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Safety Profiles of Pharmacotherapies in Primary Glaucoma: A Prospective Observational Study at a Tertiary Care Centre in South Delhi

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ABSTRACT

Background: Glaucoma is a group of ocular disorders which has become the leading cause of irreversible blindness worldwide. The cornerstone of management in primary glaucoma is the reduction of intraocular pressure (IOP), primarily achieved with topical agents. The safety of anti-glaucoma drugs needs to be widely and repeatedly evaluated to provide real-world scenario inputs for the future trends in the management of glaucoma, especially with the advent of newer ocular hypotensive agents.
Objective: The present study was conducted to evaluate and compare the safety profiles of pharmacotherapies prescribed to patients with primary glaucoma.
Material and Methods: A total of 99 adult patients with primary glaucoma were included in the present prospective observational study, after due approval from the Institutional Ethics Committee (IEC) and obtaining written informed patient consent. All observations were recorded in a structured patient record form.
Result: Out of 99 patients, the majority (40.4%) belonged to the 61–70 years age group, with a slight predominance of males (52.5%). Primary open-angle glaucoma was the most common subtype (69.7%). A positive family history was reported in 14.1% of patients. Prostaglandin analogue (PGA) monotherapy was the most frequently prescribed regimen overall. A total of 31 adverse events were reported, of which 64.5% were ocular and 35.5% were systemic, predominantly mild to moderate in severity. Conjunctival hyperemia was the most observed ocular adverse drug reaction (ADR), particularly associated with drugs belonging to the rho-kinase inhibitor and prostaglandin analogue classes. At the same time, dysgeusia was the most common systemic ADR. Some patients discontinued therapy due to conjunctival hyperemia.
Conclusion: Overall, antiglaucoma drugs were found to be safe and generally well tolerated. Ocular adverse effects were reported more frequently than systemic, with conjunctival hyperemia being the most commonly observed, particularly in patients receiving rho-kinase inhibitors. Other ocular adverse effects included excessive lacrimation, dry eye, ocular irritation or a foreign-body sensation, and transient blurring of vision. Systemic adverse effects were infrequent and usually mild to moderate, with dysgeusia reported most often. Prostaglandin analogue monotherapy remained the most commonly prescribed treatment, although a shift in trend towards increased use of combination therapy was noted at follow-up.

Keywords: Glaucoma, Primary Open-Angle Glaucoma, Adverse Effects, Rho-Kinase Inhibitors, Conjunctival Hyperemia, Dysgeusia.

INTRODUCTION

Glaucoma is a chronic optic neuropathy, which has become the second leading cause of irreversible, but preventable blindness worldwide.[1] The global burden of population ailing from glaucoma is expected to rise significantly between the 2010s and 2040s, with the number of affected individuals projected to increase from 64.3 million in 2013 to approximately

111.8 million by 2040.[1] India bears a substantial proportion of the global burden of glaucoma, as population-based studies have demonstrated that glaucoma is emerging as a major cause of blindness, accounting for approximately 12.8% of the overall burden of blindness nationwide.[2]

Glaucoma can be broadly classified into primary and secondary types based on aetiology, and categorised into open-angle and closed-angle types based on the gonioscopic findings of the anterior chamber angle. Primary glaucoma is a group of progressive optic neuropathies characterised by acquired loss of retinal ganglion cells and corresponding visual field defects, in which the disease occurs in the absence of an identifiable secondary cause, and intraocular pressure (IOP) is a major, but not exclusive, risk factor.[3,4] According to a recent systematic review and meta-analysis, the estimated pooled prevalence of glaucoma in India ranges between 2.54% - 3.92%, a subtype specific estimates indicate a prevalence of 2.07% for primary open angle glaucoma (PAOG) and 0.81% for primary angle closure glaucoma (PACG), followed by other subtypes with considerable variations in prevalence attributed to the population examined, age, sex, geographical region, rural-urban distribution and diagnostic methods employed.[5]

Owing to the fact that untreated glaucoma can result in irreversible optic nerve damage and potential blindness, the management strategies are primarily directed towards reducing intraocular pressure and maintaining lowered pressure over the long term to reduce disease progression. First-line therapy in glaucoma typically begins with a single topical IOP-lowering agent; however, achieving the target pressure often requires more than one pharmacotherapeutic agent or a combination of drug therapy belonging to one of the following major classes: Prostaglandin analogues (PGAs), β-adrenergic blockers, α-adrenergic agonists, Carbonic anhydrase inhibitors (CAIs), and drugs belonging to the newly introduced anti-glaucoma class "Rho kinase (ROCK) inhibitors".

