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Comparative efficacy of pranoprofen with sodium hyaluronate or polyvinyl alcohol in postoperative dry eye and corneal endothelial function

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Abstract: **Background**: Dry eye following eye surgery represents a common obstacle to recovery and general life satisfaction. Pranoprofen, an anti-inflammatory drug, frequently co-administered with adjuvants such as sodium hyaluronate and polyvinyl alcohol, represents a common response to dry eye. The relative efficacy of pranoprofen and sodium hyaluronate compared with pranoprofen and polyvinyl alcohol as a treatment for dry eye and as an aid to corneal endothelial function will be ascertained. **Objectives**: To assess how pranoprofen with sodium hyaluronate (Group B) compares with pranoprofen with polyvinyl alcohol (Group A) in relation to alleviating and preventing postoperative dry eye and improving endothelial function. **Methods**: A total of 159 patients were randomly assigned into either Group A (n = 80), who received pranoprofen and polyvinyl alcohol, or Group B (n = 79), who received pranoprofen and sodium hyaluronate. The parameters measured preoperatively and at one month postoperatively were dry eye symptoms, tear film stability (tear break-up time and Schirmer I test), corneal staining, endothelial cell function (percentages of hexagonal cells and endothelial cell density), and serological factors (MMP-2 and STRA6 **Results**: Group B had quicker relief from dryness, redness, and fatigue ($p<0.05$), with an improvement in tear break-up time, Schirmer I testing, and staining scores ($p<0.05$). Endothelial function values were more advantageous for Group B, with higher hexagonal cell percentage and endothelial cell density and lower MMP-2 and STRA6 expression ($p<0.05$). The rate of adverse effects was similar for both groups. **Conclusion**: Pranoprofen with sodium hyaluronate appears more effective than pranoprofen with polyvinyl alcohol in relieving postoperative dry eye and promoting corneal endothelial healing, indicating that sodium hyaluronate would be a better option for postoperative recovery.

Keywords: Corneal endothelial cells; Dry eye disease; Postoperative complications; Pranoprofen; Polyvinyl alcohol; Sodium hyaluronate

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INTRODUCTION

Dry eye is a frequent post-surgical complication of ophthalmic surgery, most commonly secondary to disruption of the ocular surface architecture. The disturbance impairs corneal innervation and tear film stability, leading to dryness, foreign body sensation and intermittent pain (Sambhi *et al.,* 2020; Kato *et al.,* 2019). If left untreated, dry eye may advance to keratoconjunctivitis, corneal keratinization, hyperemia and permanent visual loss (Garg *et al.,* 2020; D'Souza *et al.,* 2020).

Standard treatment is mostly corticosteroids and artificial tears. While sodium hyaluronate and polyvinyl alcohol are utilized as tear substitutes to manage symptoms, they do not tackle the root cause of inflammation Corticosteroids, on the contrary, suppress inflammation but are risky in terms of causing intraocular pressure increase and cataract development after long-term application. More recently, the formulation of anti-inflammatory drugs such as pranoprofen, an NSAID, with lubricants has been shown to be extremely promising (Hynnekleiv *et al.,* 2022; Cagini *et al.,* 2021; Yin and Wu, 2024; Fathi-Karkan *et al.,* 2024; Jani *et al.,* 2024; Mahaling *et al.,* 2024; Biswas *et al.,* 2023; Gugleva and Andonova, 2023). Postoperative dry eye is frequent after cataract surgery, LASIK and corneal transplantation due to trauma to corneal sensory nerves with resultant tear reflex impairment. Inflammatory mediators are released during wound healing that exacerbate ocular surface damage in a cycle of inflammation and tear film instability. Therefore, management should include the restoration of tear volume and inhibition of inflammation while promoting epithelial healing. Pranoprofen blocks cyclooxygenase enzymes, decreasing prostaglandin synthesis and ocular inflammation with less side effects compared to corticosteroids.

