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Protocol for a parallel assignment prospective, randomised, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression in China

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ABSTRACT

Introduction Assessment of near work-induced transient myopia (NITM) is important for permanent myopia development and progression. Atropine eye drop has been reported to be beneficial in reducing initial NITM and slowing down myopic progression. This study aimed to investigate the efficacy of 0.01% atropine in treating NITM and its possible association with the progression of refractive change in Chinese myopic children.

Methods and analysis The study is designed as a parallel assignment prospective, randomised, double-blinded, placebo-controlled trial conducted at He Eye Specialist Hospital in Shenyang, China. One hundred fifty participants will be randomly assigned in a 1:1 ratio to receive 0.01% atropine or placebo eye drop once nightly bilaterally for 1 year. Initial NITM, cycloplegic refraction, axial length, best-corrected visual acuity, intraocular pressure and pupil diameter will be measured at baseline, 4 weeks, 12 weeks, 24 weeks, 36 weeks and 48 weeks. Visual Function Questionnaire will be administered at baseline and each follow-up visit. Adverse events also will be monitored and documented at each subsequent follow-up visit.

Ethics and dissemination A parallel assignment prospective, randomised, double-blinded, placebo-controlled trial to evaluate the efficacy of 0.01% atropine for near work-induced transient myopia and myopic progression registered on 10 September 2023. Ethics approval number: IRB (2023) K025.01. The study's findings will be shared regardless of the effect's direction.

Trial registration number NCT06034366.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a parallel assignment prospective, randomised, double-blinded, placebo-controlled trial.
⇒ One hundred fifty participants will be randomly assigned in a 1:1 ratio to receive 0.01% atropine or placebo eye drop once nightly bilaterally for 1 year.
⇒ An evaluation of initial near work-induced transient myopia, cycloplegic refraction, axial length, best-corrected visual acuity, intraocular pressure and pupil diameter will be performed.
⇒ The limitation of the research is that it is a single-centre study.
⇒ The study is limited to 1-year follow-up.

INTRODUCTION

Background and rationale {6a}

Myopia is a common condition that develops primarily during childhood and early adulthood when excessive elongation of the eye results in images of distant objects coming into focus in front of the retina, which leads to blurred distance vision.[1] Myopia is the most common ocular disorder worldwide, with increasing prevalence over the past decades, predominantly in East Asia.[2 3] Previous studies suggested that environmental factors, such as near-work demands, likely play an important role in myopia development in the younger population.

Near work is a major environmental component in establishing and progressing permanent myopia (PM), induced via near work-induced transient myopia (NITM).[4 5] In contrast to PM, NITM refers to the prolonged period required for the accommodation of the eyes to revert to a normal level after performing a persistent near task.[6] Some years ago, it was proposed that NITM, which produces minor and chronic retinal defocus, may be one of many possible environmentally based, myopigenic, contributory factors to PM.[7 8] Initial NITM magnitude is one of the key parameters used to characterise the accommodative response following a sustained near-work task, which is defined as

the dioptric difference between the immediate pre-near and immediate post-near task distance refractive state.[6 9] Previous studies reported that initial NITM was increased in myopes than in hyperopes or emmetropes.[4 10]

As a non-selective muscarinic antagonist, atropine eye drops with different concentrations have been reported to slow down the myopic progression in myopes.[11 12] Recently, a 2-week study assessed the efficacy of a low concentration of atropine (0.01%) on the initial NITM magnitude among Chinese myopic children.[13] The results suggested that 0.01% atropine reduced the initial NITM magnitude. However, the long-term efficacy of 0.01% atropine in treating NITM and the relationship between NITM and refractive change after treatment is still unclear.

This study aimed to investigate the efficacy of 0.01% atropine in treating NITM and its possible association with the progression of refractive change in Chinese myopic children.

Objectives {7}

The primary objective of this study is to investigate the efficacy of 0.01% atropine in the treatment of NITM and its possible association with the progression of refractive change in Chinese myopic children.

