3.20 mmHg and 3.70 mmHg in right eye and left eye respectively in one patient. Minimum change observed in IOP in study group was - 0.2 mmHg in one patient in both right and left eyes and in control group it was -0.30 and - 0.20 in one patient in right and left eyes respectively. In study group patients, mean change in IOP was ( $3.25 \pm 2.3$  mmHg right,  $3.52 \pm 2.2$  mmHg left)  $3.3 \pm 2.3$  mmHg, more in stage 2 than in stage 3 ( $1.52 \pm 1.5$  mmHg right,  $1.55 \pm 1.3$  mmHg left)  $1.5 \pm 1.5$  mmHg and least in stage 4 ( $1.37 \pm 1.06$  mmHg right,  $1.38 \pm 1.2$  mmHg left)  $1.3 \pm 1.06$  mmHg, the change was statistically significant ( $p=0.035$ ). In control group the change was found to be almost same among different angles.

During distribution of change in IOP according to sex, Mean change in IOP was more in female population ( $2.18 \pm 1.76$  right eye and  $2.21 \pm 1.46$  left eye) than in male population ( $1.60 \pm 1.71$  right eye,  $1.66 \pm 1.72$  left eye) in study group. The change was

not statistically significant for right eye (p=0.065) and for left eye (0.434). The change was almost same in control group.

During distribution of angle of anterior chamber at 28th day after inhaled anticholinergics, 4 (5.71%) patients with narrow angle (stage 2) and 3 (4.28 %) patients with open angle (stage 3) developed IOP

beyond normal range (>20mmHg), but all were normal on fundoscopic examination (ocular hypertension). In study group there were 4 (5.71%) patients with ocular symptoms at the end of 28th day which disappeared after discontinuing tiotropium inhaler.

**Table 1: Comparison of IOP (mmHg) in eyes of COPD patients after starting of anti-cholinergic inhaler**

IOP			10-13	13-15	15-17	17-19	≥20	Mean±SD
Before	Control	RE	6(15)	17(42.5)	13(32.5)	4(10)	0(0)	13.774±1.540
		LE	5(12.5)	19(47.5)	14(35)	2(5)	0(0)	13.689±1.789
	Study	RE	24(34.28)	29(41.42)	09(12.85)	7(10)	1(1.42)	13.931±1.968
		LE	24(29.68)	31(44.28)	09(12.85)	6(8.57)	1(1.42)	13.931±2.221
After 2 Hours	Control	RE	3(7.5)	20(50)	15(37.5)	2(5)	0(0)	13.935±1.209
		LE	3(7.5)	20(50)	12(37.5)	5(12.5)	0(0)	13.761±1.528
	Study	RE	10(14.28)	34(48.58)	21(30)	4(5.71)	1(1.42)	14.927±2.060
		LE	12(17.14)	27(38.57)	25(35.71)	4(5.71)	2(2.85)	15.081±2.025
8 <sup>th</sup> Day	Control	RE	3(7.5)	20(50)	15(37.5)	2(5)	0(0)	13.692±1.353
		LE	3(7.5)	20(50)	12(37.5)	5(12.5)	0(0)	13.933±1.796
	Study	RE	9(7.89)	29(47.31)	20(36.84)	11(5.2)	1(1.42)	14.958±1.978
		LE	8(7.89)	30(55.2)	24(31.5)	6(5.2)	2(2.85)	15.088±2.225
15 <sup>th</sup> Day	Control	RE	3(7.5)	20(52.5)	12(30)	4(10)	1(1.42)	13.940±1.221
		LE	3(7.5)	18(45)	15(37.5)	4(10)	0(0)	13.764±1.535
	Study	RE	7(10)	27(38.55)	28(40)	4(5.71)	4(5.71)	15.118±1.993
		LE	6(8.57)	27(38.55)	31(44.71)	5(5.71)	3(4.28)	15.331±2.242
21 <sup>st</sup> day	Control	RE	5(12.5)	18(45)	15(37.50)	2(5)	0(0)	14.159±1.356
		LE	5(12.5)	21(52.5)	12(30)	2(5)	0(0)	14.002±1.359
	Study	RE	10(14.28)	19(27.14)	33(48.57)	5(7.14)	3(4.28)	15.330±2.096
		LE	5(7.14)	21(30)	30(42.87)	7(10)	4(5.71)	15.621±2.337
28 <sup>th</sup> Day	Control	RE	4(10)	21(52.5)	11(27.5)	4(10)	0(0)	14.305±1.365
		LE	4(10)	22(55)	12(30)	2(5)	0(0)	14.128±1.709
	Study	RE	6(8.57)	23(32.85)	30(42.85)	7(10)	5(7.14)	15.701±2.405
		LE	3(4.28)	21(30)	34(48.57)	8(11.42)	5(7.14)	15.755±2.370

Data is expressed as no of patients (%), IOP; intraocular pressure (mmHg), RE; right eye, LE; left eye

## DISCUSSION

This was a hospital based prospective study conducted to investigate cause of any possible rise of IOP with 2 inhaled anticholinergics namely ipratropium bromide and tiotropium bromide used for treatment of COPD. This is the first study of its kind in which anticholinergics were used as PMDI for 4 weeks to see their effect on IOP level in eyes of COPD patients.

There were notable changes in mean IOP after 2 hours, 1, 2 and 3 weeks of medication in both eyes in study group (p<0.05). Marked change in IOP was seen at 28th day in study group, the difference (between pre medication and at 28th day) in mean IOP in study group was significant and the values were 1.770±2.186 mmHg in right eye and 1.823 ±2.262 mmHg in left eye while it was 0.530± 1.452 mmHg and 0.438±1.749 mmHg in right and left eyes of controls (p<0.05). It suggests that only inhaled PMDI anticholinergics cause rise in IOP.

Basoglu et al found that inhaled Ipratropium bromide did not change intraocular pressure after single dose, but after 45 days, statistically important (P value not reported) but clinically non-significant increase in IOP was found.<sup>[7]</sup> The mean increase in IOP in our study was 1.770±2.186 mmHg in right

eye and 1.823 ±2.262 mmHg in left eye at the end of 28th day (p = 0.000).

RajuMandapati J S et al did a study to assess the change in IOP due to systemic steroid use. In this study change in IOP was different, in 30–40% individuals IOP increased by at least 6 mm Hg, and in 5–6% of individuals IOP raised by 16 mmHg.<sup>[8]</sup> It concluded that systemic steroids taken for more than 8 weeks lead to rise in IOP. In current study inhaled corticosteroids (fluticasone) were used in both study and control groups in same dose. There were only small changes in mean IOP after 1, 2, 3, and 4 weeks in both eyes in control group, however notable change was noticed in IOP in both eyes in study group. It suggests that fluticasone (inhaled steroid) did not lead to rise in IOP.

## CONCLUSION

The inhaled anticholinergics (tiotropium) once a day along with formetrol and fluticasone twice a day given to COPD patients by metered dose inhalers with spacer lead to significant increase in IOP after 2 hours, 1 week, 2 weeks, 3 weeks and 4 weeks of starting treatment whereas in control group, COPD patients were given only formetrol and fluticasone by metered dose inhalers that did not cause any

significant change in IOP. Minor changes seen in some patients were within clinical therapeutic range. Inhaled Anti-cholinergic drugs given as PMDI can lead to ocular hypertension in COPD patients whose eyes were normal at initial clinical examination.

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