Although ocular hypotensive agents have generally shown acceptable safety profiles, the long-term use of these drugs entails a safety concern. Also, with the advent of newer topical hypotensive agents, such as Rho-kinase inhibitors, safety, tolerability, and additive effects, when used as monotherapy or combined with other ocular hypotensive agents, are likely to influence overall safety and patients' tolerability.

A few previous studies have examined the safety profiles of newer ocular hypotensive agents used in the management of glaucoma.[6,7] However, there is a paucity of literature on the relative incidence of treatment-emergent adverse events of the newly introduced ocular hypotensive agents and other anti-glaucoma drug regimens used in the management of primary glaucomas. The safety of ocular hypotensive agents needs to be widely and repeatedly studied to provide real-world insights into future trends in glaucoma management. Hence, this prospective study was conducted to evaluate the ocular and systemic adverse effects of anti-glaucoma treatment regimens used in patients with primary glaucoma at a tertiary care hospital in South Delhi.

MATERIAL & METHOD

Study design and setting

The present study was a prospective, observational study conducted at a single centre by the Department of Pharmacology in collaboration with the Department of Ophthalmology, Hamdard Institute of Medical Sciences & Research (HIMSR), New Delhi (India), between September 2024 and February 2026. A total of 99 adult patients with primary glaucoma who were initiated on anti-glaucoma pharmacotherapy and were attending the outpatient and occasionally inpatient clinics of the Department of Ophthalmology at HAHC Hospital (Hospital attached to HIMSR), were included in the study, based on inclusion and exclusion criteria. The study was conducted in accordance with GCP-ICH guidelines, with due approval from the Institutional Ethics Committee (IEC) and informed written patient consent.

Data Collection

Once the patients with primary glaucoma were thus selected, baseline data collection was conducted using the patient's prescription record and medication profile in a structured patient record form, a prescribed pharmacotherapy form, and an adverse drug reaction (ADR) monitoring documentation form. The baseline parameters recorded included demographic information (age, gender, socio-economic data, and personal and family history of illness), a detailed review of medical and ocular history and readings from standard ophthalmic examinations (Best-corrected visual acuity, Intraocular pressure measurements using Goldmann applanation tonometry and others). The details of the prescribed anti-glaucoma treatment regimen, including combination therapy (fixed-dose combination/ unfixed combination) for patients with different types of primary glaucoma, were recorded after a thorough patient interview and checking the patients' OPD/IPD records at baseline and at follow-up visits at 4 and 12 weeks. The safety profile of the prescribed therapy was assessed at each follow-up visit, based on the patient's history of any treatment-emergent adverse events or on ocular or clinical examinations, followed by closed-ended questions about the details of these events. The severity, causal relationship to the study drug and outcomes of almost all adverse events were documented using the Naranjo scale. Adverse events (AEs) with a clear temporal relationship were reported to the HIMSR's Adverse Drug Reaction Monitoring (AMC) centre. Patients presenting with acute primary angle-closure glaucoma (PACG), with a sudden and marked rise in IOP, were initially managed as per standard treatment protocols, which required initial treatment to lower the IOP promptly, and were only enrolled after resolution of acute symptoms of PACG.

Statistical Analysis

After the study period, the data from the patient record form were compiled and analysed in an Excel document for statistical significance. The categorical variables were expressed as frequencies and percentages. Relevant statistical methods were applied to the data generated from the study observations.