Trial design {8}

This is a prospective, randomised, double-blind, placebo-controlled trial performed at He Eye Specialist Hospital (ethics approval number: IRB (2023) K025.01). The study adheres to the tenets of the Declaration of Helsinki and is registered at ClinicalTrails.gov (NCT06034366) using the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[14] Randomisation will be performed using a web-based, online, sealed envelope-based system (https://www.sealedenvelope.com). Specific study information sheets will be provided to patients prior to their consent. Following a dedicated screening and randomisation visit for eligible patients, participants will be randomised to one of two trial arms (figure 1).

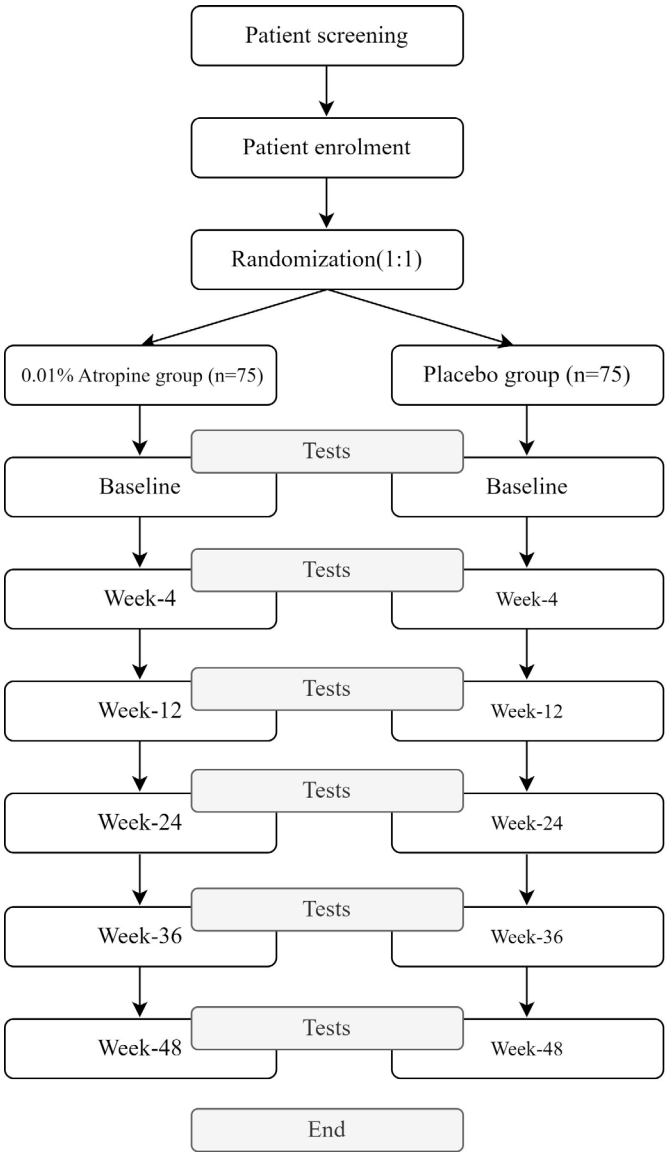

Figure 1 Study flow chart.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting {9}

This study will be conducted between 1 October 2023 and 30 May 2025. Participants will be recruited at the Department of Ophthalmology, He Eye Specialist Hospital, Shenyang, China.

Patient and public involvement

Patients and the public will not be involved in this study's design, implementation, reporting or dissemination plans.

Eligibility criteria {10}

Inclusion criteria

1. Age 6–12 years.
2. Subjects and their guardians agreed to participate in this study.
3. Best-corrected visual acuity (BCVA) 0.1 (log minimum angle of resolution, LogMAR) or better.
4. Initial NITM (spherical equivalent) ≤ −0.25 D.
5. Cycloplegic refractions ≥ −1.0 D and astigmatism ≤2.5 D in both eyes.
6. Anisometropia in both eyes≤1.5 D.

Exclusion criteria

1. Children with existing systemic diseases including asthma, collagen disease, immune system disorders, prostate hypertrophy, spastic paralysis, Down's syndrome, severe cardiac, pulmonary, hepatic and renal dysfunction.
2. Patients with glaucoma or high intraocular pressure (IOP), ocular inflammatory diseases, strabismus, amblyopia, corneal diseases, diseases of lens, retinal and optic neuropathy.