Its topical application with moisturizing agents like sodium hyaluronate, which has been recognized for epithelial healing and viscoelasticity, or polyvinyl alcohol, a surface-wetting agent, has the potential to augment synergistically therapeutic outcomes. Aside from clinical trials, this research determined the degree of two serum biomarkers-matrix metalloproteinase-2 (MMP-2) and stimulated by retinoic acid 6 (STRA6)-to determine their involvement in postoperative dry eye. MMP-2 is implicated in extracellular matrix remodeling and has been linked to corneal epithelial barrier breach and inflammatory injury

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in dry eye disease. Abnormal high levels of MMP-2 are indicators of ocular surface inflammation and healing impairment. STRA6 is a retinol-binding protein membrane receptor that participates in vitamin A transport and epithelial renewal. STRA6 disregulation is linked to ocular surface disease and impaired healing processes. By quantifying these biomarkers, we sought to link systemic inflammatory responses to endothelial function and ocular surface recovery. The present study compares the clinical effectiveness of pranoprofen with that of either sodium hyaluronate or polyvinyl alcohol for patients with postoperative dry eye in terms of corneal endothelial function and symptomatic relief.

MATERIALS AND METHODS

Study design and participants

A total of 159 patients with postoperative dry eye who presented at the Ophthalmology Clinic of Jiaozhou Center Hospital of Qingdao Institution from September 2020 to September 2021 were enrolled in this prospective, randomized controlled trial. Patients were randomized in a 1:1 ratio to two treatment groups: Group A (n=80), which received pranoprofen with polyvinyl alcohol and Group B (n=79), which received pranoprofen with sodium hyaluronate. Baseline data for age, sex, duration of symptoms and initial dry eye severity were similar in the groups ($p > 0.05$).

Randomization and patient flow

Randomization was done using a computer-generated random sequence developed by an independent statistician. Block randomization with a block size of four was employed to ensure group balance. Allocation was blinded by sealed, opaque, sequentially numbered envelopes. The trial was open-label. Participants and treating clinicians were not blind to group allocation, but outcome measures were assessed by an independent ophthalmologist masked to the treatment allocations. Patient flow is shown in fig. 1.

Inclusion and exclusion criteria

Patients may be eligible if they experienced new-onset postoperative dry eye after uncomplicated ophthalmic surgery, tear breakup time (BUT) of 3-10 seconds, Schirmer I test (SIT) of ≤ 5 mm/5 min, complete eyelid closure without trauma, no allergy to the study medications and no previous treatment for dry eye. Exclusion criteria included congenital dry eye diseases, postoperative corneal edema, concomitant ocular disease, psychiatric or cognitive impairment, systemic autoimmune disease like rheumatoid arthritis and nonadherence or inability to return for follow-up.

Treatment plan

Standard dry eye therapy was provided to all the patients, consisting of eyelid hygiene, warm compresses and infection management. Group A also received pranoprofen (0.1%) and polyvinyl alcohol eye drops, thrice daily (a drop each time) for one month. Group B also received pranoprofen (0.1%) and sodium hyaluronate eye drops, four times daily (a drop each time) for the same period.

Outcome measures

Outcome variables were subjective symptoms and objective clinical evaluation. Subjective symptoms-visual fatigue, dryness, redness, swelling and foreign body sensation-were documented until resolution. Objective tests were tear breakup time (BUT), defined as mean of three measures following instillation of fluorescein; Schirmer I test (SIT), defined by the extent of strip wetting after five minutes of closed eyes; and corneal fluorescein staining (FL), graded on a 0 to 3 scale under cobalt blue light according to pattern of staining.

Corneal endothelial cell assessment

Central endothelial cell density, coefficient of variation, hexagonal cell percentage and mean cell area were determined by a non-contact specular microscope (Model, Manufacturer).

Serum biomarker analysis

Venous blood samples under fasting conditions were taken and preserved at -20°C. Serum MMP-2 and STRA6 were quantified using ELISA kits (Manufacturer, Country) following the manufacturer's protocol. Procedural details of ELISA are given in the Supplementary Material.