RESULTS

A total of 99 patients with primary glaucoma were enrolled in the present study. Of these, 52 patients (52.5%) were males, and 47 (47.5%) were females, indicating that primary glaucoma is more common in males than in females. The age range between 61–70 years had the maximum number of patients, 40 (40.4%), followed by the 51–60 years of age group, which included 33 patients (33.4%) (**Fig. 1)**. Among the 99 enrolled patients of primary glaucoma, the most prevalent subtype was primary open-angle glaucoma (POAG), accounting for 69 patients (69.7%) and 118 (71.5%) eyes, followed by primary angle-closure glaucoma (PACG), which was observed in 21 patients (21.2%), accounting for 30 (18.2%) eyes. Normal-tension glaucoma (NTG) was the least common subtype of primary glaucoma, observed in 9 patients (9.1%) and involving 17 eyes (10.3%). A positive family history of glaucoma was observed in 11 (15.9%) of POAG patients, 2 (9.5%) of PACG patients, and 1 (11.1%) of NTG patients. At baseline, 47 patients (47.5%) were prescribed monotherapy with different anti-glaucoma drug classes, whereas 52 patients (52.5%) received combination therapy, of which 9 received multiple-drug therapy (polytherapy). First follow-up visit at 4 weeks, a change in pharmacotherapy was observed in 14 patients (14.2%), accounting for 25 (25.2%) eyes, with a trend toward combination therapy (**Fig. 2)**. These changes in the regimen likely reflect optimisation of intraocular pressure control, where inadequate response to initial therapy necessitated step-up therapy. Apart from that, the patient's poor tolerance to the prescribed regimen, adverse events, and clinician preference have also influenced the shift in therapy at the follow-up visit.

The average baseline intraocular pressure of the POAG patients was 23.8 ± 3.4 mm Hg, and the baseline intraocular pressure of the PACG patients was 23.9 ± 4.3 mm Hg. In comparison, that of the NTG patients was 18.2 ± 1.6 mm Hg. At baseline, treatment started as monotherapy in 47 patients (47.4%), and 52 patients (52.5%) received combination therapy with topical pharmacotherapeutic agents. Prostaglandin analogues monotherapy (PGAs) was the most commonly prescribed regimen among all, accounting for 20 (20.2%) patients and 40 (24.2%) eyes, and this proportion remained unchanged at 4 weeks. This was followed by β-adrenergic blocker monotherapy, as the second most commonly prescribed regimen, given in 18 (18.2%) of patients and 29 (17.6%) of eyes at baseline, with a marginal decline at 4 weeks to 17.2% of patients, while the proportion of eyes remained the same (17.6%). The newer anti-glaucoma class, rho-kinase inhibitors, has been prescribed as monotherapy in 9 (9.1%) patients and 13 (7.9%) eyes at baseline, with a slight increase in the number of patients and eyes at 4 weeks, indicating a modest rise in their utilisation. Among prescribed combination therapies, the combination of an α-adrenergic agonist and a carbonic anhydrase inhibitor (CAI) was the most commonly prescribed regimen at baseline, with a remarkable change in therapy observed at 4 weeks in terms of patients and eyes. A shift towards combination therapy with PGAs and β-blockers at 4 weeks has been noted, suggesting a clinician's preference towards this dual therapy. The combination of the newer class rho-kinase inhibitor with a β-adrenergic blocker was prescribed in 9 (9.1%) patients and 11 (6.7%) eyes at baseline, with the patient proportion remaining unchanged at follow-up. Polytherapy regimens involving multiple agents (PGAs ± β-adrenergic blockers ± CAIs ± Rho-kinase inhibitors ± α-adrenergic agonists) were used in 9 (9.1%) of patients and 16 (9.7%) of eyes at baseline, with a stable patient proportion at 4 weeks.

