



## EFFECT OF INHALED TIOTROPIUM ON INTRAOCULAR PRESSURE IN PATIENTS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

### Pulmonary Medicine

|                              |  |
|------------------------------|--|
| <b>Dr. Amit Kumar Verma*</b> | Associate Professor(TB & Chest), Department of Medicine, UCMS and GTB Hospital, Dilshad garden, Delhi. *Corresponding Author |
| <b>Dr. Naweed Alam</b>       | Post graduate student. Department of Medicine, UCMS and GTB Hospital Dilshad Garden, Delhi                                   |
| <b>Dr. P.K. Sahu</b>         | Director Professor, Department of Ophthalmology, UCMS and GTB Hospital, Dilshad Garden, Delhi                                |
| <b>Dr Shiva Narang</b>       | Professor, Department of Medicine, UCMS and GTB Hospital, Dilshad Garden, Delhi  |
| <b>Dr Khan Amir Maroof</b>   | Associate Professor, Department of community Medicine, UCMS and GTB Hospital, Dilshad Garden, Delhi                          |

### ABSTRACT

**Introduction:** Tiotropium is a long acting anti-muscarinic agent (LAMA) recommended in management of chronic obstructive pulmonary disease (COPD) as a bronchodilator. Being anti-muscarinic agent, it has many other effects on body like dryness of mouth, urinary retention, raised intra ocular pressure (IOP) and rarely angina. In eye it causes pupillary dilation leading closure of anterior chamber angle, rise in intra ocular pressure and precipitate glaucoma.

In this regard available data has conflicting reports. Some suggest rise in intra ocular pressure but others oppose it. So we planned this study to see effect of tiotropium on intra ocular pressure.

**Aim:** To study the effect of inhaled antimuscarinic agent tiotropium on intraocular pressure in patients of chronic obstructive pulmonary disease (COPD).

**Objective:** To measure intra ocular pressure changes in COPD patients on tiotropium at baseline, at one month and after three months follow up.

**Materials and methods:** 65 patients were recruited from chest clinic and OPD from department of Medicine of UCMS and GTB Hospital. It was a prospective observational cohort study conducted from November 2017 – April 2019. Ophthalmological assessment of patients was done by using Goldmann applanation tonometer. This was done in department of ophthalmology by the same observer each time.

**Results:** There was a statistically significant difference observed in IOP over three months when compared by using paired t-test and p-value was 0.002.

**Conclusion:** There was statistically significant change in mean IOP at the end of study compared to baseline by use of inhaled tiotropium bromide in COPD patients.

### KEYWORDS

Tiotropium, COPD, Intra ocular pressure

#### INTRODUCTION :

Chronic obstructive pulmonary disease (COPD) is an under diagnosed, progressive, incurable lung disease. Its prevalence is on rise globally as well as in India. COPD is currently the fourth leading cause of death in the world<sup>1</sup> but it's projected to be third leading cause by 2020.<sup>2</sup>

A combination of environmental, genetic, constitutional, familial, behavioral and socio demographic factors predispose patients to COPD, with smoking being the most common cause. It comprises of emphysema and chronic bronchitis the two distinct processes, although mostly present in combination.<sup>3</sup> COPD is characterized by reduced mean expiratory flow during forced exhalation and persistent respiratory symptoms that is due to airway and alveolar abnormality.

Tiotropium bromide a long acting antimuscarinic agent (LAMA) used in our study has well known documented effect on improving lung function and quality of life. As antimuscarinic drugs are antagonist to acetylcholine, they have may have many other effects in body as side effects. In the eye it cause pupil dilation, leading to closure of anterior chamber angles, consequently leading to increased intra ocular pressure and precipitate glaucoma.

There are various studies from India and world, some support the fact that tiotropium is associated with increase in intraocular pressure while others oppose it. Hence we planned this study to see the effect of tiotropium bromide on intraocular pressure.

**Aim:** To study the effect of tiotropium bromide on in traocular pressure in patients of chronic obstructive pulmonary disease.

