# A Case Control Study on Risk Factors and Drug Prescription Patterns in Glaucoma at a tertiary eye care center in a city of Western India

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**Abstract:**

**Introduction:** Glaucoma is an idiopathic, progressive optic disc neuropathy complicating into irreversible blindness if untreated. Early diagnosis by screening cases from high-risk populations has a pivotal role in managing this major public health problem with high treatment expenditures. **Objectives:** To identify the various ocular and non ocular risk factors of glaucoma and to identify the drug prescription pattern among glaucoma patients. **Method:** This was an observational, case-control study including 165 adult Glaucoma patients on treatment as cases and 165 age and sex-matched healthy individuals as controls, all of which were randomly selected from the patients visiting a tertiary eye care center. Various risk factors, drug prescription pattern and symptoms of the patients were recorded and analyzed. **Results**: A total of 165 adult Glaucoma patients and age and gender matched 165 controls were enrolled. Majority of the patients (41.21%) complained of blurring of vision at the time of study. The Odds ratios for Family history, Hypertension, Diabetes Mellitus, Migraine, Sleep apnea and Smoking showed strong association as risk factors for Glaucoma and the differences between the two groups were statistically significant (p value < 0.05). The mean number of drugs per prescription ± SD was 1.88 ± 0.79. Fixed drug formulations were prescribed in 42.4% patients. All the drugs were prescribed by their brand names and majority of them were in the form of eye drops. **Conclusion**: Primary Open Angle Glaucoma (POAG) was the most common subtype in the study. Age, Family history, Myopia, Hypertension, Diabetes Mellitus, Sleep Apnea, Migraine, Corticosteroid usage and Smoking emerged as putative risk factors. In consistence with present guidelines, Prostaglandin analogs were the most prescribed antiglaucoma drugs. The considerable proportion of asymptomatic cases (23%) suggests the need for periodic eye examinations to detect glaucomatous changes at an early stage.

**Keywords:** Drug Prescription Patterns,Glaucoma, Intraocular Pressure, Risk Factors

## Introduction:

Glaucoma is a multifactorial, idiopathic, progressive optic disc neuropathy leading to irreversible blindness if not treated -aptly entitled the 'silent thief of sight'.[1, 2] Open Angle Glaucoma is the commonest type (~90%), others including Angle Closure Glaucoma and Normal Tension Glaucoma.

Risk factors for Glaucoma include elevated Intraocular Pressure (IOP>21 mm Hg), a positive family history, Myopia, Hypertension, Diabetes Mellitus etc. Open Angle Glaucoma ensues due to inadequate drainage of aqueous humor through the trabecular meshwork, while in Angle Closure Glaucoma the iris apposes against the trabecular meshwork.[3]

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Workup includes IOP estimation by Tonometry,[4] Iridocorneal angle assessment by Gonioscopy and fundus examination for Cup-to-Disc Ratio (CDR) and vascular changes. Glaucoma is the second leading cause of blindness worldwide with around 12 million patients in India.[5,6] A large proportion of patients come from the elderly age group who generally ignore it as an age-related inevitability.[7] Early diagnosis and treatment plays a very important role in management.[7.8]

Various drugs including Prostaglandin (PG) analogs, β-blockers, α2 agonists, Miotics and Carbonic anhydrase inhibitors are used in the treatment of Glaucoma. Depending on the CDR and other parameters, Glaucoma is categorized as mild, moderate and severe and accordingly a target IOP range which prevents further damage is decided.[9] PG analogs are introduced first in the treatment regimen, due to their long duration of action, good IOP lowering action and once-daily dosing.[10] In case of poor control with PG analogs, drugs from other classes/drug combinations are added as required.

With rising treatment costs and an aging population, Glaucoma is becoming a major public health problem.[11] Hence we decided to undertake this study to assess the presence of various ocular and systemic risk factors in Glaucoma patients versus controls and to analyze drug utilization patterns in Glaucoma patients.

