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Research article

A protocol for a single center, randomized, controlled trial assessing the effects of spectacles or orthokeratology on dry eye parameters in children and adolescents☆

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ABSTRACT

Background: The prevalence of myopia among adolescents is increasing precipitously in China, and the popularity of orthokeratology (OK) lenses as an effective treatment for controlling myopia progression is rising. This protocol assessed and compared the clinical dry eye parameters in children and adolescents with myopia treated with spectacles or OK lenses.

Methods and analysis: This single-masked randomized control trial will include 300 participants (aged 8–17 years) with myopia treated with OK lens (study group) or spectacles (control group). We will record the ocular surface disease index, visual analog scale score, noninvasive tear breakup time, tear meniscus height, meibomian gland score, ocular redness score, visual acuity, tear Matrix Metalloproteinase-9 concentration, tear Lymphotoxin alpha levels at baseline, and after 1-, 3-, 6-, and 12-month.

Discussion: This study will be a standardized, scientific, clinical trial designed to evaluate the dry eye parameters in children and adolescents with myopia treated with OK lenses for myopia control.

Ethics and dissemination: This study has been approved by the Ethics Committee of He Eye Specialist Hospital [ethics approval number: IRB(2023)K024.01]. Before participating in the trial, written informed consent will be obtained from all patient's parents or guardians. The findings of this study will be showcased at both local and international conferences and will also be submitted for publication in reputable peer-reviewed journals.

Trial registration number: Clinicaltrials.gov: NCT06023108 {2a, 2b}

☆ Note: the numbers in curly brackets in this protocol refer to the SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-state-ment-defining-standard-protocol-items-for-clinical-trials/).

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1. Introduction {6a, 6b}

In recent years, the prevalence of myopia has significantly increased in China [1]. The incidence rate of myopia among children and adolescents in China has risen considerably [2,3]. Severe myopia can cause complications such as glaucoma and macula disease [4], leading to an increased burden on society. Currently, in China, correcting myopia with the aid of orthokeratology (OK) and spectacles is popular. The clinical use of OK lenses in children and adolescents has increasingly been confirmed to control the progression of myopia and has, therefore gained popularity in China [5,6]. Primarily, the overnight administration of OK lens alters the refractive power of the eye by reshaping the corneal epithelium (leading to the redistribution of corneal epithelium) [7]. Since the OK lens comes in direct contact with the ocular surface, the patients may experience signs and symptoms of dry eye disease (DED), which may impact the ocular surface health, including potential complications such as keratitis [2]. In addition, long-term OK lens wearers frequently develop corneal staining, which is an indication of corneal abrasion [8]. However, on the other hand, studies have reported that the use of OK lenses for over 12 months has negligible impact on ocular surface health [9]. Nonetheless, it is commonly known that wearing disposable contact lenses for an extended time can lead to tear film instability, meibomian gland dysfunction, and ocular inflammation [10–12]. This study was conducted to assess the impact of OK lenses on the ocular surface and meibomian gland function in children and adolescents to assess the long-term safety of using OK lenses in this population.

1.1. Objectives {7}

This study aims to assess the effects of orthokeratology and spectacles on dry eye parameters in children and adolescents.

1.2. Trail design {8}

This single-masked, randomized controlled trial will include 300 myopic Chinese Asian participants aged 8–17 years. They will be randomized into the OK lenses group (n = 150) or spectacles group (n = 150). This clinical trial will be conducted at He Eye Specialist Hospital's (HESH's) Department of Myopia Control in Shenyang, a nationally accredited clinical trial site.

2. Methods: participants, interventions, and outcomes

2.1. Study setting {9}

Children and adolescents diagnosed with myopia who have decided to get treatment with OK lenses or spectacles will be invited to participate in this study to assess the clinical parameters of dry eye.

