Original article

Effect of inhaled anticholinergic drugs on intraocular pressure in chronic obstructive pulmonary disease patients

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Abstract

Introduction: Glaucoma is frequently seen in patients with chronic bronchitis who require treatment with nebulized Beta2 agonists and ipratropium due to accidental instillation in eyes. Significance of anticholinergic drugs used as inhalers by Chronic Obstructive Pulmonary Disease (COPD) causing raised intraocular pressure is unknown.

Material and Methods: In this prospective study 132 COPD patients were included, 14 patients were excluded because on initial examination they had hyper mature senile cataract. 10 patients were excluded because they were not co-operating with the study protocol .108 patients on whom study were done were divided into 70 patients (study group) who received Ipratropium or Tiotropium with formetrol and fluticasone and 38 patients(contol group) took formetrol with fluticasone without ipratropium / tiotropium as Metered dose Inhaler (pMDI). General ophthalmic examination, and Gonioscopy was done as pre-treatment. Intra-ocular pressure measurement done in all patients before starting treatment, 2 hours after first dose and thereafter weekly for four weeks.

Observation and Result: The mean intraocular pressure (IOP) of right eye and left eye of study group and control group before medication and after inhalation of drugs compared and it was found that some change in IOP was seen at 28th day in both the group in each eye but that change was not significant in either group. All values of IOP are within normal clinical range in each group.

Conclusion: The inhaled anticholinergics all by MDI did not lead to any significant change in IOP after 2 hours, 1st, 2nd, 3rd and at 4th week of starting treatment.

Keywords: Inhaled Anticolinergics, Intraocular Pressure, Glaucoma

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality globally.The prevalence and mortality of COPD are expected to increase in the coming decades and it is predicted to become the third commonest cause of death and the fifth commonest cause of disability in the world by 2020. [1] Pharmacotherapy for COPD has been used to alleviate symptoms, prevent exacerbations, and improves exercise capacity and quality of life. When the lungs are irritated, bands of muscle become tightened, making the bronchi narrower. Anticholinergics drugs are group of bronchodilators which affect the muscles around the bronchi (large airways) and work by stopping the muscles from tightening. Antimuscarinic drugs

are antagonists of acetylcholine, in the eye they cause pupil dilation leading to closure of the anterior chamber drainage angles consequently lead to increase in intraocular pressure and precipitate glaucoma**.** Glaucoma is frequently seen in patients with chronic bronchitis who require treatment with nebulised bronchodilator drugs. Though ipratr-opium bromide, a widely used methyl atropine congener, can potentially raise intraocular pressure in predisposed individuals, its significance in clinical practice is unknown. [2]

Aims and objective

To study the effect of inhaled anticholinergics (Tiotropium/ Ipratropium bromide) on intraocular pressure in COPD patients to evaluate their safety in borderline or potential glaucoma patients.

Material and Method

The study was conducted in the "Department of Tuberculosis and Respiratory Diseases" from January 2012 to June 2013. All the patients of COPD of aged 40 to 80 years of either sex who were diagnosed according to Gold criteria 2009 and not on anticholinergic drugs were included in the study. Patient having glaucoma and those who has under gone glaucoma surgery or those who had cataract (Hyper mature cataract, Morgagnian cataract) or those having family history of glaucoma were excluded from the study. Patients who had corneal opacity, or corneal dystrophy and already on medications with propensity to cause changes in intraocular pressure were excluded. All the patients who were included in the study were advised not to change their routine food and amount of fluid intake significantly before eye examination, and if it were to be, they were asked to tell before eye examination so that there examination can be accordingly planned.

Initially 132 patients were included. 14 patients were excluded because on initial examination they had hyper mature senile cataract. 10 patients were excluded because they were not co-operating with the study protocol. 108 patients on whom study were done were divided into study group and control group. Study" group which comprised of 70 patients received Ipratropium 40µg eight hourly or Tiotropium 18 µg once a day and Formetrol 6 µg twice a day plus Fluticasone 125 µg twice a day. The "control" group which comprised of 38 patients received above medicines and a placebo in place of Ipratropium or Tiotropium. All the inhalers were given as metered dose Inhaler (pMDI). Ophthalmic examination and Gonioscopy were done as prereatment. Intraocular ocular pressure (IOP) measurements were done by Applanation tonometer before starting treatment, 2 hours after first dose and thereafter weekly for four weeks at 2.00 pm every day. Level of Intraocular pressure (IOP) before medication and after inhalation of drug in study group and in control group at 2nd hour, 8thday, 15th day, 22th day and at 28th day of both eyes were analysed.

Result

The patients of stage-3 COPD were maximum 60 (55.55%) and the patients of stage-4 COPD were 48(44.45) while there was no patient of stage-1 or stage-2 enrolled in the study.The distribution of angle of anterior chamber of eye as 62 (57.50%) patients of grade III, and 46(42%) of grade IV.In study group 47(67.14%) patients of grade III and 23(32.86%) of grade IV and in control group 24 (63.15%) patients of gradIII and14 (36.75%).There was no patient of grade I or grade II.