**Method:**

This was an observational, case-control study carried out at a tertiary care eye hospital for a period of 3 months in the year 2019. Total 165 Cases attended the Glaucoma unit during the study duration. Sampling technique used was Purposive. Adult patients suffering from any type of Glaucoma on treatment, willing to give informed consent were enrolled as cases. They underwent a comprehensive ophthalmological examination consisting of Slit lamp examination, Gonioscopy, Non-contact Tonometry (NCT), fundus evaluation, Pachymetry and optic disc photography. In Gonioscopy, anterior chamber was classified according to Schaeffer's grading. [12] Grades 3 and 4 were considered as 'Open angle' while angles of Grade 2 and less were considered as 'Occludable'. Demographic details, chief complaints, clinical diagnosis, medical history and drug prescriptions were noted with a detailed focus on the presence of risk factors.

Age and sex-matched healthy adult individuals not having Glaucoma and consenting to participate were enrolled as controls and subjected to detailed history taking and examination. Total 165 control were included in the study.

Variables and risk factors assessed in the study participants were; Ocular measurements [e.g. IOP, Central corneal thickness (CCT), CDR], Family history, Spherical refractive error, Systemic disorders (e.g. Hypertension, Diabetes Mellitus, Hypothyroidism), Sleep apnea, Migraine, Smoking, Use of corticosteroids etc. The prescription pattern was recorded and analyzed in detail including data on dosage form, route of administration, single/combination therapy etc.

**Results:**

A case control study was conducted among 165 cases (glaucoma) and 165 Controls (without glaucoma) at a tertiary eye care center, after obtaining their informed consent.

Table 1 depicts the age and gender distribution among enrolled cases and controls.

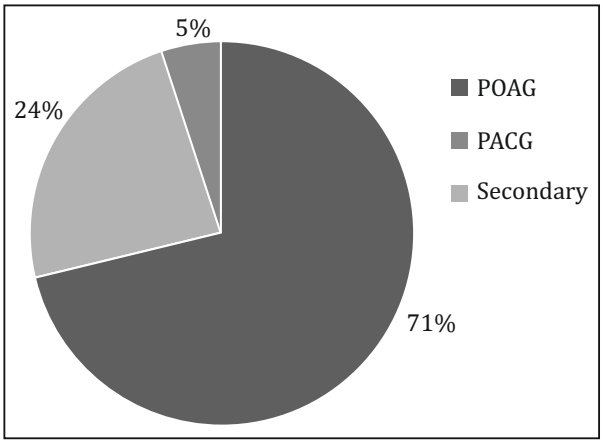
In case of symptomatology, majority of the patients (41.21%) complained of blurring of vision, other complaints being watering (24.8%), redness in the eye (26%) etc. There were 23.03% cases in which the diagnosis was accidental where the patients did not show any symptoms of the disease.

**Table 1 : Age and Gender wise Distribution of Study Participants**

| Variables | Cases (n=165) * (%) | Controls (n=165) * (%) |
|---|---|---|
| **Age groups (in years) (Mean age: 56.31 ± 13.49 years)** | | |
| 18-20 | 6 (3.64) | 5 (3.03) |
| 21-30 | 2 (1.21) | 4 (2.42) |
| 31-40 | 12 (7.28) | 9 (5.46) |
| 41-50 | 26 (17.76) | 28 (16.97) |
| 51-60 | 48 (29.09) | 48 (29.09) |
| 61-70 | 55 (33.33) | 55 (33.33) |
| >70 | 16 (9.7) | 16 (9.7) |
| **Gender** | | |
| Male | 103 (62.42) | 100 (60.6) |
| Female | 62 (37.58) | 65 (39.4) |

Glaucoma being a chronic disease, the history of glaucoma in the patients ranged from being as fresh as less than a year to being as old as 20 years. Majority of the patients (60%) had duration of disease between 1-5 years. Figure 1 shows the distribution of various subtypes of Glaucoma amongst the patients.