3. Eligibility criteria {10}

3.1. Inclusion criteria

(1) Participants aged 8–17 years; (2) Myopia with a range between −5.50 Diopters to −1.00 Diopter (D), and keratometry from 40.00 D to 45.00 D, astigmatism with the rule of up to 1.50 D or astigmatism against the rule less than 0.50 D; (3) Guardians of patients consenting for their children to be randomly allocated and engage in future follow-up and assessments. Minors who have satisfied the above conditions need to acquire the minor's assent and parent's/guardian's consent.

3.2. Exclusion criteria

(1) Participants were previously diagnosed with dry eye disease (DED); (2) Keratitis or any ocular inflammation or infection; wearing contact lenses; allergy; (3) glaucoma, (4) active uveitis, or (5) retinal disease; (6) Other eye treatments or previous eye surgery; (7) systemic disorders.

3.3. Who will take informed consent {26a}

Clinical doctors who have received specialized training will obtain informed consent from participants' immediate family members or guardians and the minor's assent.

3.4. Additional consent provisions regarding collection and use of participant data and biological specimens {26b}

Not applicable.

3.5. Interventions {6b,11a,11b,11c,11d}

Eligible participants will be randomly assigned in a 1:1 ratio to the OK lenses group and spectacles group after being selected for this study. It is recommended that participants in the OK lenses group are obliged to wear OK lenses overnight for at least 8 hours.

Participants will only use a single manufacturer of OK lenses uniformly. Participants will be examined for DED parameters at baseline, 1, 3, 6, and 12 months respectively. During the study, participants showing severe signs and symptoms of DED or serious conditions such as microbial keratitis will be discontinued from the clinical trial, recorded, and administered the necessary treatment. Professional clinical training will be given to the clinical research staff to facilitate enrollment treatment procedures, clearly mentioning the study's pros and cons and data collection processes. Participants and their families will be sufficiently informed, and compliance education will be administered to enhance participation, reducing the incidence of non-compliance among the participants. Participants and their guardians will be proactively contacted by phone or text message in advance during the clinical research. During the study period, all participants will be required to wear the OK lenses every night during the entire course of the study. They will be asked to use appropriate OK lens care solutions for cleaning and disinfecting the lens every morning and evening (Menicon Progent Contact Lens Cleaner, Nagoya, Japan). Parental assistance will also be mandated to periodically eliminate proteins adhered to the OK lenses. In addition, it will be advised that all participants in the trial utilize sodium hyaluronate eye drops without preservatives as a lubricant while removing and wearing the OK lenses [13]. Using topical (other than the above-mentioned sodium hyaluronate eye drops without preservatives) or systemic interventions (such as anti-inflammatory medications) to treat or mitigate dry eye symptoms will be prohibited under normal circumstances. If any adverse event occurs, such as unbearable DED and corneal or conjunctival infection, it will be recorded and referred to the P.I. immediately. Furthermore, to improve trial compliance, participants and their caretakers will be suggested to use e-Diaries or paper diaries to ensure that compliance expectations are met.

3.6. Provisions for post-trial care {30}

Participants who experience symptoms of conjunctivitis, keratitis, or other adverse reactions during and after 1 year of the research ending will receive timely targeted treatment and recorded in the adverse event record.

4. Outcomes {12}

4.1. Primary outcomes {12}

The primary outcomes are (1) ocular surface disease index (OSDI), (2) visual analog scale (VAS) score for ocular surface discomfort (OSD), and (3) NITBUT. The participant's ocular surface condition will be assessed using slit-lamp microscopy during the follow-up periods.

Ocular Surface Disease Index (OSDI): A Chinese-translated and validated version of OSDI (Allergan. Ivinc, CA) will be used to assess the frequency and impact of dry eye symptoms on vision-related functions [14]. It contains 12 questions and four frequency options related to ocular surface diseases: no time, occasional time, most time, and all time. The total score ranges from 0 (asymptomatic) to 100 (severe symptoms); 0–12 points represent normal, 13–22 points represent mild dry eye, 23–32 points represent moderate dry eye, and 33 points and above represent severe dry eye [15].

