# Evaluation of Drug Use with a Focus on Prostaglandin Analogues and Assessment of Medication Adherence and Quality of Life in Patients with Primary Open Angle Glaucoma: A Prospective Study at a Tertiary Care Eye Hospital.

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## Abstract
**Background:** Glaucoma, a chronic, progressive and most often asymptomatic disease 2nd leadingcause of irreversible blindness. Objectives: To study the drug use pattern in patients of Glaucoma, to evaluate the safety aspect with preservative or preservative free drugs, to evaluate quality of lifeusing the National Eye Institute Visual Function Questionnaire (NEI-VFQ25) and to evaluatemedication adherence using Glaucoma Treatment Compliance Assessment Tool (GTCAT). **Materials and Method:** Prospective observational follow up study was carried out for 18 months. IEC permission and Written Informed Consent from the patients were taken before hand. Patients above 18 years of age and of either gender and diagnosed with POAG and were on medication for past three months were included in the study. **Results:** In a total of 312 patients, POAG was prevalent in age group of 51-60 years. A total of 102(32.7%) patients were on monotherapy whilerest 210(67.3%) were prescribed combination. Most commonly used preservative wasBenzalkonium chloride. Bimatoprost caused a significantly higher mean percent reduction in IOP than Latanoprost and Travoprost, when compared to baseline values. The Bimatoprost had a significantly higher percentage of adverse events compared to the Latanoprost, but no significant difference found when compared to Travoprost. **Conclusion:** Travoprost was most frequently prescribed. Drugs containing preservative BAK were reported higher incidence of ocular sideeffects when compared to preservative free eye drops. Nearly half of the patients were adherent totheir antiglaucoma medications.
**Keywords:** Adherence, Drug use pattern, Glaucoma Treatment Compliance Assessment Tool(GTCAT), NEI-VFQ-25, PG analogues, Quality of life

## Introduction
Glaucoma, a chronic, progressive, and most often asymptomatic disease, is the second leading cause of blindness.[1] In India, it is the leading cause of treatable irreversible blindness; it is estimated to become two-fold in next decade.[2] Drug therapy has revolutionized treatment of glaucoma both in terms of reduction in intraocular pressure (IOP) as well as damage to the optic nerve hence the drug utilization pattern of glaucoma needs to be analysed in a developing country like India. Periodic audit of prescription is essential to increase the therapeutic efficacy, to decrease adverse effects and to provide feedback to the prescribers.[3]Preservatives mainly used in most eye drops to provide a level of antimicrobial activity. Benzalkonium chloride (BAK) is the most common preservative used.[4] The study shows comparison of prostaglandin analogues (PGA) with preservative and preservative free drugs. For a successful glaucoma

treatment adherence with medications is a key component. The Glaucoma Treatment Compliance Assessment Tool (GTCAT), shows excellent repeatability, content, construct, and predictive validity for glaucoma adherence.[5] Preservation of patients' visual function and quality of life (QoL) is the ultimate goal of glaucoma management. It affects the QoL and superimposed on it are various anti glaucoma drugs that can also have a negative impact on QoL of the patient because of numerous adverse effects.[6]National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) is a reliable and widely used questionnaire to assess QoL.

## Aims and Objectives

1. To study the drug use pattern in patients diagnosed with primary open angle glaucoma.
2. To compare the efficacy among the prostaglandin analogues.
3. To evaluate the safety aspect with preservative or preservative free drugs.
4. To evaluate quality of life using NEI VFQ-25.
5. To evaluate medication adherence using GTCAT.

## Materials and Method

Ethics committee approval was obtained prior to commencement of the study. Patients presenting to the Outpatient department of Ophthalmologywere included in our study for the duration of 18 months. It was a prospective, observational, non-interventional, single centre, follow-up study.Patients 18 years and above belonging to either gender, diagnosed with Primary open angle Glaucoma (POAG), on topical antiglaucoma medications for past three months and who were willing to give their written informed consent were included in the study and patients with ocular comorbidities, secondary glaucoma, who were surgically treated for POAG, patients having psychiatric illness and with poor general condition were excluded. Once the ophthalmologist's consultation was over, the data of the patient enrolled was collected and the patients were subjected to the questionnaire for quality of life and assessmentmedicationadherence on subsequent follow up visit at 1 month and 2 months.