3. Regular use of medications that may affect the efficacy of 0.01% atropine, including hairy fruit rutabaga eye drops, tropicamide eye drops, anticholinergic drugs such as pirenzepine and tropicamide, and cholinergic drugs such as carbachol and hairy fruit rutabaga.
4. Previous experiences with myopia control therapy.
5. A history of allergies to atropine.
6. Patients were deemed inappropriate for trial participation by the lead investigator.

Informed consent {26a}

Trained and experienced clinicians will seek informed permission from prospective participants and guardians.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This trial does not involve collecting biological specimens.

INTERVENTIONS

The explanation for the choice of comparators {6b}

After enrolment in the study, treatments will be initiated immediately after randomisation. Participants in the study group will use 0.01% atropine (3 mL unit concentration, preservative free) once nightly in both eyes for 48 weeks, while those in the control group will use placebo eye drops (0.9% sodium chloride, 3 mL unit concentration, preservative free) once nightly in both eyes for 48 weeks. All eye drops will be prepared by He Eye Specialist Hospital, Co, Shenyang, China, with the same packaging.

Intervention description {11a}

In this study, patients receive either 0.01% atropine or placebo eye drops for 48 weeks based on the group they are placed in. Five follow-up visits will be performed at week 4 (±3 days), week 12 (±7 days), week 24 (±7 days), week 36 (±7 days) and week 48 (±7 days) in both groups; a paediatric ophthalmologist will conduct comprehensive eye exams, including primary outcomes, secondary outcomes and safety evaluation.

Criteria for discontinuing or modifying allocated interventions {11b}

After enrolment in the study, participants will receive one drop of 0.01% atropine or placebo eye drops once nightly in both eyes for 48 weeks. In case of allergic reactions or adverse events (AE) related to the study drug, the principal investigator (PI) (Emmanuel Eric Pazo) will decide if participants can continue further. Participants who onset other serious diseases or refuse to continue participating in the study will be stopped from using the designated eye drops.

Strategies to improve adherence to interventions {11c}

Participants and guardians will be reminded by phone and email every week, and appointments will be booked in advance based on their availability time. Patients will be provided a medication record booklet and their medication status will be verified at each follow-up session to enhance adherence.

In the case of outside the allowance, participants will be contacted by phone or email to make sure if they want to continue or discontinue the study. Subjects who could not complete the follow-up inside the allowance will be removed from this study.

Relevant concomitant care permitted or prohibited during the trial {11d}

Subjects will be allowed to use single-vision lenses during treatment. Any other treatment or therapy for myopia control will be prohibited during the course of this study, including the orthokeratology lens, multifunctional defocus lens and red-light feeding instrument. Besides, any eye drops and systemic medications that may affect the outcome will be prohibited, including hairy fruit rutabaga eye drops, tropicamide eye drops, anticholinergic drugs, such as pirenzepine and tropicamide, and cholinergic drugs such as carbachol and hairy fruit rutabaga.

Provisions for post-trial care {30}

The placebo group will be transferred to the atropine group for treatment in the following year.

Outcomes {12}

Online supplemental table 1 displays the timeline for data collection and site visits. The assessments will be conducted in accordance with a predetermined order. A trained physician (GHQ) will do an in-person medical examination and lifestyle-related information interview. Comprehensive eye exams will be conducted by an ophthalmologist, including assessments mentioned below at baseline, week 4, week 12, week 24, week 36 and week 48.

PRIMARY OUTCOME

Initial NITM will be evaluated by an open-field infrared autorefractor (WAM-5500; Grand Seiko, Japan), including the following steps.[15]

Pretask: subjects will be taught to binocularly fixate on a photopic high-contrast Maltese cross target situated at 5 m, and their accommodative response will be monitored dynamically for 10 s.

Task: subjects will complete a 5-min near-work task with a 5D accommodating demand. To guarantee that subjects pay attention to the near target, we will use pairs of high-contrast black-and-white photographs with 10 small differences in each pair, and they will be instructed to discover as many differences as possible throughout the 5-min task. Two pairs of targets will be used, with a different pair employed for each experimental session. The targets will be displayed on a digital screen (iPad mini6, Apple, Cupertino, California; 8.3in.). To get a satisfactory instrument alignment with the visual axis, both targets are closely placed, one above the other.