Clinical efficacy criteria

Therapeutic effect was graded into four degrees: Recovery, meaning remission of symptoms and normal slit-lamp findings; Effective, meaning symptom score < 2 with excellent clinical improvement; Markedly Effective, meaning symptom score of 2-6 with slight residual corneal damage; and No Effect, meaning no improvement or aggravation of symptoms. Total effective rate was determined by employing the formula: (Recovery + Effective + Markedly Effective) / Total cases × 100%.

Adverse events

Complications were watched for in patients, such as eye pain, blurred vision, vitreous hemorrhage, or retinal detachment. Adverse events were reported and contrasted between groups.

Statistical analysis

Statistical analysis was conducted using SPSS version 24.0 (IBM Corp., USA). Continuous data were expressed as mean ± standard deviation and compared with independent-sample t-tests or one-way ANOVA where appropriate. Non-parametric tests were used where assumptions of normality were violated. Categorical data were compared with chi-square tests and ordinal data with rank-sum tests. $p < 0.05$ was regarded as statistically significant.

RESULTS

Symptom relief

Group B (pranoprofen + sodium hyaluronate) also had significantly faster relief of visual fatigue, dryness,

congestion/swelling and foreign body sensation than Group A (pranoprofen + polyvinyl alcohol). Recovery times for all symptoms were significantly faster in Group B ($p < 0.001$ for all), as indicated in table 1. "Nasal congestion" was changed to ocular surface congestion.

These results, while subjectively characterized and without the use of a standardized questionnaire (e.g., OSDI), suggest faster symptom improvement in Group B. Because of the open-label design and unblinded assessment of symptoms, these findings must be interpreted cautiously.

Dry eye clinical tests

Both groups had significant changes in tear film breakup time (BUT), Schirmer I test (SIT) and fluorescein staining (FL) scores following one month of treatment ($p < 0.05$ in each group). Group B had significantly better improvement compared with Group A in all three parameters ($p < 0.01$), as indicated in table 2. Baseline values between the two groups were not significantly different ($p > 0.05$).

Corneal endothelial cell parameters

There were no differences at baseline between the two groups. Following treatment, corneal endothelial cell density and hexagonal cell ratio increased and coefficient of variation and mean cell area decreased ($p < 0.05$). The improvements were more significant in Group B ($p < 0.01$), as indicated in table 3.

Serum biomarker levels

Pre-treatment serum MMP-2 and STRA6 levels were similar in all the groups. After treatment, the two markers declined significantly in both groups, with an even higher decline in Group B ($p < 0.001$), as explained in table 4.

Clinical efficacy

Group B showed much better global clinical efficacy (93.33%) than Group A (83.33%) ($\chi^2 = 4.132$, $p = 0.045$), as shown in table 5. Results are indicative of better therapeutic advantage with pranoprofen + sodium hyaluronate. Utilization of a non-standardized efficacy scoring system, nonetheless, constricts generalizability and results must be interpreted in light of this limitation.

Adverse reactions

The overall incidence of side effects was low and did not vary significantly between groups ($p > 0.05$). Two patients in Group A experienced temporary pain in the eye and one experienced blurred vision. One patient in Group B reported mild burning sensation and one experienced temporary blurred vision. Retinal detachment, vitreous hemorrhage, or any other complication were not observed in any case.

DISCUSSION

Dry eye syndrome is the most frequent postoperative complication in eye clinics, which is featured by tear film instability and is usually accompanied by a lack of tear secretion, causing ocular surface damage and pain (Tsubota *et al.,* 2020; Huang *et al.,* 2022). The artificial tears sodium hyaluronate and polyvinyl alcohol, although, provide symptomatic relief but fails to treat underlying inflammation.