Data of every patient was entered in standard Case Record form.Patients were provided patient information sheet with detailed information of present study.Patient's detailed history was noted. Assessment of medication adherence was done by GTCAT which included 47 statements and a 5-interval Likert-type scale response with anchoring definitions. QoL was done using the interviewer-administered format of the NEI VFQ-25 questionnaires which included 25 items and 12 sub-scales.

The complete data was entered in Microsoft Excel version 2019. The statistical evaluation was done with the help of Statistical Package for Social Science (SPSS) version 23.0 manufactured by IBM (demo version) and Microsoft Excel 2019.Efficacy of Prostaglandin analogues was measured in individual group at every follow up by using paired t-test and among groups by using one-way ANOVA test.Safety of drugs with preservatives and preservative free drugs was measured using independent t-test, association of comorbidities with glaucoma and comparison between two drug groups was done using Fisher's exact test.Correlation between age, side effects and NEI-VFQ score was established using Pearson correlation. P value $<0.05$ considered statistically significant.

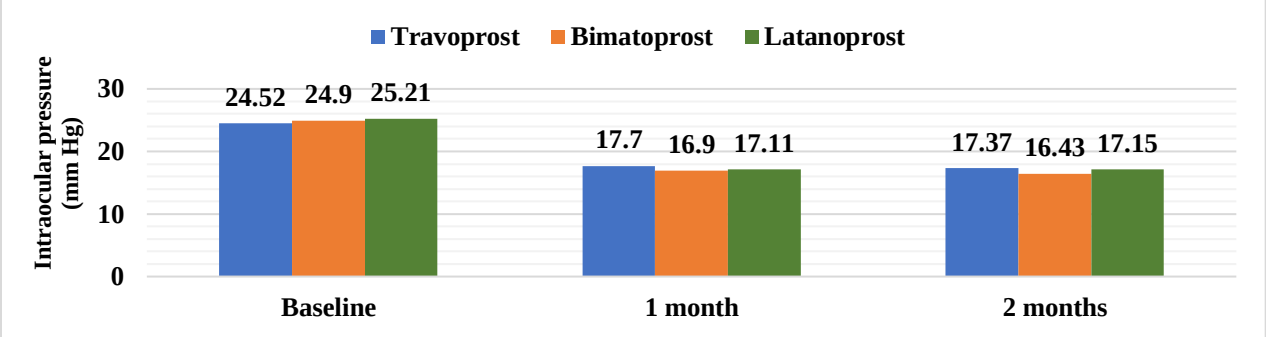
## Results

A total of 312 patients met the inclusion criteria of the study, of which 144(46%) were male and 168(54%) were female. Ratio of Male : Female = 0.86:1. POAG was prevalent in age group of 51-60 years (34.0%). The mean age of patients was 55.21± SD 12.59 years. All the patients enrolled in the study were having bilateral POAG, so total eyes examined were 624 eyes. Majority of the patients were asymptomatic at the time of enrolment, rest were presented with symptoms like decreased peripheral vision 97(31.1%) dimension of vision73(23.4%), ocular pain 60(19.2%), headache 22(7.1%) and redness16(5.1%). A total of 95(30.45%) patients had past history of ocular surgery, 48(20%) patients were having diabetes mellitus, 111(47%) patients were having hypertension. patients a total of 82(26%) had family history of glaucoma.