Post task: the near work task will be swiftly removed after the 5-min near work activity, and subjects will be instructed to focus for a 3-min period on the photopic high-contrast Maltese cross target positioned at 5 m.

The NITM dioptric magnitude will be the mean spherical equivalent of the post-task minus pretask values. This measure will be computed in the first 10-s interval . The first 10-s interval is referred to as the initial NITM. The initial NITM dioptric magnitude is represented by the MSE of the post-task minus pretask value.

SECONDARY OUTCOMES

All students will receive a cycloplegic autorefraction (WAM-5500; Grand Seiko Co, Hiroshima, Japan) after NITM testing during each visit, whereas the parents will receive a non-cycloplegic autorefraction (ARK-1, NIDEK, Japan) during the baseline examination. Cycloplegic autorefraction will be performed 20 min after instilling three drops of cyclopentolate 1% (Cyclogyl, Alcon). Three readings will be obtained in each eye and averaged within and across each group.

Ocular axial length (AL) will be measured on a Zeiss IOL Master 700 (Carl Zeiss Meditec Inc, Dublin, CA) based on non-contact partial coherence interferometry.

A validated Chinese version of the 25-item National Eye Institute Visual Function Questionnaire will be provided to all subjects to determine the impact of different treatment groups on the vision-related quality of life.[16]

SAFETY EVALUATION

BCVA in the logMAR will be assessed by an optometrist.

IOP will be evaluated using a non-contact tonometer (NT-510, NIDEK, Japan).

Mesopic pupil size and photopic pupil size will be measured with the OPD-Scan III (Nidek, Gamagori, Japan).

Anterior segment examination will be performed by Slit-lamp biomicroscopy and indirect ophthalmoscopy through a dilated pupil.

Participant timeline {13}

The schedule for data collection and visits is shown in online supplemental table 1. After registration for this study, the assigned treatment intervention will be administered for 48 weeks. Furthermore, the effect of eyedrops will be examined at the week 4, week 12, week 24, week 36 and week 48 follow-ups (figure 1).

Sample size {14}

The sample size calculation is based on the primary outcome measures of initial NITM to establish the superiority of the 0.01% atropine group compared with the placebo group in terms of the changes in the mean from the baseline in the initial NITM at week 48. We took the estimated initial NITM for 0.01% atropine and placebo groups to be −0.076 D and −0.41 D.[13] The expected SD within a group was assumed to be 0.20 D. A sample size of 16 subjects could achieve 90% power at a 0.05 significance level. According to Chinese《preparation supervision measures for the administration of medical institutions》(2005), the number of participants should be at least 60. Considering a maximum dropout rate of 20%, the sample size required is 150 (75 per group).

Recruitment {15}

This study will be conducted between 1 October 2023, and 30 May 2025. This clinical study will be done in a single site, with participants blinded to the treatment assignment. This research is open to children who met the inclusion criteria at He Eye Specialist Hospital's Department of Ophthalmology. Participants will be recruited using adverts in the distribution pamphlets, the website and social media postings. Participants' demographic information will be collected during the first (screening) appointment.

ASSIGNMENT OF INTERVENTIONS: ALLOCATION

Sequence generation {16a}

A web-based randomisation application will be used (https://www.project-redcap.org/). Allocation will be done using block randomisation and stratified according to age (allocation factor: 12 years≥age 6 years). (Known only to the statistical team, not stated here to maintain masking.) Participants will be in a 1:1 allocation ratio to 0.01% atropine or placebo groups.

Concealment mechanism {16b}

The block size will be concealed from other researchers, and the randomisation table will not be available for assessment by anyone involved in the study.[17] An independent biostatistician performs randomisation. The biostatistician is the only one who has access to check the file. The allocation list is kept in a separate file on a different computer (as described in Chen *et al*).[18]

Implementation {16c}

Opaque and sealed (A randomisation list for each stratum) envelopes containing serial numbers will be prepared by an independent statistician and delivered to the clinical trial centre.

