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Assessment of Ocular Surface Disease Status in New Patients Initiating Anti-Glaucoma Medication: A Prospective Study

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ABSTRACT

Introduction: Glaucoma is a chronic progressive optic neuropathy and a leading cause of irreversible blindness. Topical medications are first-line therapy, but preserved formulations, especially those with benzalkonium chloride, can damage the ocular surface, causing discomfort, instability and poor adherence. Data from Nepal on early ocular surface changes after treatment initiation are limited.

Objectives: The study aimed to evaluate ocular surface disease status in newly diagnosed glaucoma patients initiating topical anti-glaucoma medications over a six-month period.

Methodology: This prospective cohort study was conducted in the Glaucoma Department of Biratnagar Eye Hospital over 10 months. Ninety-eight patients above 35 years with newly diagnosed primary open-angle glaucoma, normal tension glaucoma, or ocular hypertension were enrolled. Patients with pre-existing ocular surface disease, recent topical therapy, prior ocular surgery, or systemic diseases affecting the ocular surface were excluded. Ocular surface assessment included Ocular Surface Disease Index (OSDI), tear film break up time (TBUT), Schirmer's I test, and Oxford grading of corneal/conjunctival staining, recorded at baseline, 1, 3, and 6 months. Medications included timolol, brimonidine, travoprost, dorzolamide, and fixed timolol + brimonidine combinations. Data were analysed using SPSS v26.

Results: At baseline, ocular surface parameters were within normal limits. At 6 months, OSDI increased to 30.2 ± 9.1, TBUT declined to 7.1 ± 2.7 sec, Schirmer's reduced to 10.6 ± 2.9 mm, and staining worsened significantly ($p<0.001$). Patients on fixed combinations and prostaglandin analogues showed the greatest deterioration.

Conclusion: Newly diagnosed glaucoma patients developed significant ocular surface disease within six months of starting preserved medications. Regular monitoring and reducing preservative exposure are vital for adherence and outcomes.

Introduction

Glaucoma is a chronic progressive optic neuropathy characterized by loss of retinal ganglion cells and visual field defects, and it is one of the leading causes of irreversible blindness worldwide.[1] More than 76 million people worldwide suffered from glaucoma in 2020, and estimates indicate that by 2040, there would be over 110 million cases, the majority of which will occur in Asia.[2] According to

population-based surveys, the prevalence of glaucoma in Nepal ranges from 1.9% to 3.2%, with many instances going undetected until they are at an advanced stage.[3]

For the majority of newly diagnosed glaucoma patients, topical intraocular pressure (IOP) lowering drugs continue to be the first line treatment.[4] These consist of fixed combinations, alpha-agonists, beta-blockers, prostaglandin analogues, and carbonic anhydrase inhibitors. Although these medications effectively lower intraocular pressure and prevent progression, long-term use of them is frequently linked to adverse consequences on the ocular surface.[5] Ocular surface disease (OSD), a multifactorial condition marked by tear film instability, hyperosmolarity, ocular surface inflammation, and sensations of discomfort or dryness, is the most common consequence.[6]

The pathophysiology of OSD in glaucoma patients is complex. The preservative used in topical preparations is one of the main causes. The most common preservative, benzalkonium chloride (BAK), has detergent-like qualities that cause the lipid layer of the tear film to break down, increase epithelial permeability, and cause conjunctival and corneal epithelial cells to undergo apoptosis.[7] Prolonged exposure to BAK has been demonstrated to degrade tear film stability, raise inflammatory cytokines, and decrease goblet cell density.[8]

Despite increasing recognition of this problem internationally, there is limited prospective evidence from Nepal. Given the widespread use of preserved medications and lack of preservative free alternatives in our setting, it is important to evaluate how quickly OSD develops and how it varies with different drug classes.

Thus, the purpose of this study was to evaluate ocular surface changes in recently diagnosed patients at Biratnagar Eye Hospital who had started taking anti-glaucoma drugs. The findings will give clinicians locally relevant evidence to help them monitor, counsel and manage patients in order to maximize long-term glaucoma outcomes as well as the health of the ocular surface.