A total number of antiglaucoma drugs prescribed were 659 with a Mean ± SD = 2.11±0.93 per prescription. It ranged from 1 to 4 drugs per patient. A total of 102(32.7%) patients were on monotherapy while rest 210(67.3%) were prescribed combination of two or more antiglaucoma medications. Out of 102 patients with monotherapy most of them, 85(83.33%) were prescribed PGA, rest were given Beta blockers and Alpha-adrenergic agonists. All the medications were prescribed as a topical eye-drops. Most common class was PGA in 239(76.6%) patients both as a monotherapy as well as a combination with other medications followed by other drug classes. A total of 6 different types of FDCwere prescribed to 141(45.19%) patients, commonest was Brimonidine-Timolol combination givenin 72(23.07%). Most commonly used preservative in antiglaucoma drugs was Benzalkonium chloride (BAK) in 360(54.62%) drug formulations followed by oxychlorocomplex 108(16.39%).A total number of ocular side effects reported were 316 with Mean ± SD = 1.01±1.1. Most common ocular side effects were Itching 116(37.71%), followed by dry eye72(23.07%), burning38(12.17%), hyperemia36(11.53%), blurred vision19(23.07%), photophobia, allergy, stinging, eyelash changes and eyelid problems.No Systemic side effects were reported.

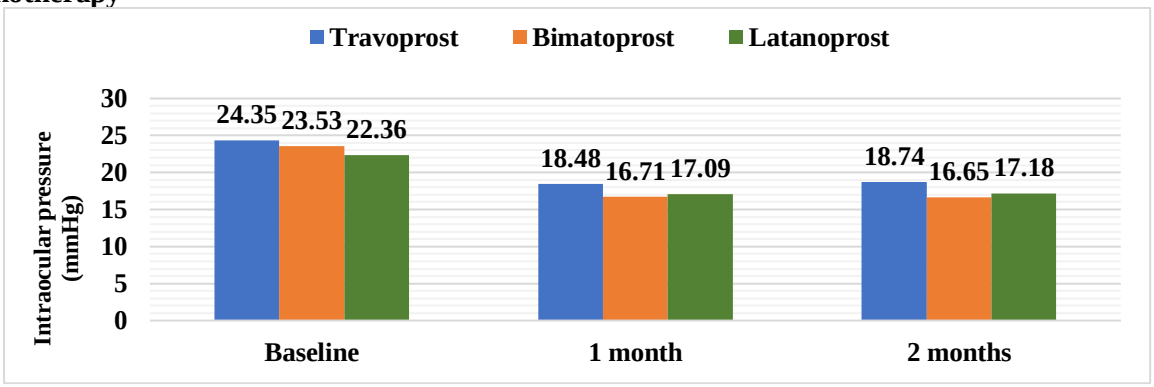
**PGA as a combination therapy:** Of 154 patients on combination therapy, 86 received Travoprost, 42 received Bimatoprost and 26 received Latanoprost. Mean reduction in IOP at 1 month and 2 months compared to baseline was statistically significant (p=0.0001) in all 3 groups (Figure 2). Mean reduction in IOP in each study group at 1 month was as following: Travoprost group (7.01 ± 2.45 mmHg), Bimatoprost group (7.47 ± 3.61 mmHg), and Latanoprost group (7.37 ± 3.14 mmHg). As a combination therapy with other anti-glaucoma drugs, all the 3 analogues were comparable in efficacy. (p = 0.42)

**Figure 1: Mean IOP at different time points in patients with PGA combination therapy**



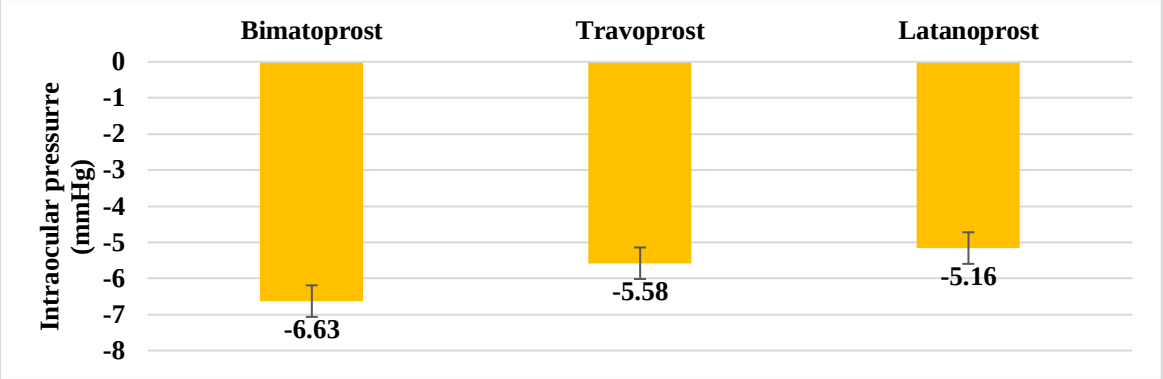

PGA as a monotherapy:Out of 85 patients on monotherapy therapy 41 received Travoprost, 32 received Bimatoprost and 12 received Latanoprost.The mean reduction in IOP (mmHg) at 1 month and 2 months compared to baseline was statistically significant (p=0.001) in all 3 groups. (Figure 2)