Visual analog scale (VAS) score for ocular surface discomfort (OSD): VAS will be used to evaluate OSD [16]. Composed of a 100 mm straight line, the endpoints are defined as the limit of OSD to be measured. The patients will rate the degree of eye discomfort by marking the continuity from "no eye discomfort" (score 0) to "my eye discomfort all the time" (score 100). The patient marks the position on the pain scale. Then, the examiner measures the VAS score with a ruler and records the data [17].

Noninvasive tear breakup time (NITBUT): Keratograph 5M (Oculus, Germany) will be used to assess NITBUT. Measurements will be repeated three times, and the median result will be used for analysis [17].

4.2. Secondary outcomes

Tear meniscus height (TMH): A Keratograph 5M (Oculus, Germany) device will be used to measure the TMH three consecutive times, and the median value will be recorded [18].

Meibomian glands (M.G.) score: Keratograph 5M (Oculus, Germany) will be used to capture images of the upper and lower eyelids meibomian glands. Partial or complete loss of the meibomian glands will be assessed and graded using the following criteria (M.G. score) for each eyelid: grade 0, meibomian glands are intact; grade 1, loss of area less than a third of the total area; grade 2, loss of area between one third and two thirds; grade 3, loss of area more than two thirds [19].

Conjunctival hyperemia (R.S.) score: Using Keratograph 5M (Oculus, Germany), participants' red score (R.S.) is generated automatically by assessing the nasal margin, temporal margin, bulbous nasal region, bulbous temporal region of the eye. The software score is the percentage of area between the blood vessel and the rest of the analysis area. R.S. score from 0.0 to 4.0 [20].

Visual acuity (V.A.): The Snellen E chart will be used to test participants' vision at a distance of 5 meters from the chart. First, the right eye will be assessed when the left eye is covered. Then, the left eye will be evaluated, and the right eye will be covered. Finally, a trained optometrist will assess V.A.; if it is less than or equal to 1.0, it is defined as abnormal [21].

Tear Lymphotoxin alpha (LTA) test and MMP-9 concentration: Instant detection of tear LT-alpha concentration and MMP-9 concentration will be assessed using commercial test strips based on colloidal gold and immunochromatographic analysis (Seinda Biomedical Corporation, Guangdong, China) [10]. A disposable tear collector (Seinda, Guangdong, China) will collect a tear sample from the outer corner of the eye. A 10 μL sample of tears will be obtained without anesthesia or causing irritation to the cornea or conjunctiva to avoid reflex tearing. Samples of tears will be taken by instilling 60 μL of phosphate-buffered saline into the inferior fornix without topical anesthetic, then moving the eyes to mix the tear fluid. About 30 μL of unstimulated tear fluid and buffer were

collected from the inferior tear meniscus of each eye using a glass capillary micropipette (Seinda, Guangdong, China) at the lateral canthus. After transporting samples in a 200-μL Eppendorf tube, they were kept at a temperature of −80 °C for further testing [10].

Axial length (A.L.): Zeiss IOL master 700 (Zeiss, Germany) will be used to measure axial changes in participants to assess myopia progression.

4.3. Participant timeline {13}

During the study, participants will undergo ocular surface dry eye parameters examinations at baseline, 1, 3, 6, and 12 months respectively. The study procedures for participant recruitment, intervention, assessment, and data follow-up from the study are consistent with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Table 1), as shown in the flowchart for participant study procedures. The research process is illustrated in Fig. 1.

4.4. Sample size {14}

Two sample t-tests were used for statistical analysis. Calculated at a level of significance 0.05, a 95 % confidence interval, and a power of 80 %, based on clinical data published in previous studies [10], taking into account an estimated 10 % loss rate for follow-up participants, the minimum of required sample size is 300 (150 in each group).

4.5. Recruitment {15}

This study will be conducted from January 2024 to December 2024. Patients will receive the invitation to participate in the study at the Department of Ophthalmology, He Eye Specialist Hospital (HESH). This study is open to children and adolescents diagnosed with myopia at the HESH, Shenyang, China. Participants will be recruited through posters, online advertisements, and social media platforms. Demographic information of the participants will be collected by specialized professionals during the initial diagnosis.