Methodology

This was a hospital-based, prospective cohort study conducted in the Glaucoma Department of Biratnagar Eye Hospital, a tertiary referral centre in eastern Nepal. The study duration was 10 months, from November 2024 to August 2025. An Ethical clearance was obtained from Biratnagar Eye Hospital Institutional Review Committee (BEH/IRC-115/2024). The study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Ninety-eight patients above the age of 35 years, with newly diagnosed glaucoma were enrolled in our study. The diagnosis of primary open-angle glaucoma (POAG), normal tension glaucoma (NTG), or ocular hypertension (OHTN) was made based on clinical evaluation, gonioscopy, intraocular pressure (IOP) measurement, optic nerve head assessment, and standard automated perimetry. Patients with pre-existing ocular surface disease such as dry eye syndrome and blepharitis, previous ocular surgeries, history of Sjögren's syndrome, use of medications affecting ocular surface, contact lens wearer were excluded from the study.

The sample size was calculated using $n = [z^2 \times p \times q] / d^2$. Using $z = 1.96$, $p = 0.724$, $q = 1 - p$, and $d = 0.10$, the value becomes $n = [1.96^2 \times 0.724 \times 0.276] / (0.10)^2 = 0.76764/0.01 = 76.76$. Thus, the minimum required sample size was 77.

All enrolled patients were started on a single class of benzalkonium chloride (BAK) preserved anti-glaucoma medication as clinically indicated. The medications used included: Timolol (beta-blocker), Brimonidine (alpha-agonist), Travoprost (prostaglandin analogue), Dorzolamide (carbonic anhydrase inhibitor), Fixed combination (Timolol + Brimonidine). Choice of drug was at the discretion of the treating ophthalmologist, based on diagnosis and intraocular pressure levels. Patients were examined at baseline (before starting therapy), and at 1 month, 3 months, and 6 months after initiation of anti-glaucoma medications. At each visit, both subjective and objective ocular surface evaluations were performed.

Subjective assessment

The Ocular Surface Disease Index (OSDI) questionnaire was administered at each visit and OSDI score calculated. This validated tool consists of 12 items evaluating symptoms of ocular irritation, vision-related function, and environmental triggers. Scores range from 0 to 100, with higher scores indicating greater disability.

Objective assessments

Tear film break-up time (TBUT): After instillation of fluorescein dye, the interval between the last blink and first corneal dark spot was measured under slit-lamp cobalt blue illumination. Three readings were taken and averaged. TBUT <10 seconds was considered abnormal.

Schirmer's test I (without anaesthesia): A standard Schirmer strip (Whatman filter paper number 41) was placed in the lower fornix at the junction of the middle and lateral third for 5 minutes and tear production was measured after 5 minutes in millimetres of strip wetting. Wetting <10 mm was considered abnormal.

Corneal and conjunctival staining: Ocular surface staining was determined by comparing the combined corneal and conjunctival staining appearance with the panels on the Oxford grading scheme following consecutive instillations of fluorescein and lissamine green dyes for corneal and conjunctival epithelial staining, respectively. The fluorescein and lissamine green dye were generated from sterile strips impregnated with fluorescein and lissamine green. A diagnosis of OSD based on ocular surface staining was taken as Oxford scheme grade I or higher.

A structured proforma was designed to collect demographic details, clinical diagnosis, prescribed medications, and ocular surface parameters at each visit. Data were entered into Microsoft Excel and analysed using SPSS v26. Repeated-measures ANOVA was used for within-group comparisons over time. A p-value <0.05 was considered statistically significant.

Results

Table 1: Demographic and clinical characteristics of patients (n = 98)

Variable	Value (number)	Percentage
Mean age (years)	**57.2 ± 9.1 (36–78)**	
Gender:		
Male	54	55.1%
Female	44	44.9%
Diagnosis:		
POAG	58	59.2%
NTG	15	15.3%
OHTN	25	25.5%
Medications prescribed:		
Timolol	28	28.6%
Brimonidine	16	16.3%
Travoprost	24	24.5%
Dorzolamide	12	12.2%
Fixed Combination (Timolol + Brimonidine)	18	18.4%

POAG = primary open-angle glaucoma; NTG = normal tension glaucoma; OHTN = ocular hypertension.