**Figure 2: Mean intraocular pressure at different time points in patients with Prostaglandin monotherapy**



The Bimatoprost group had a significantly higher mean reduction in IOP when compared to the Travoprost and Latanoprost groups. ($p < 0.007$) No significant difference in mean IOP reduction was found between Travoprost and Latanoprost. (p=0.336) Bimatoprost (28.20 ±3.5%) caused a significantly higher mean percent reduction in IOP than Latanoprost (23.15 ± 3.1%), Travoprost (22.8 ± 3.6%), when compared to baseline values. ($p < 0.007$) The mean reduction in IOP (mmHg) in each study group is shown in figure 3.

**Figure 3: Mean intraocular pressure reductions in patients with PGA monotherapy**




Ocular side effects observed in are presented in table 1. The Bimatoprost group had a significantly higher percentage of adverse events compared to the latanoprost group ($p = 0.04$), but no significant difference found when compared to Travoprost. (p=0.05)Latanoprost and Travoprost did not show any significant difference in adverse events. (p =0.4)

**Table 1: Ocular side effects in patients with Prostaglandin analogues as a monotherapy**

| **Ocular side effects** | **Travoprost (n=41)** | **Bimatoprost (n=32)** | **Latanoprost (n=12)** |
|---|---|---|---|
| Hyperaemia | 2(4.87%) | 9(28.12%) | 1(8.33%) |
| Dry eye | 5(12.19%) | 2(6.25%) | 0(0.0%) |
| Itching | 3(9.75%) | 4(12.5%) | 1(8.33%) |
| Blurred vision | 1(2.43%) | 0(0.0%) | 0(0.0%) |
| Trichiasis | 0(0.0%) | 1(3.12%) | 0(0.0%) |
| **Total** | **11(26.82%)** | **16(53.12%)** | **2(16.67%)** |

Out of 85 patients who were on monotherapy, 42(49%) were prescribed drugs containing preservatives while 43(51%) received preservative free drugs. Patients with preservativesdrugs had higher incidence of side effects (45.23%) than preservative free drug group (23.25%). Significant difference was found between these two drug groups. (p=0.004) The mean reduction in IOP (mmHg) at 1 month and 2 months compared to baseline was statistically significant in each of the groups: drugs with preservative (p=0.002) and preservative free drugs. (p=0.003)A significant difference in mean IOP reduction was found between the two groups at each follow up visit of 1 and 2 months.

**Table 2: Mean IOP values at each visit**

| **Follow up** | **Drugs containing preservative** | **Preservative free drugs** | **p-Value** |
|---|---|---|---|
| Baseline | 25.10±6.5 mmHg | 25.94±4.3 mmHg | 0.515 |
| 1 month | 24.91±3.9 mmHg | 22.88±2.8 mmHg | **0.008*** |
| 2 months | 19.2±4.1 mmHg | 17.1±2.57 mmHg | **0.12*** |

*P value <0.05 considered significant

In our study we used GTCAT which contains 9 domains: Table 3 represents the mean percentage of responses in each domain given by all patients.