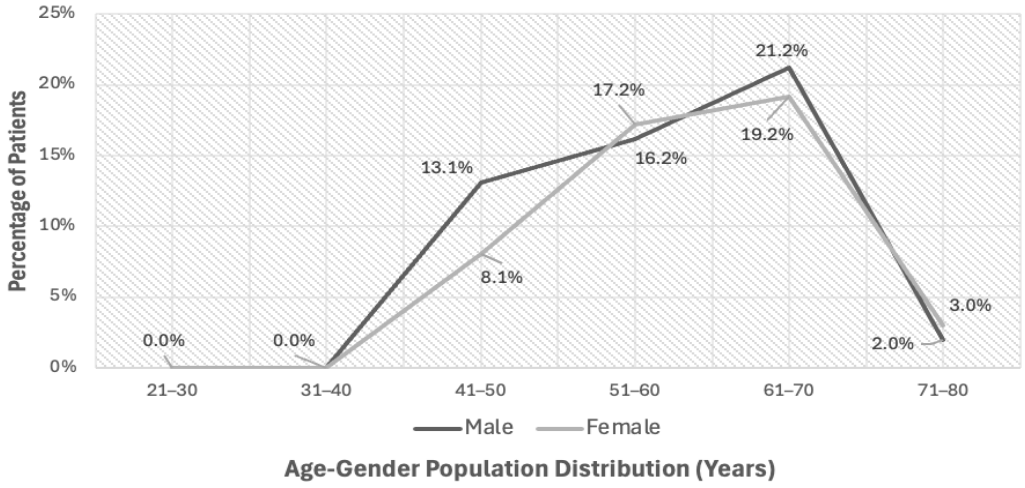

Fig 1: Age-Gender population distribution of patients with primary glaucoma

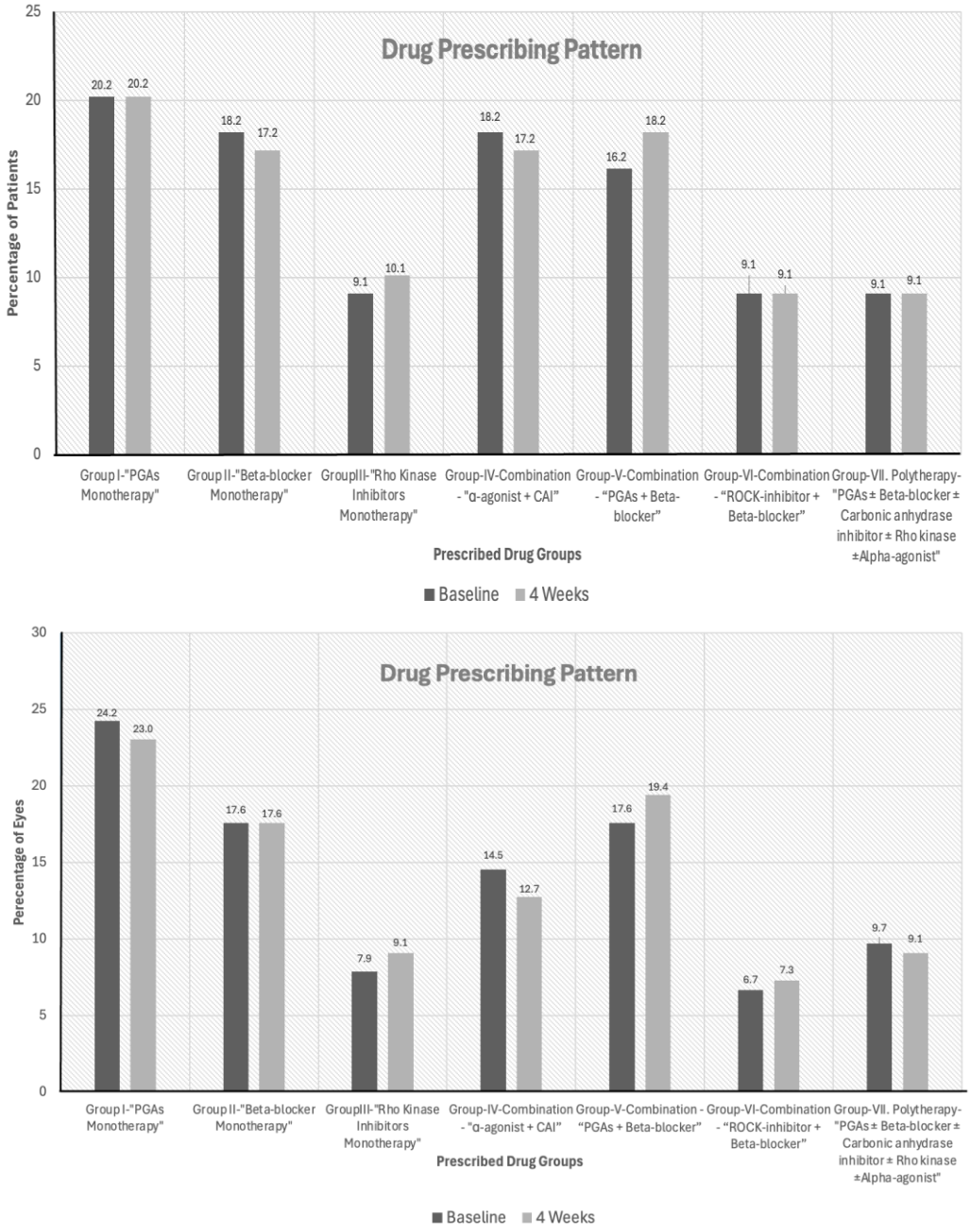

Fig 2: Drug prescribing pattern in patients of primary glaucoma

In the present study, a total of 31 adverse events (AEs) were recorded, of which 20 (64.5%) were ocular, and 11(35.5%) were systemic, mostly mild to moderate in severity. The most frequently reported ocular adverse drug reaction (ADR) was conjunctival hyperemia, and the most frequently reported systemic ADR was bitter/metallic taste in the mouth (dysgeusia). Ocular adverse drug reactions were observed across all treatment groups, with conjunctival hyperemia (redness of eyes) being the most frequently reported ocular ADR, seen in six patients, out of which four reported cases were by the patients on Rho-kinase (ROCK) inhibitor monotherapy (Group-III), one case was reported by the patient on PGA monotherapy (Group-I), and another one by the patient on combination therapy with PGAs and β -blockers (Group-V). This was followed by three cases of excessive lacrimation or eye discharge, one each in patients on combination therapy with an alpha-agonist and carbonic anhydrase inhibitor (Group-IV), a combination of a rho-kinase inhibitor and a beta-blocker (Group-VI) and the polytherapy group (Group-VII). Two episodes of dry eye were also noted in patients receiving Group I. Other adverse effects, including