**Objective :** To measure intra ocular pressure changes in patients of COPD on tiotropium at baseline, at one month and after three months follow up period.

#### MATERIALS AND METHODS:

**Setting:** 65 patients were recruited from chest clinic and OPD from department of Medicine of UCMS and GTB Hospital.

**Study design:** Prospective observational cohort study

**Time period:** Nov 2017 - April 2019

**Study subjects:** Patients with diagnosis of COPD presenting in chest clinic and OPD and receiving inhaled tiotropium bromide drug.

#### Inclusion criteria

- All patients diagnosed with COPD in GOLD-2017 stage B and C.
- Patients between 40-70 years of age

#### Exclusion criteria

- Known cases of asthma, allergic rhinitis, atopy
- Patients in stage A & D GOLD-2017 guidelines.
- Patients having acute exacerbation in last one month.
- Patients with symptomatic GERD
- Patients on oral corticosteroids

#### METHODS:

Ethical clearance was taken from the institutional ethics committee and informed written consent was taken from each subject. During the study period following medications was prescribed: bronchodilators: LAMA (tiotropium) in dose of 18 µg/dose per day, LABA (salmeterol) 50 µg/dose as twice a day, LAMA (tiotropium) was given either alone or in combination with LABA (salmeterol). For this standard protocol as prescribed by GOLD-2017 was followed.

#### Ophthalmological assessment:

Goldmann applanation tonometer was used to assess the IOP at baseline, at end of one month and end of follow up period of three months. This was measured in department of ophthalmology by the same observer each time.

#### Statistical Analysis:

Data was entered in MS EXCEL and analysed using SPSS 20.0

software and R package version 2.4 and descriptive statistics was compiled in the form of mean and standard deviation for continuous variables and as proportion for categorical variables. P-value <0.05 was considered as statistically significant. Applied paired t test for comparing iop.0, iop.1, and iop.3 and found that all the differences are statistically significant.

## RESULTS:

**Age distribution:** The age of subjects ranged from 40 to 70 years. The mean (SD) was  $57.91 \pm 7.89$  years.

**Gender distribution:** There were 57 males and 8 females as shown in Table 1

**Table 1: Gender distribution**

| Sex distribution | Numbers | Percentage |
|------------------|---------|------------|
| Males            | 57      | 87.6       |
| Females          | 08      | 12.3       |

### Age at diagnosis of COPD in the present study:

The mean age of diagnosis of COPD patients in my study was  $55.26 \pm 7.28$ . The minimum and maximum age of diagnosis of patients was 39 to 70 years.

### Intra ocular pressure (IOP) of right eye

Intraocular pressure right eye of patient was measured at 0, 1 and 3 months of study. In table 2 there was significant change in IOP after 1st month of start of drug (p-value = 0.009) and no significant statistical change observed at end of 3rd months of study compared to 1st month. So there is significant change in mean IOP of right eye at end of follow up study compared to start of study (p-value=0.002)

**Table 2: Comparison of IOP right eye**

| Group wise comparison      | IOP (mm Hg±SD) mean±sd   | Observed difference | P value* |
|----------------------------|--------------------------|---------------------|----------|
| Baseline vs 1 month        | 14.31±2.92<br>14.42±2.79 | 0.11                | 0.009    |
| 1 month vs 3 months        | 14.42±2.79<br>14.65±2.91 | 0.23                | 0.04     |
| Baseline value vs 3 months | 14.31±2.92<br>14.65±2.91 | 0.34                | 0.002    |

Paired t-test was applied

### Intra ocular pressure (IOP) of left eye

Intraocular pressure left eye of patient was calculated at 0, 1 and 3 months. In table 3 there significant change in IOP after 1<sup>st</sup> month of start of drug, and no significant statistical change observed at end of 3<sup>rd</sup> months of study compared to 1<sup>st</sup> month. So there is significant change in mean IOP of left eye at end of follow up study compared to start of study as it was in right eye.