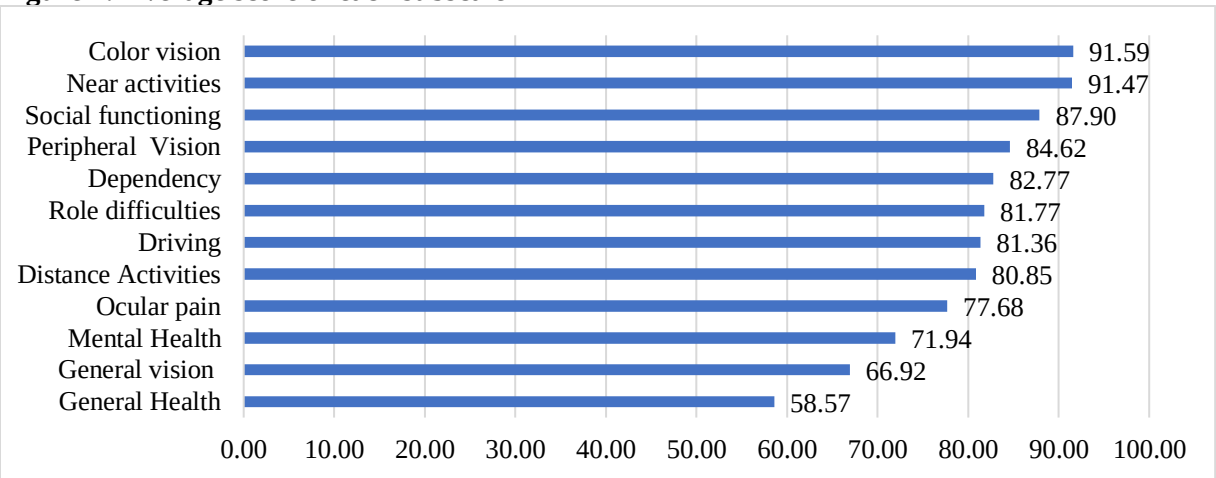
**Table 3: Domain wise mean percentage of responses in patients**

| Sr. no. | Domains | 1 Disagree a lot (lowest score) | 2 Disagree a little | 3 No opinion | 4 Agree a little | 5 Agree a lot (highest score) |
|---|---|---|---|---|---|---|
| 1 | Self-report adherence | 38.46% | 10.58% | 1.28% | 1.60% | 48.08% |
| 2 | Barriers | 57.69% | 4.13% | 1.88% | 8.77% | 27.52% |
| 3 | Benefits | 0.85% | 0.00% | 8.44% | 3.42% | 86.75% |
| 4 | Cues-to-action | 53.21% | 0.00% | 41.35% | 0.00% | 5.45% |
| 5 | Knowledge | 19.63% | 1.33% | 48.50% | 7.45% | 23.10% |
| 6 | Self-efficacy | 6.94% | 1.34% | 29.11% | 3.74% | 58.87% |
| 7 | Severity | 11.54% | 3.93% | 15.38% | 2.40% | 66.75% |
| 8 | Susceptibility | 4.81% | 0.16% | 21.85% | 4.91% | 68.06% |
| 9 | Patient-physician relationship | 0.00% | 0.00% | 1.28% | 2.67% | 96.05% |

Out of 312 patients, about half of them were adherent to their antiglaucoma medications, about 36.30% were facing different barriers for taking their antiglaucoma medications, about 82.05% patients felt that their eye drops were not reasonably priced, almost 90.30% were knew the benefits of taking their antiglaucoma medications, about 42.63% used reminders for taking their medications. Around half of them had a knowledge regarding glaucoma as a disease, nearly 84.29% didn't know whether they can do any things to control or prevent their disease and about 86.28% were self-efficient for using their eye drops. About 68.06% aware of the severity of glaucoma and 66.75% patients aware of their susceptibility regarding glaucoma. About 96.05% patients were satisfied with their treating ophthalmologist and the treatment prescribed.

We recorded the response of the patients at 1 month follow up. The subscale wise average score is depicted in figure 4. The lowest possible score was 0 and the highest score was 100.