Level of Intraocular pressure (IOP) before medi-cation and after inhalation of drug in study group and in control group after 2nd hour, 8thday, 15th day, 22th day and at 28th day of both eyes were analysed. It was observed that level of IOP in both eyes of study group and in control group at 2nd hour, 8th day ,15th day and 22nd day of inhalation of medication were same as before medication. There

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was change in IOP was seen at 28th day in 13 patients of study group and only 5 patients of control group. Therefore the levels of intraocular pressure (IOP) in both the eyes (before medication and after inhalation of drug on 28th day) had been analysed by paired t test in each group and between study and control group by student t test (Independent Samples Test) by using Statistical Package For Social Science (SPSS) software (window version 22), the results were

1. The mean IOP of right eye and left eye of study group before medication was 14.49 ±1.40 mmHg and 14.41 ±1.36 mmHg respectively. The mean IOP of right eye of the study group at 28th day of inhalation of anticholinergics was 14.70 ±1.43 mmHg and of left eye was 14.66 ±1.24 mm Hg. (Table no. 1 and 2)

2. The mean IOP (baseline) of right eye and left eye of control group was 14.71 ±1.33 mmHg and 14.65 ±1.38 mmHg respectively. The mean IOP of right eye of the control group at 28th day was 14.91 ±1.36 mmHg and of left eye was 14.75±1.25 mmHg. (Table no. 1 and 2)

3. The difference between mean IOP of right eye of study group (between baseline and at 28th day) was 0.21±.47 mmHg with t= 3.763 and p = 0.295 which was not statistically significant and of left eye was 0.24 ± 0.47 mmHg with t = 3.224 and p = 0.279 which was also not statistically significant. (Table no. 3)

4. The difference between mean IOP of right eye of control group (between baseline and at 28th day) was 0.20 ±.67 mmHg with t = 1.90 and p= 0.076 which was not statistically significant and of left eye was 0.10 ±.44 mmHg with t = 1.272 and p = 0.211 which was also not statistically significant. (Table no.3)

As change in intraocular pressure was seen at 28th day in study group and control group, therefore these two groups compared by student t test (Independent Samples Test) and result were:

5. The difference in mean intraocular pressure between study and control group (premedication) was 0.22 ±.64 mmHg in right eye with t= 0.789 and p= 0.432 which was not statistically significant and of left eye was 0.23 ±.34 mmHg with t=0.749 and p = 0.412 which was also not statistically significant. (Table no.4)

6. The difference in mean intraocular pressure between study and control group at 28th day was 0.047± 0.10 mmHg in right eye with t= 0.475 and p= 0.636 which was not statistically significant and of left eye was 0.054± 0.09 mmHg with t = 0.502 and p = 0.312 which was also not statistically significant. (Table no.4)

Discussion

Two inhaled anticholinergics namely ipratropium bromide and Tiotropium bromide used for treatment of COPD were investigated for causing any possible rise of intra-ocular pressure. We selected patients whose eyes were absolutely normal on initial examination because of very limited experience in literature whether anticholinergics used as metered dose inhaler (pMDI) in therapeutic doses can lead to rise in intra ocular pressure.

This is the first study of its kind with pMDIs and we did not want Glaucoma or potential Glaucoma patients put to risk without declaring safety in patients with normal eyes. In our study inhaled anticholinergics (Ipratropium or Tiotropium) given to study group and a placebo in place of Ipratropium or Tiotropium to the control group, other inhaled drugs namely Formetrol (long acting β2 agonist) and Fluticasone (inhaled steroid) were given to all COPD patients in study group and control group. There was no change in mean IOP after 2 hours, one week, second week and third week and in both eyes in each group. Some change

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in IOP was seen at 28th day in study and control group, the difference in mean (between premedication and at 28th day of medication) intraocular pressure (IOP) in both groups was not significant. It suggests that not only inhaled (pMDI) anticholinergics but also Fluticasone (inhaled steroid) and Formetrol (long acting β2 agonist) did not cause rise in intraocular pressure when used as metered dose inhaler (pMDI).

Kalra L and Bone MF (1988) did a controlled double-blind crossover study of ocular complications associated with nebulised ipratropium bromide and salbutamol therapy for respiratory distress was in 46 chronic bronchitis patients and found there was no significant rise in intraocular pressure. [2]

Helprin GA, Clarke GM. (1986) found in their study that angle closure glaucoma following treatment with nebulised ipratropium alone and acute angle closure glaucoma after treatment with nebulised ipratropium and salbutamol both were more common. They also found in study that the administration of a combination of nebulised salbutamol plus ipratropium bromide and salbutamol caused a transient increase in IOP in all patients having narrow drainage angles; however, no significant increase in IOP was found when swimming goggles were used or when antiglaucoma medications were continued**.** [3]

Basoglu et al. (2001) found in his study that intraocular pressure did not change after single dose inhaled ipratropium bromide, but after 45 days, statistically important (P value not reported) but clinically non -significant increases in IOP were found. The lack of any significant increase in IOP after single-dose administration of ipratropium bromide in the current study does not ensure the tolerability of ipratropium bromide in patients receiving long-term therapy. [4]

McCrary DC Brown CD (2005) found that acute angle closure glaucoma which emerged as a result of the medication during critical episode of the patient is an infrequent complication, Ipratropium bromide is an anticholinergics agent which induced mydriasis its action mechanism at the ocular level is local with deposit on the conjunctiva and corneal surface of the spray, due to faulty placement of the mask.

