Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/17093
DOI URL: http://dx.doi.org/10.21474/IJAR01/17093

RESEARCH ARTICLE

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

Dr. Fifi Francis, Dr. Manoj D.K, Dr. Rajani M., Dr. Muhammad Shafeek K. and Dr. Padmanabhan K.V

Manuscript Info

Manuscript History
Received: 15 April 2023
Final Accepted: 19 May 2023
Published: June 2023

Key words:-
Tiotropium Bromide, Intraocular Pressure, Chronic Obstructive Pulmonary Disease

Abstract

Introduction: Chronic Obstructive Pulmonary Disease is one of the leading causes of morbidity and mortality with increasing prevalence worldwide. Tiotropium bromide a long acting antimuscarinic agent used in management. In the eye it causes pupil dilation, leading to closure of anterior chamber angles, consequently leading to increased intra ocular pressure.

Objectives: To study the effect of inhaled tiotropium on intraocular pressure in patients of Chronic Obstructive Pulmonary Disease.

Methods: This is a prospective observational study done over a period of one year on 100 patients of Chronic Obstructive Pulmonary Disease using tiotropium inhaler and fulfilling the inclusion and exclusion criteria. Clinical details and other essential information had been collected using a proforma that was filled by the investigator. During study period tiotropium is administered at a dose of 18mcg/day. The Schiotz tonometer is used to assess intraocular pressure at baseline, at the end of 1 month and 3 month follow up period. The results were organized and analyzed statistically.

Results: A total of 100 patients recruited for study which included 88 males and 12 females. Intra ocular pressure (IOP) of both eyes were compared in our study using Schiotz tonometer at baseline, one month and at end of follow up period of three months. We found a statistically significant difference in mean IOP by paired t-test at baseline and 3rd month, one month as well as three months, but changes in IOP was not significant between baseline and one month.

Conclusion: We found a statistically significant difference in mean IOP by paired t-test at baseline and third month.

Introduction:-

Chronic obstructive pulmonary disease is a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development, significant comorbidities may have an impact on morbidity and mortality [1].

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of morbidity and mortality with increasing prevalence worldwide[2].The prevalence of COPD in India was 4.2% in 2016 and it is higher than the

Corresponding Author:- Dr. Fifi Francis

global average [3]. A study conducted in Thiruvananthapuram showed that there were many patients who were not diagnosed by the initial care providers as having COPD [4].

A combination of environmental, genetic, constitutional, familial, behavioral and socio demographic factors predispose patients to COPD, with smoking being the most common cause. 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 causes pupil dilation, leading to closure of anterior chamber angles, consequently leading to increased intra ocular pressure and precipitate glaucoma [5].

The aim of the study was to study the effect of inhaled tiotropium on intraocular pressure in patients of chronic obstructive pulmonary disease.

Relevance of the study: Long-acting muscarinic antagonist are now first choice in COPD as per GOLD guidelines, in groups B, C, D. Tiotropium is more potent, once daily administration, significant improvement in FEV1, dysnoea, health related quality of life and lower COPD exacerbations and hospitalisation. Hence tiotropium inhaler is widely used. Hence its side effects need to be addressed and not clearly understood.

Materials & Methods:-

Study Design:
Prospective observational study

Study setting:
Department of Respiratory Medicine & Department of Ophthalmology, Government Medical College, Kannur

Study Period:
The study was conducted for a period of 1 year, from March 2020 -march 2021.

Sample size:
Minimum sample size for the study was calculated as 200.

Sample size is calculated using reference article 5

Sample size is calculated using formula

Sample size,

$$n = \left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{\Delta} \right)^2 + \frac{(Z_{1-\alpha/2})^2}{2}$$

$$\Delta = \frac{\mu_2 - \mu_1}{\sigma}, \sigma = \frac{\sigma_1 + \sigma_2}{2}$$

Were,
μ_2 = Post test mean (14.66).
μ_1 = Pretest mean (14.41).
σ_1 = Pretest Standard Deviation (1.36).
$\sigma 2$ = Post Test Standard Deviation (1.24).
$Z_1 - \alpha/2$ = standard normal variate value corresponding to 5% level of significance = 1.96.
$Z_1 - \beta$= standard normal variate value corresponding to 80% power = 0.84.

Sampling:
Consecutive sampling.

Study subjects:
All diagnosed cases of chronic obstructive pulmonary disease in department of respiratory medicine, government medical college kannur.

Inclusion criteria:
All patients diagnosed with chronic obstructive pulmonary disease aged more than 40 Years

Exclusion criteria:
1. Patients with glaucoma
2. Patients with benign prostatic hypertrophy
3. Patients on long term oral corticosteroids
4. Patients with coronary artery disease.