Likewise, pranoprofen monotherapy in the long term is not therapeutically highly effective and also risky with regard to surface irritation upon application over long durations (Robert *et al.,* 2016). This research examined clinical efficacy of the combination of pranoprofen with sodium hyaluronate or polyvinyl alcohol in treating newly developed dry eye after uneventful eye surgery. Clinical efficacy was determined based on subjective symptomatology improvement and objective tests such as tear film breakup time (BUT), Schirmer I test (SIT), corneal fluorescein staining (FL), corneal endothelial cell morphology and inflammatory markers (MMP-2 and STRA6).

Patients in Group B who were administered pranoprofen and sodium hyaluronate showed quicker symptomatic relief, better tear dynamics and better endothelial recovery than patients in Group A who received pranoprofen and polyvinyl alcohol. Sodium hyaluronate's benefit is probably due to its closest similarity to natural tears and highest molecular weight, which enhance viscoelasticity and ocular surface retention. It lowers tear film osmolarity, stabilizes the epithelial microenvironment and heals wounds by creating a lubricating barrier and facilitating epithelial cell migration and proliferation (Buzzonetti *et al.*, 2022; Guarise *et al.,* 2023).

These agents not only eliminate dryness and irritation but also promote healing of the ocular surface structure. Polyvinyl alcohol, however, is primarily a wetting agent with no considerable bioactivity. Intraocular procedures like phacoemulsification or LASIK may injure corneal nerve and endothelial cells via mechanical trauma and inflammation, causing impaired tear secretion and unstable tear film. The cascade includes leukocyte infiltration, release of cytokines and prostaglandin-mediated inflammation, which can impair ocular surface integrity and decrease corneal sensation (Lu *et al.,* 2022; Zuo *et al.,* 2022; Villani *et al.,* 2018).

Our results correlate with this pathophysiology: Group B had a significantly greater endothelial cell density and hexagonal cell percentage and smaller coefficient of variation and mean cell area, indicative of improved endothelial preservation and recovery. Group B also biochemically showed considerable decreases in serum MMP-2 and STRA6 levels. MMP-2 is involved in extracellular matrix breakdown and is linked with epithelial barrier disruption in dry eye. STRA6, a retinol transporter, could indicate epithelial stress or irregular vitamin A metabolism, which is vital for corneal health.