**Table3: comparison of IOP left eye**

| Group wise comparison   | IOP (mm Hg±SD) mean±sd   | Observed difference | P value |
|-------------------------|--------------------------|---------------------|---------|
| Baseline value 1 month  | 14.17±2.83<br>14.26±2.76 | 0.09                | 0.009   |
| 1 month 3 months        | 14.26±2.76<br>14.40±2.68 | 0.14                | 0.004   |
| Baseline value 3 months | 14.17±2.83<br>14.40±2.68 | 0.23                | 0.002   |

Paired t-test was applied

### Side effects observed with use of tiotropium:

Out of 65 patients we followed up in our study some patients complained of side effects such as dry mouth, pharyngitis, URTI, constipation with use of tiotropium.

## DISCUSSION:

A total of 65 patients were recruited for study which included 57(87.7%) males and 8 (12.3%) females. The age of subjects ranged from 40 to 70 years. Tiotropium might worsen the signs and symptoms of narrow angle glaucoma or increase intra ocular pressure if the drug were inadvertently deposited in the eye. But its association to increase intra ocular pressure when used in inhaler form is a much debated topic.

Intra ocular pressure(IOP) of both eyes were compared in our study

using goldmann applanation tonometer at baseline, one month and at end of follow up period of three months. Even though there was a statistically significant difference observed when IOP over three time points were compared. We found a statistically significant difference in mean IOP by paired t-test at baseline and 3rd month but changes in IOP was not significant between one and three months.

In a study by Brreintos et al<sup>5</sup> concluded that anticholinergics like ipratropium and salbutamol increase the IOP and may cause acute angle closure glaucoma in susceptible patients. In another study done in India by Yadav P et al<sup>6</sup> found that inhaled anticholinergics (ipratropium or tiotropium) did not lead to any significant change in IOP after 2 hours first, second and fourth week of treatment. In another study by Kumar et al<sup>7</sup> inhaled formoterol and fluticasone with anticholinergic drugs given by PMDI leads to ocular hypertension in COPD patients whose eyes were normal initially. However, formoterol and fluticasone without anticholinergics did not lead to any significant increase in IOP. Basoglu et al<sup>8</sup> found that inhaled anticholinergics did not change IOP after single dose but after 45 days statistically important but clinically non-significant increase in IOP was found.

In another study of pharmacokinetics and tolerability with particular reference to ocular safety of tiotropium by Feifel U et al<sup>9</sup> tiotropium did not affect pupil diameter, papillary reflex, accommodation, intraocular pressure

## CONCLUSION:

We observed a statistically significant difference observed when IOP over three time points were compared. We found a statistically significant difference in mean IOP by paired t-test at baseline and 3rd month but changes in IOP was not significant between one and three months, thus future studies are needed in large group of patients.

## REFERENCES-

- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: asystematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380(9859):2095-128.
- Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349(9064):1498-504.
- National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax*. 2004;59Suppl 1:1-232.
- Kumar R, Bhushan M, 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). 2016;2(6):67-70.
- Brreintos F, Jimenez SM, Delacasa M, Hernandez MC. Acute angle-closure glaucoma resulting from treatment with nebulised bronchodilators. *Garcia-Feijoo J2006*;81(11):657-60.
- Prashant Y, Sourabh P, Aditya G, Anand K, Sudhir C. Effect of inhaled anticholinergic drugs on intraocular pressure in chronic obstructive pulmonary disease patients. *Indian J Basic Appl Med Res* 2015;4:458-464.
- Kumar R, Bhushan M, 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). 2016;2(6):67-70.
- Basoglu OK, Emre S, Bacakoglu F, Ates H. Glaucoma associated with metered-dose bronchodilator therapy. *Respir Med*. 2001;95(10):844-5.
- Feifel U, Wallenstein G, Rominger KL, Trommehauser D, Platz J. Pharmacokinetics and tolerability (Study 1) with particular reference to ocular safety (Study 2) of tiotropium Respimat soft mist inhaler: findings from two dose-ranging studies in healthy men. *Int J Chron Obstruct Pulmon Dis*. 2008;3(3):397-403.