An independent researcher will distribute the envelopes to participants and allocate them into study groups at 1:1 without implementing stratification.

Before the random assignment, all participants will be informed that they will be allocated to one of two groups. Random allocation will be conducted at visit 2. Random numbers with corresponding participants will be determined in the order of the time of the second visit. They will be opened by the clinician prescribing the eye drops (0.01% atropine or placebo eye drop). The allocation result will not be announced to the participants until the end of the data collection phase of the trial. Researchers

collecting and analysing data related to this trial will be blinded to the participant allocation results.[18]

ASSIGNMENT OF INTERVENTIONS

Blinding {17a}

The treatment assignment for the study will be triple masked. Participants in the research would be unable to recognise the contents. A masked examiner for all clinical assessments will not be involved in this research's data collection or group allocation procedure. The investigator will not be aware of the three groups. Participants will be randomly assigned to 0.01% atropine group or placebo group. The box containing ampoules will be labelled with a batch number, including the study reference number, participant ID, contact number, investigator name, site address, the expiration date of the eye drops, storage instructions and a statement informing the participant that the eye drops are for use only in clinical trials and should not be ingested.

Procedure for unblinding if needed {17b}

The PI will determine and perform the circumstances and procedures under which unblinding is permissible.

PARTICIPANT WITHDRAWAL

Based on the following criteria, patients will be removed from the research.

1. When it is deemed challenging to continue, the study is owing to the emergence of new ailments.
2. The participant who lost to follow-up.
3. When participants or their legal guardians want to end their participation in a study.
4. When the participant's caretaker cannot guarantee their participation in the study.
5. When the research project has concluded.
6. When the lead investigator and subinvestigators believe it is acceptable to cease the study due to AEs.

DATA COLLECTION AND MANAGEMENT

Plans for assessment and collection of outcomes {18a}

Data administration is the responsibility of Jiayan Chen, Department of Clinical Research, as chosen by the PI. This research will collect data using a proprietary EMR case report form (CRF) and management application. Following the database lock, the individual responsible for the statistical analysis will get the locked data following the database. The data management handbook will provide the details on any specific information. At the end of the study, a report on the implementation and the status of data management will be compiled and sent to the PI with the locked research data.[18]

Plans to promote participant retention and complete follow-up {18b}

Informed consent will include information regarding follow-up assessments for all participants. If participants discontinue or deviate from intervention protocols, the study team will initiate contact and prioritise addressing any concerns that may be impacting their adherence to the intervention protocols. If these concerns cannot be resolved, the participants will be requested to complete subsequent self-assessment questionnaires online.

Data will be gathered during prerandomisation, termination and follow-up periods at week 4, week 12, week 24, week 36 and week 48. The method of data collection for this study will involve the use of clinical tests and self-report questionnaires, which will be administered through an online platform. To guarantee the completeness and accuracy of the gathered data, the online questionnaires will be encoded in a manner that necessitates respondents to provide comprehensive responses to all inquiries before submitting their answers.

Data management {19}

Separately experienced staff members at He Eye Specialist Hospital, Department of Clinical Research, performed data collection and entry. Supervision and double confirmation were performed by Guanghao Qin, along with weekly backup, to ensure data quality.

Confidentiality {27}

Each participant's personal information will be kept confidential in the same way as their medical histories in the hospital before, during and after the trial.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not Applicable-There will be no biological specimens collected.

STATISTICAL METHODS

Statistical methods for primary and secondary outcomes {20a}

Unless otherwise mentioned, this study's significance level is set to 5% two sided, and the confidence coefficient is set to 95%. The background of the study's subjects will be tabulated by calculating the mean and SD for continuous variables and the frequency and percentage for categorical variables. Suppose the continuous variables do not follow a normal distribution. In that case, they will be converted appropriately by logarithmic transformation or other means and aggregated with the mean and SD, or the median and IQR will be used as descriptive statistics. For the primary endpoint, between-group comparisons using baseline as a covariate and an analysis of covariance will be made to produce the adjusted mean, its 95% CI, and the p value. A paired t-test will be used to make within-group comparisons. To ensure participant safety, frequencies and proportions will be computed for each group and item, and comparisons between groups will be made using Fisher's exact probability test or the

χ^2 statistic. Correlation analysis will be used to assess the relationship between NITM and myopic progression.