Methodology:-

The study was conducted after obtaining approval from institutional research committee and institutional ethics committee. Informed consent was taken from patients before including them in the study. Clinical details and other essential information were collected using a proforma that was filled by the investigator. Detailed history of patients including history of cough, quantity and type of expectoration, breathlessness, fever was taken. Patients were specifically asked for comorbid conditions such as diabetes mellitus, hypertension and family history of glaucoma. Exposure history including smoking status, passive smoking, biomass fuel exposure was taken. Dyspnea scale was assessed using MMRC grading. COPD assessment test was done to measure impact of COPD on patients' life. During study period tiotropium will be administered at a dose of 18mcg /day. Schiotz tonometer will be used to assess intraocular pressure at baseline, at end of 1 month and at the end of 3 month follow up period. IOP measurement was done with the help of an ophthalmologist.

Variables studied:
Smoking status, comorbidities, family history of glaucoma, modified medical research council scale, COPD assessment test, intraocular pressure, age, sex.

Statistical Analysis
Descriptive statistical tools like frequency, percentage, mean and standard deviation were used. Applied paired t test for comparing intraocular pressure at baseline, one month and three months. P value of < 0.05 was taken as significant.

Observations And Results:-

Total 100 patients were included in the study.

Table 1:-Sociodemographic profile.

VARIABLE	frequency	Percentage
AGE		
40-50	2	2
51-60	21	21
61-70	51	51
71-80	22	22
81-90	4	4
GENDER		
Male	88	88
Female	12	12

Out of the 100 patients studied, 37% had cough at presentation of which 19 patients had scanty expectoration, 11% moderate expectoration and 7% had copious expectoration. All of the patients had breathlessness. Majority (38%) of patients had MMRC grade1 dysnoea.31% of patients had fever at presentation.

The comorbidities observed in present study population diabetes mellitus (5%), hypertension (26%) and family history of glaucoma (2%). Majority (72%) Had habit of smoking, 5% had significant biomass fuel exposure.

Table 2:- Intraocular Pressure.

		N	Mean ± SD	Mean difference ± SD	t	P VALUE
Pair 1	INTRA OCULAR PRESSURE (mmHg) BASELINE RE	100	14.34±1.73	-0.1±0.61	-1.67	0.098
	INTRA OCULAR PRESSURE (mmHg) 1 MONTH RE	100	14.44±1.6			
Pair 2	INTRA OCULAR PRESSURE (mmHg) BASELINE RE	100	14.34±1.73	-0.34±0.75	-4.53	**<0.001**
	INTRA OCULAR PRESSURE (mmHg) 3 MONTH RE	100	14.68±1.48			
Pair 3	INTRA OCULAR PRESSURE (mmHg) 1 MONTH RE	100	14.44±1.6	-0.24±0.65	-3.65	**<0.001**
	INTRA OCULAR PRESSURE (mmHg) 3 MONTH RE	100	14.68±1.48			
Pair 4	INTRA OCULAR PRESSURE (mmHg) BASELINE LE	100	14.2±1.67	-0.1±0.69	-1.38	0.17
	INTRA OCULAR PRESSURE (mmHg) 1 MONTH LE	100	14.29±1.68			
Pair 5	INTRA OCULAR PRESSURE (mmHg) BASELINE LE	100	14.2±1.67	-0.24±0.84	-2.87	**0.005**
	INTRA OCULAR PRESSURE (mmHg) 3 MONTH LE	100	14.44±1.52			
Pair 6	INTRA OCULAR PRESSURE (mmHg) 1 MONTH LE	100	14.29±1.68	-0.14±0.57	-2.52	**0.013**
	INTRA OCULAR PRESSURE (mmHg) 3 MONTH LE	100	14.44±1.52			

On comparison of the mean values of INTRA OCULAR PRESSURE (mmHg) BASELINE RE and INTRA OCULAR PRESSURE (mmHg) 1 MONTH RE the mean values of INTRA OCULAR PRESSURE (mmHg) 1 MONTH RE is higher with a difference of 0.102 is statistically not significant with a p value of 0.098.

On comparison of the mean values of INTRA OCULAR PRESSURE (mmHg) BASELINE RE and INTRA OCULAR PRESSURE (mmHg) 3 MONTHS RE the mean values of INTRA OCULAR PRESSURE (mmHg) 3 MONTHS RE is higher with a difference of 0.341 is statistically significant with a p value of <0.001.

On comparison of the mean values of INTRA OCULAR PRESSURE (mmHg) 1 MONTH RE and INTRA OCULAR PRESSURE (mmHg) 3 MONTHS RE the mean values of INTRA OCULAR PRESSURE (mmHg) 3 MONTHS RE is higher with a difference of 0.239 is statistically significant with a p value of <0.001.