**Figure 1 : Distribution of various subtypes of Glaucoma in the patients**




PACG- Primary Angle Closure Glaucoma, POAG- Primary Open Angle Glaucoma, Secondary glaucoma due to Vitreous degeneration, Retinal detachment, Corticosteroid usage

**Risk factor assessment:**

**A) OCULAR VARIABLES:**

IOP was found to be raised in 53(32.12 %) patients despite treatment. The highest value recorded was 46 mm Hg (Mean- 32 ± .6 mm Hg, Normal-10 to 21 mm Hg). CCT was measured by Pachymetry and was found to be low in 134 (81.21%) patients. CDR was also found to be high in 134 (81.21%) of the patients. (Normal value: d" 0.4) CDR asymmetry- difference in CDR of both eyes >0.2 was found to be present in 34 (20.6%) patients. IOP and CDR were normal in all controls.

**B) SYSTEMIC RISK FACTORS:**

Table 2 shows the analysis of systemic risk factors. The Odds ratios for Smoking, Migraine, Family history, Sleep apnea, Diabetes Mellitus Hypertension and Myopia showed significant association of these as risk factors for Glaucoma and the differences between the two groups were statistically significant.

**Table 2 : Systemic Risk Factors Among Cases And Controls**

| Systemic Risk Factors | CASES (n=165) *(%) | CONTROLS (N=165) *(%) | Chi-Square, p Value* Odds Ratio (OR) |
|---|---|---|---|
| Smoking | 11 (6.7%) | 2 (1.21%) | $\chi^2$=6.486 (df=1); **p=0.011; OR=5.82** |
| Migraine | 30 (18.2%) | 9 (5.45%) | $\chi^2$=12.923 (df=1); **p=0.0003; OR=3.85** |
| Family history | 40 (24.2%) | 16 (9.69%) | $\chi^2$=12.830 (df=1); **p=0.0004; OR=2.98** |
| Sleep apnea | 52 (31.5%) | 25 (15.15%) | $\chi^2$=12.388 (df=1); **p=0.0004; OR=2.58** |
| Diabetes Mellitus | 41 (24.8%) | 21 (12.73%) | $\chi^2$=7.994 (df=1); **p=0.0048; OR=2.267** |
| Hypertension | 56 (33.9%) | 32 (19.39%) | $\chi^2$=9.75 (df=1); **p=0.0046; OR=2.032** |
| Myopia | 113 (68.5%) | 93 (56.36%) | $\chi^2$=5.167 (df=1); **p=0.023; OR=1.682** |
| Use of corticosteroids | 8 (4.85%) | 2 (1.21%) | **p=0.1041** (by Fisher's exact test); OR=2.75 |
| Hypothyroidism | 4 (2.43%) | 11 (6.67%) | $\chi^2$=3.422 (df=1); **p=0.064; OR=0.35** |

*p-value<0.05 was considered as statistically significant

**Drug Prescription Pattern:**

A total of 292 drug formulations were prescribed to 165 patients. The mean number of drugs per prescription ± SD was 1.88 ± 0.79.

**Table 3 : Drug Prescription Pattern of Antiglaucoma medications among cases (n=165)**

| Antiglaucoma Drug/ FDC | Number of patients prescribed* (%) |
|---|---|
| Prostaglandin Analogs (Bimatoprost, Travoprost, Latanoprost) | 131 (79.39%) |
| Brimonidine and Timolol | 52 (31.51%) |
| Brimonidine | 26 (15.76%) |
| Brinzolamide | 18 (10.9%) |
| Dorzolamide | 17 (10.3%) |
| Timolol | 14 (8.48%) |
| Brimonidine and Brinzolamide | 10 (6.06%) |
| Betaxolol | 7 (4.24%) |
| Travoprost and Timolol | 7 (4.24%) |
| Dorzolamide and Timolol | 4 (2.42%) |
| Pilocarpine | 2 (1.21%) |
| Oral Acetazolamide | 1 (0.61%) |
| Mannitol I.V. | 1 (0.61%) |