**Figure 4: Average score of each subscale**




An average composite score of all patients was 80.73±17.33. A total of 34(10.89%) scored between 0 to 60, almost half of the patients 162(51.92%) scored between 61 to 90 and 116(37.18%) scored more than 90.Majority of the patients 248(79.48%) reported good health. Most of the patients 234(74%) reported score of more than 50 representing good mental health. A total of 107(34.3%) patients were worried about their eyesight. Only 5.8% of them feltembarrassedbecause of their eyesight.About 13% felt difficulty in accomplishing target work and were able to perform limited activities in a day. Nearly15.38% of the respondents felt dependent on others for their functioning and social needs. When questioned about their

eyesight majority of the them 262(83.9%) had fair to excellent vision, while around 50(16%) responded that vision was impaired even with the use of glasses or contact lenses. Majority of them 287(92%) had mild to moderate pain, rest 25(8%) of the respondents had severe symptoms of glaucoma in the form of pain or discomfort in the eye. These 8% had impaired QoL due to pain, ache in the eyes because of the diseases. Significant correlation found between age and general vision, mental age and composite score. General vision and mental health score were poor in elderly patients. Correlation of age and NEIVFQ-25 was 0.131. Negative correlation was found between side effects and composite score of NEI-VFQ-25. ($r=-0.284$, $p<0.0001$) As number of side effects increased the individual subscale score and overall composite score also got affected. Negative correlation was found between IOP and composite score of NEI-VFQ-25. ($r=0.17$, $p<0.05$) Poor score in patients with high IOP values. Significant correlation was found between IOP and Ocular pain.

**Table 4: Correlation between age, side effects and NEI-VFQ score**

| | **General Vision** | **Ocular pain** | **Mental Health** | **Composite score NEI-VFQ** |
|---|---|---|---|---|
| Age | **0.00001**** | 0.622 | **0.00075**** | **0.0205*** |
| Number of side effects | **0.0001**** | **0.0001**** | **0.0001**** | **0.0004**** |
| Intraocular pressure (mmHg) | 0.53 | **0.006*** | 0.76 | **0.04*** |

**Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed).

## Discussion

A meta-analysis on a global prevalence of glaucoma estimated the total number of people (aged 40-80 years) with glaucoma were 64.3 million in 2013, with approximately 60% of the world's total glaucoma cases in Asia alone.[1] In our study POAG was found to be most prevalent in age group 40-60 years with the mean age of 55.21±12.59 years and slight female preponderance. These findings are consistent with some studies,[7,8] while male preponderance isalso reported.[1,9]

In the present study, 20% of the patients were diabetic and 47% patients were hypertensive, from these about 13.1% patients were having both. Majority of the evidence from several epidemiologic studies suggests an increased risk of POAG in persons with diabetes. Recent findings from many studies suggest that the risk of glaucoma among diabetic patients may be greater than once believed in the past. One study compared IOP changes in diabetic and non-diabetics and observed that hyperglycemia during oral glucose tolerance testing has a positive correlation with IOP.[10]In a meta-analysis of 47 studies relative risk of glaucoma of 1.48 in patients with diabetes compared to non-diabetics was observed.[11]

A positive correlation between IOP and systemic hypertension, particularly elevated systolic blood pressure had been reported in several.[12] In contrast, some did not find a correlation between systemic hypertension and incidence or progression of glaucoma.[13] A Meta-analysis reported that individuals with systemic hypertension had a pooled odds ratio of 1.2 for the development of glaucoma compared to normotensive individuals.[14]

In present study, we found one in four patients had family history of glaucoma and majority of themhad their first-degree relatives with glaucoma.One study concluded that around 50% of all POAG patients had a positive family history, and their first-degree relatives had an approximately 9-fold increased risk of developing glaucoma.[15]A2018 meta-analysis concluded that genetic prediction models likely play a role in the future of POAG screening and treatment as they identified 112 loci, including 68 novel loci, associated with IOP and the development of POAG.[16]

No class of ocular hypotensive drugs has changed the therapeutic landscape as dramatically as the PGA. The drugs in this class represent an almost unheard-of combination in medicine: the safest and most effective glaucoma drugs till date. Because of these two key characteristics they have replaced beta blockers as the preferred first-line agents.[17]In present study, PGA were the most commonly prescribed followed by β-blockers, α-2-adrenergics and carbonic anhydrase inhibitors.