On comparison of the mean values of INTRA OCULAR PRESSURE (mmHg) BASELINE LE and INTRA OCULAR PRESSURE (mmHg) 1 MONTH LE the mean values of INTRA OCULAR PRESSURE (mmHg) 1 MONTH LE is higher with a difference of 0.096 is statistically not significant with a p value of 0.17.

On comparison of the mean values of INTRA OCULAR PRESSURE (mmHg) BASELINE LE and INTRA OCULAR PRESSURE (mmHg) 3 MONTH LE the mean values of INTRA OCULAR PRESSURE (mmHg) 3 MONTH LE are higher with a difference of 0.24 is statistically significant with a p value of 0.005.

On comparison of the mean values of INTRA OCULAR PRESSURE (mmHg) 1 MONTH LE and INTRA OCULAR PRESSURE (mmHg) 3 MONTH LE the mean values of INTRA OCULAR PRESSURE (mmHg) 3 MONTH LE is higher with a difference of 0.144 is statistically significant with a p value of 0.013.

Discussion:-

This study was conducted in Government Medical College Kannur which is a tertiary care centre in northern Kerala over a period of 1 year from March 2020 to March 2021.

In the study it was seen that majority of patients with COPD was in age group 61-70 years accounting for 51% of study population followed by age group 71-80 years accounting for 22%.According to study conducted in UK mean age at COPD diagnosis decreased from 68.1 years in 2000 to 66.7 years in 2009 [6].In another study from Japan median age is 72 years [7].

In our study, there was male preponderance with 88% males. According to gender specific estimates of COPD, prevalence of COPD 9.23% in men and 6.16% in women [8]. The pooled prevalence for COPD at 9.8% among men and 5.6% among women [9].

It was found that 36% were underweight in our study. Like in other studies around 20-50% were underweight.Among patients with FEV_1 of less than 35% predicted, 50% were undernourished. The severity of airway obstruction increases the risk of undernutrition. Further stratification showed that in case of severe COPD, BMI was a significant independent predictor of all-cause mortality [10].

In our study cough was present in 37% at presentation. An international survey conducted showed 46% of patients had daily cough.Cough rates were very high during the acute phase and correlated with both systemic and airway measures of inflammation. However, after antibiotic treatment, cough rates were decreased and correlated with sputum volume, but not with inflammatory markers [11]

All patients had breathlessness in our study. The level of dyspnea was categorized based on MMRC grading. Around 38% had grade 1 dyspnea and 22% had grade 2 dyspnea on exertion.A COPD cohort was identified in the Clinical Practice Research Datalink (CPRD), an anonymized collection from general practices in England and Wales managed by the Medicines and Healthcare products Regulatory Agency.Mild dyspnea (MRC=2; equal to mMRC 1) was the most frequently reported single grade (38%); 44% of patients were classified as having moderate-to-severe dyspnea (MRC≥3, equal to mMRC≥2) [12].

Prevalence of DM among our study population was 5%. The reported prevalence of diabetes among patients with COPD ranges from 1.6 to 16%. As in COPD, smoking has been established as a risk factor for diabetes, quitting for more than 5 to 10 years mitigates that risk [13] Prevalence of hypertension in study population was 26%. A significant relationship was found between COPD and the presence of comorbid HTN. Prevalence of hypertension in COPD subjects was 37.25% [14].

Majority of patients were smokers in our study.47% former smokers and 25% current smokers.28% were nonsmokers. Among COPD patients, current smokers' prevalence is between 33.6% and 47.2%. Moreover, current smoking prevalence has been found to be higher among COPD patients compared to healthy individuals in international studies [15]. Passive smoking and biomass fuel exposure may have contributed to development of COPD in nonsmokers.

Majority of patients had a COPD assessment test score in range of 10-20 followed by 21-30 in the study. Range of CAT scores from 0–40. Higher scores denote a more severe impact of COPD on a patient's life. Several studies were done previously.The mean CAT score was 19.61±8.07 SD. The correlation between the severity of smoking and GOLD classification was significant (p=0.006). There was a significant association between the FEV1 Predicted and total CAT score [16] .

Effect of tiotropium inhaler on intraocular pressure at baseline, 1 month and 3 month was compared in our study. Mean value of IOP of right eye at baseline, 1 month and 3 month were 14.34, 14.44 and 14.68. Mean value of IOP of left eye were 14.2, 14.29 and 14.44. Mean values of intraocular pressure at baseline, 1month and 3 month was compared. The results showed statistically significant difference between baseline and 3month, 1 month and 3 month, but no statistical significance between baseline and 1 month.