In this Study, A total of 98 newly diagnosed glaucoma patients were enrolled. Mean age was 57.2 ± 9.1 years (36–78) with a 55.1% male predominance. POAG comprised 59.2% of cases (NTG 15.3%, OHTN 25.5%). Most started monotherapy timolol (28.6%), travoprost (24.5%), brimonidine (16.3%), dorzolamide (12.2%) while 18.4% received a fixed combination timolol + brimonidine , likely reflecting greater baseline IOP needs.

Table 2: Ocular surface parameters over time (Mean ± SD, n = 98)

Parameter	Baseline	1 Month	3 Months	6 Months	p-value
OSDI Score	11.2 ± 5.3	17.9 ± 6.8	24.8 ± 8.2	30.2 ± 9.1	<0.001
TBUT (sec)	12.0 ± 2.6	10.2 ± 2.4	8.5 ± 2.3	7.1 ± 2.7	<0.001
Schirmer's (mm)	15.1 ± 3.4	13.6 ± 3.0	12.1 ± 2.8	10.6 ± 2.9	<0.001
Oxford Staining Score	0.5 ± 0.3	1.2 ± 0.6	2.0 ± 0.9	2.9 ± 1.0	<0.001

OSDI = Ocular surface disease index; TBUT = Tear film break-up time.

At baseline, mean OSDI was 11.2 ± 5.3, TBUT 12.0 ± 2.6 sec, and Schirmer's 15.1 ± 3.4 mm, with minimal Oxford staining (0.5 ± 0.3). All parameters worsened significantly over 6 months ($p < 0.001$). OSDI rose from 11.2 to 30.2 (moderate severe symptoms). TBUT fell from 12.0 s to 7.1 s, dropping below the 10 s abnormal threshold by 1 month. Schirmer's I declined from 15.1 mm to 10.6 mm, nearing the <10 mm cutoff at 6 months, while Oxford staining increased from 0.5to 2.9, indicating progressive epithelial damage. Progressive deterioration in subjective and objective parameters was observed across all follow-up visits (Table 2).

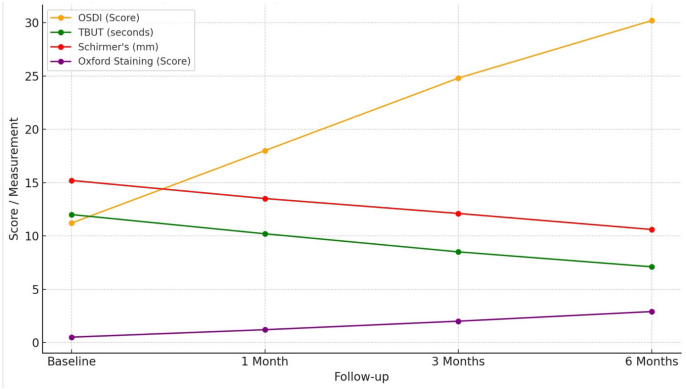

Figure 1: Longitudinal changes in ocular surface parameters over 6 months

The line graph demonstrates progressive worsening of ocular surface parameters over 6 months following initiation of anti-glaucoma medications (Figure 1).

Table 3: OSDI changes by drug class (Baseline vs 6 Months, n = 98)

Drug Class	Baseline OSDI	6-Month OSDI	Change
Timolol	10.9 ± 5.0	27.1 ± 8.4	+16.2
Brimonidine	11.4 ± 5.2	28.5 ± 8.6	+17.1
Travoprost	11.6 ± 5.5	31.8 ± 9.0	+20.2
Dorzolamide	10.2 ± 4.7	25.6 ± 7.8	+15.4
Fixed Combination (Timolol+Brimonidine)	11.3 ± 5.4	34.1 ± 9.5	+22.8

OSDI = Ocular surface disease index.

All drug classes showed substantial OSDI worsening from baseline to 6 months. The largest increases occurred with fixed combination timolol +brimonidine (+22.8; to 34.1 ± 9.5) and travoprost (+20.2; to 31.8 ± 9.0), intermediate with brimonidine (+17.1) and timolol (+16.2), and smallest with dorzolamide (+15.4; to 25.6 ± 7.8). Overall, fixed combinations and prostaglandin analogues were associated with the most pronounced worsening of ocular surface symptoms, whereas carbonic anhydrase inhibitors had comparatively less impact.