irritation/foreign-body sensation, itching, lacrimation, burning sensation, and ocular pain, were reported sporadically across various drug groups. Less common adverse effects included eyelash thickening, trichiasis, and iris hyperpigmentation, predominantly seen in Group I. Blurring of vision was reported in a few cases in the later groups. Systemic adverse drug reactions observed in this study were relatively infrequent and mild in nature. Bitter taste (dysgeusia) is among the more commonly reported symptoms observed across multiple groups. Dry mouth, itching over the body, and insomnia were reported occasionally with individual drug groups. Less frequently, patients experienced tingling in the hands and periocular skin changes, each noted in isolated cases.

Table 1: Incidence reporting of ADRs associated with drug groups in primary glaucoma

Adverse Drug Reactions (ADRs)	Group I	Group II	Group III	Group IV	Group V	Group VI	Group VII
OCULAR							
Irritation/Foreign body sensation						1	1
Itching				1			
Lacrimation/Eye discharge				1		1	1
Burning			1				
Ocular pain							1
Dry eye		2					
Conjunctival hyperemia (Redness of Eyes)	1		4		1		
Eyelash	1						
Thickening							
Trichaiatic lashes	1						
Iris hyperpigmentation	1						
Blurring of vision						1	1
SYSTEMIC							
Dry mouth				1			
Headache			2				
Bitter taste				2		1	1
Tingling in hands							1
Itching over the body				1			
Insomnia				1			
Periocular skin changes	1						