4.6. Allocation {16a,16b,16c}

The patients will be randomly divided into two groups: the study group (OK lenses group), who will wear OK lenses for at least 8 h a day, and the control group will consist of participants wearing spectacles for myopia. It is recommended that participants wear OK lenses overnight for at least 8 hours per day. Statisticians will be responsible for randomizing the participants into OK lenses or spectacles groups, which will be achieved through the use of a network-based randomization procedure. The center with a fixed block size of 4 will stratify the randomization grouping. Sealed opaque envelopes containing the OK lenses and spectacles groups' cards will be in the principal investigator's custody, including registered participant information and intervention records.

5. Blinding {17a,17b}

5.1. Who will be blinded {17a}

The treatment assignment for the study will be single-masked. Participants in the research would be able to recognize their treatment choice (OK lenses or spectacles). However, the data analysis team and the clinical assessment staff will not know the participants group allocation. Masked examiner for all clinical assessments will not be involved in this research's data collection or group allocation procedure.

5.2. Procedure for unblinding if needed {17b}

The conditions and protocols for allowing the disclosure of information will be established and carried out by the P.I.

5.3. Data collection and management{18a,18b,19}

The clinical assessment staff will collect all dry eye parameters using the same instrument and measurement criteria. While the major emphasis of the research is not on dropped cases, however, dropped cases be collected and used for sub-analysis. These cases will be particularly useful for evaluating outcomes such as adverse events and adherence to treatment and trial. All participants will have a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA), intraocular pressure (IOP), fluorescein staining at baseline, 1, 3, 6, 12 months. When participants enroll for the study, trained clinical researchers and outpatient physicians taking part in the clinical trial will enter the information into the electronic case report forms (CRFs). All experimental data will be entered into a specialized management program and stored securely in a database to ensure confidentiality. Designated statisticians of the HESH research team will analyze the anonymized data according to the trial plan. Participant's parents and guardians will be informed in advance and encouraged to actively cooperate with the study to minimize the loss of participants. In this study, there is a rare possibility of conjunctival or corneal infection occurrence due to wearing OK lenses; therefore, in such circumstances, the use of OK lenses will be suspended upon detection of any abnormal ocular symptoms following slit lamp examination and regular telephone and text message updates. Any adverse events are recorded and reported to the trial committee. Patients who cannot finish the

Table 1
Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				
TIMEPOINT	Recruitment (-2 to -4 weeks)	Randomization (0 day)	Baseline	1M (±7 days)	3M (±7 days)	6M (±7 days)	12M (±7 days)
ENROLMENT							
Eligibility screen	X						
Informed consent and assent	X						
Randomization and Allocation		X					
INTERVENTIONS:							
Study group (OKlens group)		←	—	—	—	—	→
Control group (spectacles)		←	—	—	—	—	→

ASSESSMENTS:							
Demographic characteristics	X						
Informed consent and assent	X						
Medical record	X						
Ocular surface disease index			X	X	X	X	X
Visual analog scale			X	X	X	X	X
Noninvasive tear breakup time			X	X	X	X	X
Tear meniscus height			X	X	X	X	X
Meibomian gland score			X	X	X	X	X
Ocular redness			X	X	X	X	X

score							
Tear MMP-9 concentration			X	X	X	X	X
Point-of-care Lymphotoxin alpha test			X	X	X	X	X
Fluorescein staining			X	X	X	X	X
IOP			X	X	X	X	X

subsequent follow-up will be withdrawn from the study. Patients who experience intolerable side effects will be treated and removed immediately from the study.

5.4. Confidentiality {27}

All participants information and clinical data during the study, including personal medical history, will be kept strictly confidential.

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

Not applicable.