We found that Bimatoprost was more efficacious in terms of reductions in IOP, also had a significantly higher percentage of adverse events, which is consistent with the findings of the study done by Lin et. al.[18] A recent 2019 meta-analysis concluded Bimatoprost was more efficacious when compared to Latanoprost and Travoprost and showed lower ocular tolerability then latter two.[19]One study compared the efficacy and Ocular Surface Disease Index (OSDI) Score between PGA and demonstrated that all PGAs are equally effective in reducing IOP in patients with POAG.[20]

The findings of our study are suggestive of better efficacy and safety profile of preservative free antiglaucoma medications. The higher reduction in IOP may be because of better compliance with preservative free drugs. A double-masked randomised clinical trial concluded that IOP-lowering effect and safety profile of Bimatoprost PF with Bimatoprost containing BAK were similar.[21]A multicentre study compared preservative-added and preservative-free latanoprost eye drops in two parallel groups of glaucoma patients and showed statistically significant tolerability advantages with no disadvantage for the preservative-free eye drops in terms of efficacy.[22]

Adherence is defined as the "extent to which a which patients take medications as prescribed by their treating doctor.[23] We found almost half of the patients were adherent to their treatment. Similar finding is reported in several studies in literature with an average estimate of nonadherence at 40%.[24] Nonadherence, one of the major problems in glaucoma treatment, is thought to be a leading cause of blindness. According to the literature, the rate of nonadherence to glaucoma therapy is notably poor and varies between 5% and 80%.[23] Reasons for this are, no apparent symptoms in the earlier course for glaucoma patients, ocular side effects of medications, improper use of prescribed medication, poor knowledge about disease and requirement of lifelong treatment without direct benefits from the therapy.[25] We found that only half of the patients had a knowledge regarding glaucoma as a disease. Good knowledge about glaucoma may positively influence patients' adherence was claimed by one study.[26] POAG has a serious impact on the QoL of a large number of people around the world. Recent study reported more than two third of the population were worried about their eyesight and around half reported impaired vision. Correlation of age and NEIVFQ-25 was 0.139. Mean score of NEIVFQ-25 was 73.94±8.858.[27]

**Strengths, Limitations and Future Prospects**

Our study evaluated the commonly prescribed antiglaucoma drugs at a tertiary care eye hospital which can guide prescribers optimizing the treatments and achieving better patient care. The unique part was that it attempted to compare the PGA eye drop formulation between drugs containing preservatives and preservative free drugs in relation to the ocular side effects and intraocular pressure.The study usedGTCATto assess compliance of patients which is first of a kind in our set up. Quality of life assessment done using NEIVFQ-25 gives a more direct measure of the impact of Glaucoma on daily life.

Despite the strengths, few limitations associated with thestudy are that it concentrated on POAG only, patients having other types of glaucoma were excluded from the study. To separate out and study the efficacy of other class of antiglaucoma drugs was not attempted.Estimation of efficacy was difficult as patients were on fixed drug combinations of antiglaucoma medications.

Further studies are required with larger sample size and for longer periods at such multi-centric clinical and community. More studies comparing long term effectiveness of medical and surgical treatment are required. Economic burden on patients can be analysed to further modify the prescribing habits. There is also a need to keep updating the data in terms of quality of life, patient education, effectiveness of treatment provided and patient compliance which will aid in healthcare decisions in rational way.

## Conclusion

Glaucoma was prevalent in middle age group. As majority of the patients are asymptomatic at the early stage of the disease it is suggested to introduce screening of glaucoma in such patients.Bimatoprost showed greater efficacy in terms of lowering IOP and also had a significantly higher percentage of ocular side effects, conjunctival hyperaemia was being most significant. Drugs containing preservative BAK were reported higher incidence of ocular side effects when compared to preservative free eye drops.

Nonadherence is one of the major pitfalls in glaucoma treatment. Nearly half of the patients were adherent to their antiglaucoma medications. Most common reason for nonadherence was not having a drop at the time of instillation or forgetfulness.

Being a chronic disease, glaucoma may affect one's QoL because of visual impairment. Also, though few, but the side effects of medications may lead to difficulties in performing daily activities and hence the compliance, which can be a limiting factor for the success of the treatment. It is essential that after thorough history and clinical examination of the patients, the treatment should be modified individually, monitored regularly and altered when necessary, to minimize the side effects and maximize the outcome of the therapy.

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