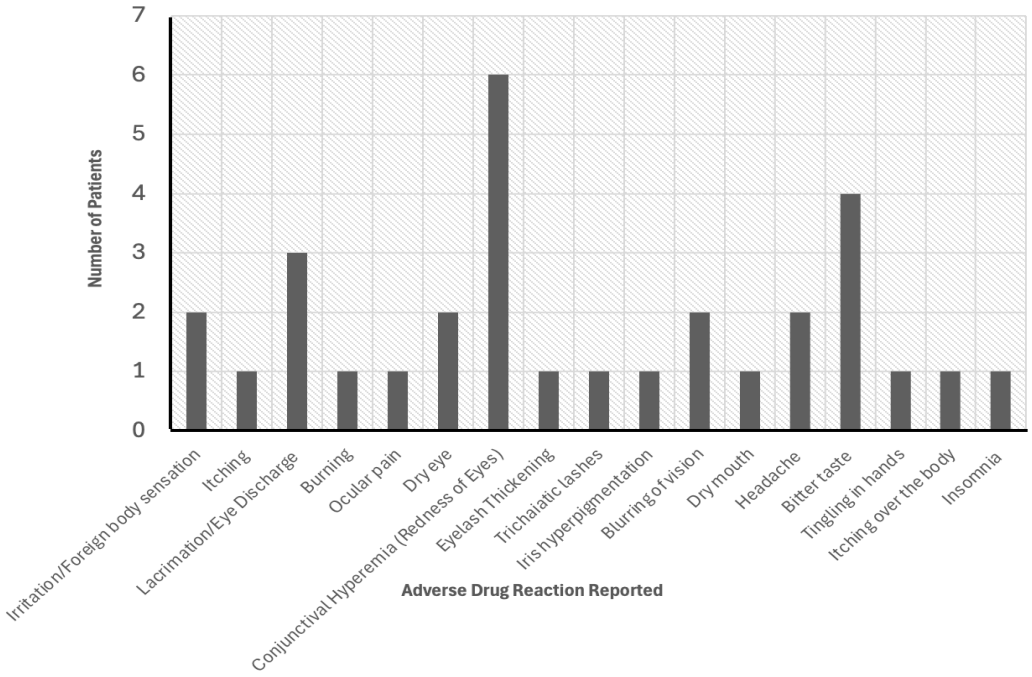

Figure 3: ADRs associated with the prescribed drug group in primary glaucoma

DISCUSSION

The medical management of glaucoma has expanded considerably over the past few years with the introduction of newer intraocular pressure-lowering agents. The present study was conducted to analyse and compare the safety profiles of pharmacotherapeutic agents used in the management of primary glaucomas by highlighting key adverse drug reactions. A total of 99 patients with primary glaucoma were enrolled in the present study; 52 (52.5%) were male, and 47 (47.5%) were female, indicating that primary glaucoma is more common in males than in females. This observation is consistent with several landmark epidemiological studies, including the Baltimore Eye Survey by JM Tielsch et al., which has also reported a marginally higher prevalence of glaucoma in males.[8] A global meta-analysis of the prevalence of primary open-angle glaucoma over the last 20 years found that 84.4% of studies reported a higher prevalence among men than among women.[9]

In our study, the age group between 61–70 years had the largest number of patients, 40 (40.4%), followed by the 51–60 years age group, with 33 patients (33.4%). According to the findings of a recent systematic review and meta-analysis on the prevalence trend of glaucoma by Banik S et al. (2025), which included 17 population-based studies, the pooled prevalence of glaucoma in the South Asian population increased with age and was higher in males, as noted in our study.[10] In the present study population, the most prevalent subtype was primary open-angle glaucoma (POAG), observed in 69 patients (69.7%) and 118 (71.5%) eyes, followed by primary angle-closure glaucoma (PACG), which was

observed in 21 patients (21.2%), accounting for 30 (18.2%) eyes. Normal-tension glaucoma (NTG) was the least common subtype of primary glaucoma, observed in 9 patients (9.1%) and involving 17 eyes (10.3%). Several large population-based studies, including The Blue Mountain Eye Study by Mitchell P et a l,[11], Chennai Glaucoma Study by Vijaya et al. (2005)[12] and the Andhra Pradesh Eye Disease Study by Dandona et al (2000),[13] have demonstrated POAG as the most prevalent type of glaucoma and frequently involving both eyes. The observations in these studies indicate that the findings of our study are consistent with global epidemiological data, demonstrating POAG as the most prevalent subtype of primary glaucoma, followed by PACG. At the same time, NTG, a variant of POAG characterised by intraocular pressure within the statistically normal range, was the least common subtype. A positive family history of glaucoma was observed in 14 (14.4%) of primary glaucoma patients in the present study, consistent with previous studies that identify family history as an important risk factor for glaucoma.[8],[11]