*Multiple responses

The most common antiglaucoma drug class prescribed was Prostaglandin analogs in 131(79.39%) patients. The most commonly prescribed FDC was Brimonidine + Timolol in 52(31.52%) patients. (Table 3)

While in case of other drugs, the most commonly prescribed drug formulation was Carboxymethyl cellulose in 15(9.09%) patients. Majority of the patients were prescribed dual therapy (47.27%).

**Discussion:**

In this study, 165 patients and 165 controls enrolled with a male: female ratio of 1.66 and 1.54 respectively. The mean± SD for age of patients was 56.31 ± 13.49 years.

These findings are similar to the studies carried out in Maharashtra[13], Brazil[14], Karnataka[15], Gujarat[16] and Uttar Pradesh[17] It has been

documented that incidence of Glaucoma rises with age.[18] This is because of decreased ganglion cell number as well as their rising vulnerability to IOP related insults.The most common presenting symptom of the patients was blurring of vision (41.21%) - this finding is in consistence with the studies conducted in Maharashtra[13] and Madhya Pradesh.[19] However, the proportion of patients with ocular pain and headache was higher compared to the study undertaken in Madhya Pradesh.[19]

A large portion of Glaucoma remains undiagnosed. In present study also, a significant proportion (23.03%) of patients were asymptomatic and were diagnosed accidentally when they came for a routine eye examination. This suggests that screening will help in exploring the hidden portion of iceberg in this disease.

Majority of the patients (71.52%) were suffering from POAG. These results are similar to those obtained in the studies done at Ahmedabad,[16] Uttar Pradesh[17] and Mangalore.[20] However, in a study done in Madhya Pradesh[19], PACG emerged as the most common subtype and proportion of secondary glaucoma patients was also higher. In this study, 75.8% patients had Glaucoma for duration greater than a year, which is very high compared to the value obtained in the South Korea study.[21]

First-degree relatives of patients with POAG have a 10 times greater risk of having the disease.[22] A study in Lucknow[23] also showed a strong association of POAG to family history with OR 4.22. In this study, family history emerged as an important risk factor with OR of 2.98 and the difference between the two groups was statistically significant. 24.2% of the patients had a positive family history of glaucoma. This value is lower than that obtained in the study conducted in Brazil[14] and much higher than those obtained in the studies carried out in Madhya Pradesh[19] and South Korea.[21] Majority of the patients had a positive family history of Glaucoma pertaining to siblings.

Myopia is also a significant risk factor for glaucoma.[24] Similar findings were obtained in this study, with OR =1.68 which was statistically significant. The proportion of myopic glaucoma patients in this study is substantially higher as compared to the studies done in Brazil[14] and Madhya Pradesh.[19]

Hypertension emerged as a statistically significant risk factor for Glaucoma with OR of 2.03. 33.9% patients in the study were known cases of hypertension on treatment. This value is much higher than that obtained in the study carried out in Madhya Pradesh.[19] While the study in Brazil showed even greater proportions of hypertensive glaucoma patients.[14] Blood pressure is a clinically modifiable risk factor and has a profound potential for new treatment strategies.[24]

Diabetes Mellitus was also found to be a major risk factor in this study with OR= 2.27 and difference between cases and controls was statistically significant, which is similar to the Lucknow study on POAG.[23] The higher incidence of glaucoma in diabetics could also be because of the fact that they frequently undergo regular eye examinations for retinal conditions and hence the odds of detection are higher in such patients.[19]

Glaucoma patients and their close relatives are said to have higher corticosteroid responsiveness and hence it is necessary to educate the patients who are prescribed such drugs, not to continue their administration for periods further than those specified by the prescriber. Similar to the study done in Lucknow[23], the Odds ratio showed strong association but it was statistically insignificant. This is likely due to the lesser number of patients with steroid-induced glaucoma in this study. Hence, studies with evenly distributed cases are required for a better picture.