Salbutamol is B2 agonists which in addition cause mydriasis, Increase the production of aqueous humor, at the eye level their adverse effects are due to local absorption. Mydriasis and Increased production of aqueous humour in predisposed Individual (narrow angle) can lead to acute angle closure due to pupillary obstruction. The development of acute angle closure glaucoma is more frequent with the combination of ipratropium and salbutamol versus individual administration. [5]

Brreintos F et al (2006) concluded in their study that Ipratropium bromide and salbutamol increases the intraocular pressure and may cause acute angle closure glaucoma (AACG) in susceptible patients (those with a shallow anterior chamber, hypermetropia, or chronic angle-closure glaucoma. [6]

Oksuz H et al (2006) found that acute angle closure glaucoma was rare form of glaucoma occurring when the filtration mechanism for aqueous humour is obstructed by apposition of the peripheral iris to the trabecular meshwork. It may be precipitated by pupillary dilatation in eye. [7]

Dada T et al (2009) found that Intraocular pressure elevation after topical steroids is quite common, it was seen that rise in IOP can develop about 4 to 8 weeks after injectable topical steroids. Irrespective of the route of administration either topical or systemic steroids use, it was associated with glaucoma. [8]

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Conclusion

The inhaled anticholinergics (Ipratropium or Tiotropium) given along with Formetrol and Fluticasone in COPD patients, all by Metered Dose Inhalers did not lead to any significant change in intraocular pressure (IOP) after 2 hours, one week , second week, third week and after 4th week of starting treatment. Minor changes were seen in some patients but they were within clinical therapeutic range. All values of intraocular pressure are within normal clinical range.

The mean base line pre-treatment Intra ocular pressures were 14.49 ±1.40 mmHg in Right Eye and 14.41±1.36 mmHg in Left eye in study group. In Control group mean baseline intraocular pressures were 14.71 ±1.34 mmHg in Right eye and 14.65 ±1.38 mmHg in Left eye. Maximum change of intraocular pressure in study group was 4.0 mmHg in both eyes in one patient and in control group it was 2.0 mmHg in both eyes in one patient at 28th day of medication.

This study did not include COPD patients whose pre-treatment eye examinations were abnormal, Glaucoma suspects or cases of self limiting glaucoma. These patients therefore, need to be watched for glaucoma before and regularly after start of treatment. A study on these type of patients is needed.

Our study results and considering review of literature favour that inhaled anticholinergics could be safer when used as metered dose inhaler (pMDI) instead of nebulization in needy who are potentially at risk of glaucoma or in whom initial eye examination are not within normal limit. In metered dose inhaler there is no possibility that drug directly escapes into the eyes.

Table 1 Intraocular Pressure Before Starting Anticholinergic Medication

INTRAOCULAR PRESSURE (IOP) in mmHg	**STUDY GROUP**		**CONTROL GROUP**	
	RIGHT EYE	**LEFT EYE**	**RIGHT EYE**	**LEFT EYE**
11 -13	7	9	2	3
13-15	41	39	17	19
15-17	17	19	13	14
17-19	5	3	6	2
MEAN IOP	14.49 ±1.40	14.41±1.35	14.71±1.33	14.65 ±1.38
TOTAL	70	70	38	38

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Table 2 Intraocular Pressure At 28th day of Starting Anticholinergic Medication

INTRAOCULAR PRESSURE (IOP) in mmHg	STUDY GROUP		CONTROL GROUP	
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE
11 -13	5	10	2	2
13-15	38	41	21	22
15-17	23	14	11	12
17-19	4	5	4	2
MEAN IOP	14.70 ± 1.43	14.66 ±1.24	14.91 ±1.36	14.75 ±1.25
TOTAL	70	70	38	38

Table 3 Difference In Mean Intraocular Pressure of Study Group And Control Group Between Premedication and at 28th day

DIFFERENCE IN MEAN INTRAOCULAR PRESSURE [in mmHg]	STUDY GROUP		CONTROL GROUP	
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE
	0.21 ±.47	0.24.±.47	0.20 ±.67	0.10 ±.44
t	3.764	3.224	1.90	1.272
p	0.295	0.279	0.076	0.211

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Table 4 Difference In Mean Intraocular Pressure Between Study Group And Control Group

DIFFERENCE IN MEAN INTRAOCULAR PRESSURE [in mmHg]	PREMEDICATION		AT 28TH DAY	
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE
	0.22 ±.64	0.23 ±.34	0.047± .10	0.054± 0.09
t	0.789	0.749	0.475	0.502
p	0.432	0.412	0.636	0.312

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