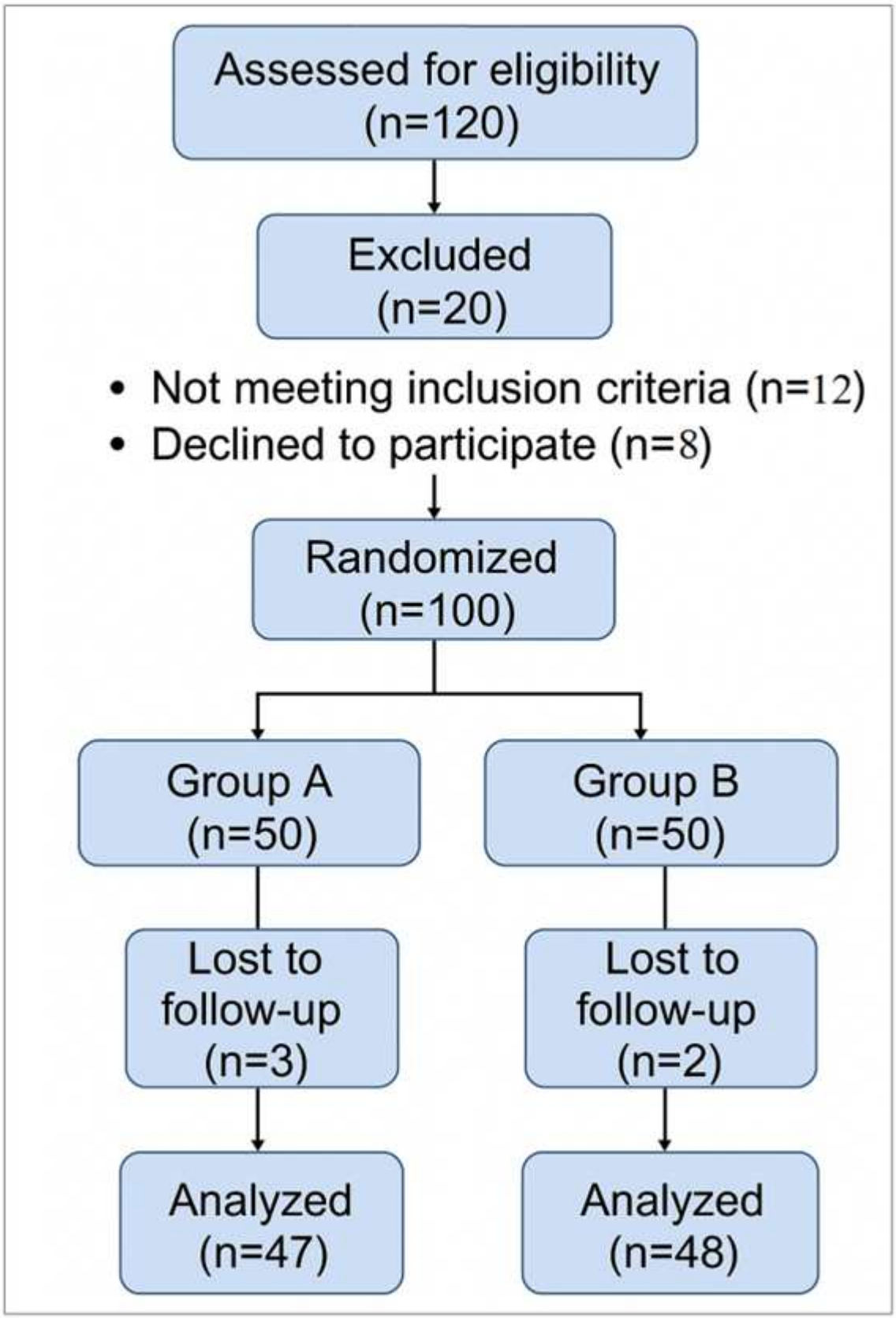

Fig. 1: CONSORT flow diagram of patient enrollment and analysis

Table 1: Group comparison of relief from symptoms (mean ± SD)

Symptom	Group A (n=60)	Group B (n=60)	t value	P value
Visual fatigue (days)	9.63 ± 1.51	6.32 ± 1.18	11.509	0.000
Dryness (days)	11.78 ± 1.44	8.11 ± 1.23	11.834	0.000
Congestion/swelling (days)	9.93 ± 1.68	6.56 ± 1.72	10.321	0.000
Foreign body sensation (days)	11.62 ± 1.50	8.24 ± 1.39	10.954	0.000

Table 2: Dry eye indices before and after treatment (mean ± SD)

Parameter	Group A Before	Group B Before	p-value	Group A After	Group B After	p-value
BUT (s)	5.99 ± 0.73	6.03 ± 0.56	0.641	9.46 ± 1.16[1]	11.91 ± 1.72[1]	0.000
SIT (mm)	3.71 ± 0.68	4.00 ± 0.79	0.258	8.24 ± 1.19[1]	10.86 ± 1.01[1]	0.001
FL score	2.90 ± 0.25	2.67 ± 0.16	0.385	1.63 ± 0.09[1]	0.94 ± 0.05[1]	0.003

Note: [1] $p < 0.05$ vs. baseline in the same group.

Table 3: Corneal endothelial cell parameters pre-treatment and post-treatment (mean ± SD)

Parameter	Group A Before	Group B Before	p-value	Group A After	Group B After	p-value
Cell density (cells/mm²)	1968.52 ± 238.82	1979.64 ± 223.46	0.462	2143.81 ± 543.59[1]	2381.29 ± 250.38[1]	0.002
Coefficient of variation (%)	36.29 ± 3.14	36.32 ± 3.89	0.720	34.78 ± 2.88[1]	30.15 ± 3.63[1]	0.001
Hexagonal cell ratio (%)	29.83 ± 4.50	29.31 ± 4.07	0.105	34.53 ± 2.42[1]	38.85 ± 10.32[1]	0.003
Mean cell area (μm²)	408.68 ± 66.54	410.40 ± 61.19	0.786	375.93 ± 50.61[1]	312.96 ± 54.72[1]	0.000