A Study conducted by Dr. Amit Kumar Verma on 'Effect of inhaled tiotropium on intraocular pressure in patients of chronic obstructive pulmonary disease". The intraocular pressure were measured at baseline, 1month and 3 month

follow up period for 65 patients and 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 (5).

Limitation:
Our study included only 100 patients. Sample size was not attained due to current Covid situation. Although Schiotz tonometer is cheap and handy to use, it gives a false reading when used in eyes with abnormal scleral rigidity. Errors of indentation tonometry can occur due to contraction of extraocular muscles, ocular rigidity and due to accommodation of eye.

Conclusion:-

This study was conducted on 100 diagnosed COPD patients. Exclusion was done for patients with glaucoma, benign prostatic hypertrophy, long term oral corticosteroids and coronary artery disease.

Effect of tiotropium inhaler on intraocular pressure at baseline, 1 month and 3 month was compared in our study. Mean values of intraocular pressure at baseline, 1month and 3 months were compared. The results showed statistically significant difference between baseline and 3month, 1 month and 3 months, but no statistical significance between baseline and 1 month. This has to be proven by further studies as only limited studies are currently available. We recommend checking IOP atleast 3 months after starting an inhaled anticholinergic.

References:-

1.Global strategy for diagnosis, management and prevention of chronic obstructive pulmonary disease .2020 report. Page no: 4
2. Soriano JB, Abajobir AA, Abate KH, Abera SF, Agrawal A, Ahmed MB, et al. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017 Sep;5(9):691–706.
3. Salvi S, Kumar GA, Dhaliwal RS, Paulson K, Agrawal A, Koul PA, et al. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018 Dec;6(12):e1363–74.
4. Arjun P, Nair S, Jilisha G, Anand J, Babu V, Moosan H, et al. Assessing health-seeking behavior among Asthma and COPD patients in urban South India. J Fam Med Prim Care. 2019 Aug 28;8(8):2714–9.
5. Verma DAK, Alam DN, Sahu DPK, Narang DS, Maroof DKA. EFFECT OF INHALED TIOTROPIUM ON INTRAOCULAR PRESSURE IN PATIENTS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE. Int J Sci Res [Internet]. 2019 Nov 6 [cited 2021 Sep 19];8(10). Available from: http://worldwidejournals.org/index.php/ijsr/article/view/518
6. James GD, Donaldson GC, Wedzicha JA, Nazareth I. Trends in management and outcomes of COPD patients in primary care, 2000–2009: a retrospective cohort study. Npj Prim Care Respir Med. 2014 Nov;24(1):14015.
7. Nakayama M, Satoh H, Sekizawa K. Risk of Cancers in COPD Patients. Chest. 2003 May;123(5):1775–6.
8. Ntritsos G, Franek J, Belbasis L, Christou MA, Markozannes G, Altman P, et al. Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2018 May;Volume 13:1507–14.
9. Han MK, Postma D, Mannino DM, Giardino ND, Buist S, Curtis JL, et al. Gender and Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2007 Dec 15;176(12):1179–84.
10. King DA, Cordova F, Scharf SM. Nutritional Aspects of Chronic Obstructive Pulmonary Disease. Proc Am Thorac Soc. 2008 May 1;5(4):519–23.
11. Smith J, Woodcock A. Cough and its importance in COPD. Int J Chron Obstruct Pulmon Dis. 2006 Sep;1(3):305–14.
12. Müllerová H, Lu C, Li H, Tabberer M. Prevalence and Burden of Breathlessness in Patients with Chronic Obstructive Pulmonary Disease Managed in Primary Care. PLoS ONE. 2014 Jan 10;9(1):e85540.
13. Stojkovikj J, Zafirova-Ivanovska B, Kaeva B, Anastasova S, Angelovska I, Jovanovski S, et al. The Prevalence of Diabetes Mellitus in COPD Patients with Severe and Very Severe Stage of the Disease. Open Access Maced J Med Sci. 2016 Jun 15;4(2):253–8.
14. Mahishale V, Angadi N, Metgudmath V, Eti A, Lolly M, Khan S. Prevalence and impact of diabetes, hypertension, and cardiovascular diseases in chronic obstructive pulmonary diseases: A hospital-based cross-section study. J Transl Intern Med. 2015;3(4):155–60.

15. Karadogan D, Onal O, Sahin DS, Kanbay Y. Factors associated with current smoking in COPD patients:A cross-sectional study from the Eastern Black Sea region of Turkey. Tob Induc Dis. 2018 May 22;16:22.
16. Ghobadi H, Ahari SS, Kameli A, Lari SM. The Relationship between COPD Assessment Test (CAT) Scores and Severity of Airflow Obstruction in Stable COPD Patients. Tanaffos. 2012;11(2):22–6.