Discussion

Over the course of six months, this prospective hospital-based study assessed changes in the ocular surface in patients with newly diagnosed glaucoma who were starting anti-glaucoma drugs that contained benzalkonium chloride (BAK). Our results showed that ocular surface parameters were significantly deteriorated, with Oxford staining scores rising significantly, TBUT and Schirmer's values sharply dropping, and OSDI scores almost tripling. Patients on prostaglandin analogues and fixed combination treatment showed the most decline.

Our cohort's near-normal OSDI values at baseline (11.2 ± 5.3) were similar to the findings of Leung et al. indicating newly diagnosed patients typically do not have ocular surface

complaints.[10] The OSDI increased to 30.2 ± 9.1 at six months, indicating moderate to severe illness. In India, Sharma et al. discovered a similar pattern, with OSDI rising from 11.5 to 28.7 after three months of starting prostaglandin.[11] According to Fechtner et al., with mean OSDI values in the moderate range, about 60% of glaucoma patients taking prescribed medicines felt dryness and irritation of the eyes.[12] According to Rossi et al., the length of treatment and the quantity of drugs taken were independent indicators of worsening OSDI.[13] Our findings support the notion that subjective symptoms start to manifest shortly after treatment begins and get worse with repeated exposure.

At six months, our cohort's mean TBUT dropped from 12.0 seconds to 7.1 seconds. This is similar to the findings of Sharma et al. who documented a decline in TBUT from 12.4 to 8.1 seconds in Indian patients after three months of preserved medication use.[11] Nearly two-thirds of patients subjected to long-term topical treatment showed TBUT shortening, according to Broadway et al.[14] These results are in line with BAK's detergent action, which breaks down the lipid layer of the tear film and speeds up evaporation.[7]

Indicating decreased aqueous secretion, we saw Schirmer's test values drop from 15.1 mm to 10.6 mm. In the US, glaucoma patients experienced a similar decrease (15.4 to 11.2 mm), according to Leung et al.[10] In a German registry, Erb et al. discovered that individuals receiving long-term treatment for concomitant dry eye had mean Schirmer's values of about 11 mm.[16] This implies that decreased aqueous tear production is a consistent observation across populations, potentially brought on by subclinical conjunctival inflammation and goblet cell loss after long-term BAK exposure.[7,8]

In our investigation, Oxford staining rose from 0.5 ± 0.3 to 2.9 ± 1.0, indicating increasing damage to the epithelial cells. Long-term BAK exposure dramatically deteriorates ocular surface staining, frequently by more than two grades, as shown by Baudouin et al.[7] Higher corneal and conjunctival staining scores in patients taking several drugs were confirmed by Fechtner et al.[12] According to Broadway and Grierson, glaucoma filtration surgery has a worse long-term success rate when there are persistent conjunctival alterations.[14] Our results demonstrate the clinical utility of staining pattern monitoring as a predictor of surgical outcomes and quality of life.

The highest OSD burden was seen in patients receiving fixed combination medication and prostaglandin analogues, where OSDI increments were +22.8 and +20.2 points, respectively. This is consistent with the finding by Fechtner et al. that patients receiving numerous preserved drops report more severe symptoms than those receiving monotherapy.[12] Although prostaglandin analogues are very good at lowering intraocular pressure, they are more likely than beta-blockers or carbonic anhydrase inhibitors to cause inflammation on the surface of the eye.[11] The least worsening, but still statistically significant, was shown by dorzolamide users in our group, which is in line with earlier findings that carbonic anhydrase inhibitors had comparatively less surface toxicity.[10]

Conclusion

Newly diagnosed glaucoma patients developed significant ocular surface disease within six months of initiating BAK preserved anti-glaucoma medications. Prostaglandins and fixed combinations caused the most severe ocular surface illness in patients within six months of starting benzalkonium chloride preserved anti-glaucoma drugs. Regular monitoring, timely intervention, and minimizing preservative exposure are essential to improve adherence and optimize long term outcomes.

Recommendations

Regular monitoring of ocular surface parameters in glaucoma patients on topical therapy. Use preservative free formulations whenever possible to reduce ocular surface toxicity.

Limitations of the study

Its single center design and lack of a preservative-free comparison group may limit generalizability and the ability to isolate preservative effects. The six-month follow-up may not capture long-term ocular surface changes, and potential observer bias or variability in self-reported OSDI symptoms could have influenced the results. Future multicenter studies with longer follow-up and comparison groups are needed to validate these findings.

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