5.6. Statistical methods {20a,20b,20c}

A power analysis was conducted using Gpower 3.1, with a power level of 0.95 and an α-error of 0.05. The minimum number of observations was set at $n = 105$. Making sure that the number of participants in each group of the experiment is enough to attain statistical significance. All statistical analyses will be conducted using SPSS software (SPSS for Windows, version 25.0, SPSS, Chicago, IL, USA). The significance level is set to 5 % two-sided, with a confidence coefficient of 95 %. Following the collection of 225 patients, an interim analysis will be conducted to evaluate the p-value. If the p-value is less than 0.05, it indicates that the experiment is meaningful. Further recruitment can be stopped by the P.I. The normality of data distribution will be assessed using the Shapiro-Wilk test. Data will be compared using two-way repeated measures ANOVA. If the hypothesis is unmet ($P > 0.05$), Greenhouse Geisser correction will be used. Multiple comparisons will be made between groups at different time points using the Bonferroni correction. The statistical significance for two-sided tests at $P < 0.05$ unless otherwise specified. To ensure the safety of participants, it is essential to describe the distribution of adverse events (A.E.) in both groups. The incidence rates of A.E. in the two groups were compared using the Chi-square test or Fisher's exact probability test.

5.7. Interim analyses {21b}

Every 3 months, interim analysis will be performed to assess adverse events, adherence to treatment, loss of follow-up, statistical power of the study and myopia progression.

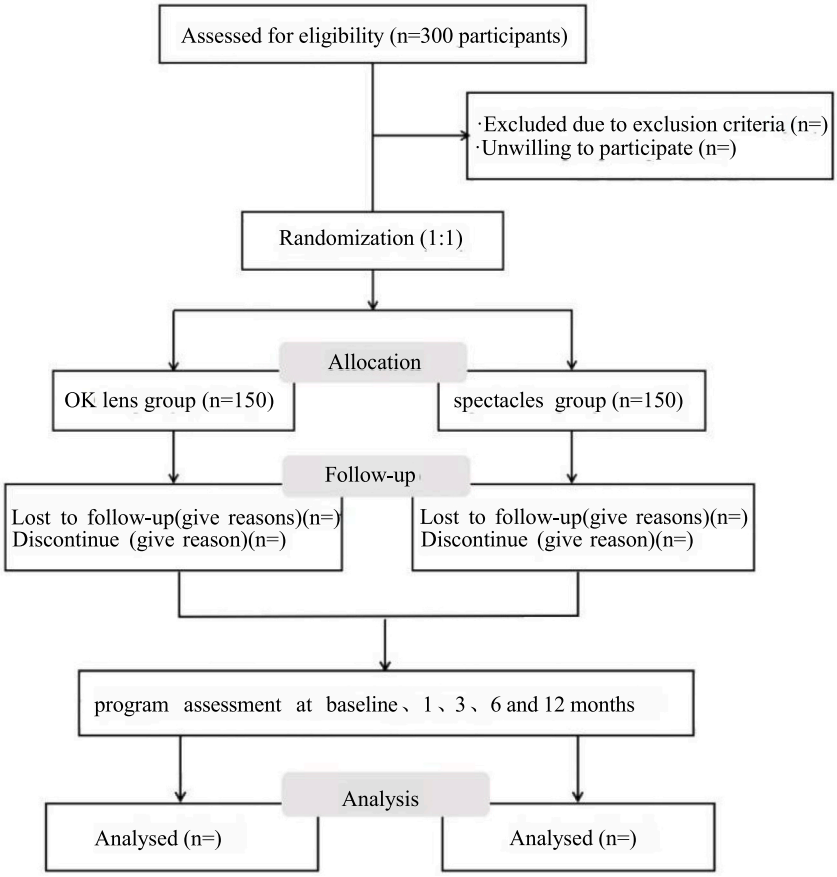

Fig. 1. Study flow diagram.

5.8. Ethics and dissemination{24,31a,31c}

This study will comply with the principles in the Declaration of Helsinki and has received ethics approval from the Institutional Review Board of He Eye Specialist Hospital (HESH), Shenyang, China [ethics approval number: IRB NCT06023108]. Written informed consent and the minor's assent will be obtained.