Table 4: Pre- and post-treatment serum MMP-2 and STRA6 levels (mean ± SD)

Biomarker	Group A Before	Group B Before	p-value	Group A After	Group B After	p-value
MMP-2	28.85 ± 6.62	29.09 ± 6.05	0.652	17.54 ± 5.49[1]	10.26 ± 3.10[1]	0.000
STRA6	50.86 ± 8.11	51.07 ± 8.68	0.628	34.57 ± 4.87[1]	20.64 ± 2.13[1]	0.000

Note: [1] $p < 0.05$ compared with baseline in the same group.

Table 5: Clinical efficacy results (n = 60 for each group)

Outcome	Group A	Group B
Cured	15 (25.00%)	31 (51.67%)
Effective	19 (31.67%)	14 (23.33%)
Markedly Effective	26 (43.33%)	11 (18.33%)
Ineffective	10 (16.67%)	4 (6.67%)
Total Efficacy	50 (83.33%)	56 (93.33%)

Although not yet incorporated into standard dry eye evaluation, their reductions can mirror reduced inflammation and enhanced epithelial homeostasis with therapy. Nonetheless, we are aware, the clinical relevance of STRA6 and MMP-2 in dry eye is also exploratory and needs additional study. Pranoprofen, which is an NSAID, exerts an anti-inflammatory action through the inhibition of cyclooxygenase-mediated prostaglandin synthesis.

It does not, unlike corticosteroids, increase intraocular pressure nor cause cataract formation. It is synergistic with sodium hyaluronate in the way that it not only inhibits inflammation but also promotes ocular surface healing. Patients in Group B recovered more quickly from symptoms of dryness, foreign body sensation and fatigue and had a better overall clinical efficacy rate. Notably, the frequency of adverse events was not different between groups, attesting to the safety of the combination regimen.

There are several limitations to this study, however. First, the study was not blinded and this can introduce bias, particularly in the measurement of subjective symptoms. Second, there was no validated dry eye symptom questionnaire such as the OSDI used to evaluate symptoms, which detracts from the objectivity of patient-reported results. Third, dosing frequency differed between groups (three times vs. four times a day) and this may be a confounding variable. These limitations have been identified and must be addressed in future studies by the use of standardized grading systems, blinded assessments and matched dosing schedules. Lastly, while one month was sufficient for observation of early therapeutic

response, longer follow-up is required to assess the effect of prolonged effects on corneal healing and symptom recurrence.

CONCLUSION

Briefly, the combined use of pranoprofen and sodium hyaluronate eye drops is of tremendous therapeutic significance for the postoperative treatment of dry eye syndrome. Combined therapy has the certain effects of accelerating tear secretion, stabilizing the tear film, promoting corneal endothelial healing and suppressing inflammatory reactions and thereby significantly improving patient prognosis. However, this study is limited by a relatively small sample size and short follow-up. Thus, larger-scale, long-term clinical trials are justified to further replicate and expand upon these results.

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Author's contributions
Huating Bi contributed to patient recruitment, data collection, and statistical analysis. Fang Xu supervised the project, contributed to the study design, data interpretation, and critically revised the manuscript for important intellectual content. Both authors contributed to drafting the manuscript, reviewed the final version, and approved it for submission.

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Data availability statement
The data available to support the findings from this research can be found within this article and additional sources. Other information associated with the research and patient data will be made available on request from the corresponding author. Justification and compliance with confidentiality and research standards will be required for distribution.

Ethical approval
The study was approved by the Department of Ophthalmology, Jiaozhou Center Hospital of Qingdao, Ethics Committee (Approval No. JCHQ-2023-02). Written informed consent was obtained from all the participants prior to their recruitment.

Conflict of interest
There are no conflict of interest.

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