It has been found that people with Sleep apnea have 1.67 times more risk of development of glaucoma.[12] In our study also, in case of Sleep apnea an OR of 2.58 showed a strong positive association

which was statistically significant. In this study, Smoking was also found to be a major risk factor for Glaucoma with OR 5.82 which was statistically significant. 6.7% of the enrolled patients were found to be smokers, which is similar to the findings of the study done in Madhya Pradesh.[19]

It has been documented that hypothyroidism may lead to Glaucoma by hyaluronate like substances blocking the trabecular meshwork and levothyroxine therapy normalizes IOP in such patients.[25,26] Hypothyroidism could not be established as a risk factor in this study, with OR <1 and P-value >0.05. The study carried out at Lucknow also did not find thyroid dysfunction as a significant risk factor. [23]

The mean number of drugs per prescription ± SD was 1.88 ±0.79 which is lower than the value obtained in the study carried out at Mangalore[20] and higher than those obtained in the studies of Uttar Pradesh[17] and Central India.[27] This is because our study was conducted in a tertiary care eye hospital where many patients already on treatment with uncontrolled disease are referred.

The most common antiglaucoma drug class prescribed was Prostaglandin analogs, which is in consistence with the latest guidelines enlisting them as first line drugs, overshadowing topical β-blockers which might be prescribed due to cost considerations. Brimonidine + Timolol was the most commonly prescribed FDC in this study, similar to the studies carried out in Karnataka[15], Ahmedabad[16] and Uttar Pradesh.[17] However, Timolol was the most prescribed drug as monotherapy in a few other studies.[15,27] Out of the Prostaglandin analogs, Bimatoprostis prescribed more because of lower cost and single bedtime instillation.[28] Moreover, Latanoprost requires refrigeration for storage.[29]

Almost all of the drugs prescribed in this study were in the form of eye drops, which supports the use of topical formulations owing to their site-specific action, lesser systemic absorption and fewer adverse effects. However, all the drugs were prescribed by their brand names. Many clinicians do not rely on the bioavailability of generic drugs-hence it needs to be ensured that generic drugs meet the essential quality standards. This is of paramount importance in Glaucoma as the cost of treatment is pretty high.

Total 42.4% of the patients in this study were prescribed fixed dose formulations. This leads to improved compliance and convenience due to lesser number of instillations as compared to concurrent use of separate medications.[30]

**Conclusion:**

Age, Family history, Myopia, Hypertension, Diabetes Mellitus, Sleep Apnea, Migraine, Corticosteroid usage and Smoking emerged as putative risk factors. POAG was the most common diagnosis. In consistence with guidelines, Prostaglandin analogs were the most prescribed antiglaucoma drugs. The considerable proportion of asymptomatic cases suggests the need of periodic eye examinations to detect glaucomatous changes at an early stage.

**Limitations of the study:**

Compliance to medications prescribed to the patients was not studied. Cost and side effects related data pertaining to drug prescription was not analyzed.

**Recommendations:**

This study aimed to fill the gaps in data regarding the association of various risk factors and drug prescription patterns in Indian patients suffering from Glaucoma. However, community-based studies with a larger sample size may further aid in bringing out the finer details of the same. Screening of family members of Glaucoma patients above the age of 30 for the presence of other risk factors and their tracking will lead to an earlier diagnosis and will aid in development of preventive strategies. Educating the patients regarding compliance to treatment has a pivotal role in preventing complications like blindness.

**Declaration:** DrSanket Bharadwaj, DrKavisha Goswami and DrShahnoor Gowani were interns at the time of conduction of study and they have worked under the guidance of DrReemaRaval and Dr Kintu Shah in the Glucoma Unit of C.H. Nagri Eye Hospital, Ahmedabad.

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