Recording and assessing adverse events helps understand the adverse effects of individual drugs and their combinations, possible drug interactions, severity, preventability and impacts on patients' quality of life. In the present study, an active monitoring of adverse events was performed throughout the study period. Among the 99 patients enrolled in the study, 31(31.3%) adverse events (AEs) were reported in patients receiving anti-glaucoma medications across all treatment groups. Of the reported adverse events, 20 (64.5%), were ocular, while 11 (35.5%) were systemic. Most of the reported AEs were mild to moderate in severity and categorised as "probable" or "possible" after causality assessments using the Naranjo Scale. The most frequently reported ocular adverse effect was "conjunctival hyperemia" predominantly seen in the patients receiving the newer drug class rho-kinase inhibitor monotherapy (Group-III), apart from other groups, which included PGA monotherapy (Group-I), and PGA+β-blocker combination (Group-V). Similar findings were also found in the ROCKET clinical trials, evaluating "Netarsudil" (ROCK inhibitor), where conjunctival hyperemia was identified as the most common ocular adverse effect, occurring in nearly 50–53% of patients (ROCKET-1) for Netarsudil q.d and 59% for Netarsudil (ROCKET-2) for Netarsudil b.i.d. ($P < .0001$ for Netarsudil vs timolol).[14] The Rho-kinase (ROCK) inhibitors are a first-in-kind, recently introduced novel pharmacological class with IOP-lowering efficacy, that acts through the Rho/ROCK signalling pathway and improves trabecular meshwork outflow in human eyes, whereas already existing anti-glaucoma drugs tend to reduce intraocular pressure either by decreasing production of aqueous humour from the ciliary body or by facilitating aqueous outflow through the non-conventional (uveo-scleral pathway). The proposed mechanism underlying conjunctival hyperemia associated with this drug class is inhibition of rho-kinase -mediated conjunctival vasodilation, leading to visible redness in the eyes. Again, in a recent meta-analysis and systematic review of prospective randomised trials, the most common ocular AE reported with Rho-kinase inhibitors (RKIs) was conjunctival hyperemia (19-65%), notably higher than those with other drug classes.[15]

Studies with real-world data on the newer class of rho-kinase inhibitors have shown that conjunctival hyperemia typically occurs in a dose-dependent manner and is more frequent with certain formulations, thereby affecting patients' cosmetic acceptability and tolerance, ultimately reducing adherence to the prescribed treatment.[16]

In the present study, among the patients who developed conjunctival hyperemia, a few discontinued the drug themselves before clinicians' consultation due to concerns and apprehension regarding visible redness occurring due to conjunctival hyperemia. Again, in a three-month analysis of a randomised phase-3 trial, conjunctival hyperaemia was observed as the most frequently occurring ocular adverse event, which has also led to treatment discontinuation in patients on a fixed-dose combination of netarsudil with latanoprost and in patients on netarsudil.[17] These findings underscore the potential influence of adverse effects associated with this class on treatment adherence as observed in our study.