Interim analyses {21b}

Not applicable—no anticipated problems are detrimental to the participant, so interim analysis is not warranted.

Methods for additional analyses (eg, subgroup analyses) {20b}

Subgroup analyses are not planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

After accounting for loss to follow-up and missing data in sample-size calculations, using a two-tailed t-test of difference between means with a power of 90% and a significance level of 5%, we allowed a dropout rate of 20%.

Plans to give access to the complete protocol, participant-level data and statistical code {31c}

The datasets analysed during the current study and statistical code are available from the corresponding author on reasonable request, as is the complete protocol.

OVERSIGHT AND MONITORING

Composition of the coordinating center and trial steering committee {5d}

The subject leader and the project manager will form the Steering Committee (SC). The SC is accountable for managing the whole project. The SC appoints the Monitor Group's (MG) inspectors. The MG will oversee the entire research procedure in compliance with the Good Clinical Practice requirements. The inspector will analyse the investigator's adherence to the protocol, the protection of participants' rights and interests, the quality of the CRF and the investigator's understanding of different standards before submitting inspection reports to the SC.[18]

Composition of the data monitoring committee, its role and reporting structure {21a}

Due to the projected low frequency of AEs and the modest numbers in each location, no data monitoring committee has been convened for this trial. The database will be constructed using Excel (Microsoft, USA 2022 version), and regular data monitoring will be undertaken per the sponsor's standard operating procedures. The SC will have oversight and access to the trial under the supervision of the trial manager at any time during the study.

AE reporting and harms {22}

AEs are unanticipated indications, symptoms, or illnesses seen during a clinical study, regardless of their relationship to the treatment. There may be unwanted local, general, and psychological effects. If any discomfort or new changes in condition during the study period, or any unexpected situation, whether related to the study or not, one should promptly notify the doctor, who will make a judgement and give appropriate medical treatment. According to the results, the doctor will evaluate the eye health status at the end of each examination. If the condition deteriorates or is no longer suitable for the study, the study may be terminated early. At the same time, the doctor will provide other treatment options that are ideal for the current situation to ensure health to the greatest extent. If major AEs occur, He Eye Specialist Hospital Certified Review Board will be notified; experimental treatments will be discontinued promptly, and appropriate therapies will be offered.[18]

Frequency and plans for auditing trial conduct {23}

The study will be reviewed and evaluated weekly by an independent supervisor unrelated to the PI and sponsors.

Plans for communicating significant protocol amendments to relevant parties (eg, trial participants, ethical committees) {25}

If there are modifications to eligibility criteria, outcomes or analyses, a revised protocol will be submitted for approval to the He Eye Specialist Hospital Medical Ethics Committee.

TRIAL STATUS

Recruitment began on 1 October 2023, and the approximate date when recruitment will be completed in March 2023. Protocol version 2.0 was approved in August 2022.

ETHICS AND DISSEMINATION {24}

The study was registered with the trial number NCT06034366 and was conducted in compliance with the tenets of the Declaration of Helsinki and the Institutional Review Board of the He Eye Specialist Hospital, Shenyang, China: IRB (2023) K025.01. Documented informed consent was obtained from all participants in this study. In the present study, all components with any individually identifiable information have been removed from the dataset.

The study's findings will be shared regardless of the effect's direction. All possible beneficiaries of the research, including patients, caretakers, family, doctors, advisory boards and medical boards, will receive trial data. Publications in high-impact, open-access medical journals and talks at national and international medical conferences will serve this purpose.[18]

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Contributors Conception and design of the research: all authors. Analysis and interpretation of the data: GQ, JC and EEP. Writing original draft preparation: GQ. Critical revision of the manuscript (reviewing and editing): GQ and EEP. Supervision: XH, SY and EEP.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Institutional Review Board of the He Eye Specialist Hospital, Shenyang, China: IRB (2023) K025.01 Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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