The hyperemia associated with PGAs is generally mild and transient, resulting from vasodilation of conjunctival vessels. Previous studies have also demonstrated that conjunctival hyperemia associated with Latanoprost diminishes by the fifth day of treatment and remains stable thereafter.[17] However, in a few cases, it appears to be clinically and cosmetically challenging for the patients, leading to poor compliance. Irritation/foreign body sensation, itching and lacrimation were other reported ocular effects observed in patients receiving a combination of α-agonist and a CAI and patients receiving polytherapy, Groups IV and VII, respectively. Previous studies have also reported ocular irritation and allergic symptoms associated with α-agonist carbonic anhydrase inhibitors and combinations, as seen in the present study.[18] Additionally, burning sensation and ocular pain, one each, were reported among patients in Groups III and VII. Two episodes of dry eye were documented in patients on β-blocker monotherapy (Group II). Studies have highlighted that Timolol can contribute to dry eye symptoms resulting from reduced tear production.[19] Eyelash thickening, trichiasis-like lash changes and iris hyperpigmentation have been detected in PGAs monotherapy receiving patients (Group I),which is consistent with the known safety profile of prostaglandin analogues. Transient blurring of vision, upon instillation, was noted one case each in Groups VI and VII.

The most frequently and overwhelmingly reported systemic adverse effect was "bitter taste in mouth", which was experienced by four patients, observed with the combination drug groups (Groups IV, VI and VII). Several studies have also reported bitter or metallic taste in the mouth (dysgeusia) associated with ocular hypotensive agents, which is generally mild and self-limiting.[18,20] Occurrence of episodes of dysgeusia can be explained by the pharmacokinetic course of the drugs, where the nasolacrimal drainage of the drugs into the oropharynx results in systemic absorption through

nasopharyngeal mucosa, upon instillation in the eyes, resulting in dysgeusia. However, this adverse effect can easily be minimised by reducing the drainage of the drug into the nasolacrimal system by simply placing fingertips on the medial canthus (the inner corner of eyes) and applying gentle pressure over the area where the lacrimal sac is located. Apart from the episodes of bitter taste, other systemic AEs included a couple of episodes of headache, reported by patients on rho-kinase inhibitor monotherapy (Groups-III), a case of tingling of hands, experienced by a patient who was put on the polytherapy group (Group VII), an episode itching over body, seen with the combination therapy of an α-adrenergic agonist and a CAI (Group-IV) and lastly, periocular changes which was seen in a patient receiving PGA (Bimatoprost) monotherapy (Group-I). Interestingly, one patient who was treated by a combination therapy of an α-agonist and a CAI (Group-IV) had reported insomnia, which led to a change in therapy at the follow-up visit. The rest of the AEs were consistent with the known safety profiles of anti-glaucoma drugs.[21]

CONCLUSION

This prospective observational study of 99 patients with primary glaucoma highlights that primary open-angle glaucoma (POAG) remains the most prevalent subtype, with a higher incidence in the 61-70 years of age group and a slight male predominance. Among the prescribed pharmacotherapeutic agents for patients with primary glaucoma, prostaglandin analogue-based regimens predominated, both as monotherapy and combination therapy. A noticeable shift towards combination therapy over time, reflecting the need for optimal intraocular pressure (IOP) control in routine clinical practice. The overall safety profile of topical antiglaucoma drugs was found to be acceptable, predominantly mild to moderate in severity and largely consistent with established adverse effects. Ocular adverse events were more frequently observed than systemic events, with conjunctival hyperemia emerging as the most common adverse drug reaction, particularly seen among patients receiving the newly introduced rho-kinase inhibitors. Although the hyperemia resulting from the rho-kinase inhibitor was found to be generally transient and self-limiting and particularly observed post-instillation, the apprehension associated with visible redness and cosmetic unacceptability was observed to influence patient adherence with this new anti-glaucoma drug class, which has also occasionally led to self-discontinuation of the drug. Systemic adverse effects were infrequent and mild, with dysgeusia being the most commonly reported adverse effect, likely attributed to nasolacrimal drug drainage and systemic absorption, which is preventable with proper manoeuvre during instillation. Other systemic adverse events were reported only sporadically across treatment groups.

These findings underscore the significance of active pharmacovigilance, the role of patients' counselling and individualised therapy in the management of glaucoma. Overall, while newer pharmacotherapeutic agents expand the treatment armamentarium, continuous real-world evaluation of safety and tolerability is essential to optimise therapeutic outcomes and improve long-term patient adherence in glaucoma management.

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