The research findings will be disseminated to all stakeholders, including participants, family members, physicians, advisory committees, and medical boards. High-impact medical journals and international medical conferences will be utilized for this purpose.

6. Monitoring

6.1. Composition of the trial steering committee {5d}

The Trial Steering Committee (S.C.), consisting of project leaders and decision-makers, manages and supports the study. The SC will offer comprehensive guidance throughout every phase of the research process and will prepare and submit a final report once the study is finished.

6.2. Composition of the data monitoring committee {21a}

Due to the low probability of A.E.s, the data monitoring committee will not be convened for this experiment. A database will be built using Microsoft Excel software (version 16) to collect and record data regularly according to research requirements.

6.3. Adverse event {22}

Any unforeseeable symptoms and signs that may be detrimental to the physical and mental health of the patient are considered adverse events in clinical research. Localized symptoms may include intolerable dry eye symptoms, keratitis, severe corneal ulcers, conjunctivitis, eye irritation, blurred vision, etc. In case of a severe adverse event, it will be reported to the P.I. and review committee,

the trial will be stopped immediately, and appropriate medical treatment will be given to safeguard the individual from further risk.

6.4. Auditing trial conduct {23}

This study will undergo weekly review and assessment by independent supervisors.

6.5. Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

If inclusion criteria and test results are modified, the revised protocol will be submitted to the HESH Medical Ethics Review Committee for approval.

6.6. Limitations

Initially, this study will only be conducted for 12 months. However, a more extended follow-up period is needed to determine the long-term effects of OK lenses on the ocular surface. It is also unclear whether the changes in ocular surface parameters and meibomian gland function are reversible. Secondly, this study is intended to be a single-masked clinical trial, so potential bias may still exist. Potential bias may still exist despite the objective evaluation of data by the researcher.

7. Discussion

In recent years, the safety of OK lenses in children and adolescents has received widespread concern and deserves further investigation. This trial aims to compare and study signs and symptoms of dry eye follow-up with wearing overnight OK lenses and spectacles, including changes in tear film stability, corneal staining, or meibomian gland loss [22]. Previous studies have shown that wearing OK lenses can trigger symptoms such as keratitis. Chen et al. indicated that long-term use of OK lenses affects the thickness of tear film lipid layer after 18 months [23]. Therefore, we intend to conduct a single-center, randomized, controlled, and single-masked clinical trial study. OK lens has been reported to impede the progression of myopia through a reverse geometric design that induces migration and redistribution of corneal epithelial cells while flattening the central part of the corneal [24]. As previously mentioned, one reason for corneal flattening during myopia correction with OK lenses is the hydraulic effect of tears under the lenses. Insufficient tears' quality and quantity may also decrease myopia correction's effectiveness [25,26]. However, long-term impact on tear film stability and corneal epithelium has yet to be comprehensively explored. Since TBUT and Schirmer I tests are considered essential indicators of tear function, Li et al. presented evidence that over-night use of OK lenses is more likely to decrease the stability of tears, however, that has almost no effect on primary tear secretion [27].

Previous studies have reported that OK lenses can lead to ocular inflammation due to their sustained mechanical friction and pressure on the cornea, leading to hypoxia of the ocular surface cells [28,29]. MMP-9 induces degradation of the extracellular matrix, which is associated with an accelerated rate of extracellular matrix degradation, leading to iron deposition and other substances within epithelial cells [30,22]. It plays an increasingly indispensable role in diagnosing dry eye as a promoting mechanism involved in the corneal shaping process and maintaining the effectiveness of OK lenses [31,32]. A multitude of subjects found when wearing OK lenses experienced a decrease in the quality and quantity of tears and corneal staining, mainly those with insufficient tears. The mechanical effects of contact lenses caused by anti-geometric design are considered the leading cause [33]. LTA plays a principal role in determining ocular immunity status subtypes [34]. Previous studies have demonstrated that LTA has pro-inflammatory effects by inducing the production of inflammatory cytokines and stimulating the production of chemokines [35]. There has yet to be a clinical study on LTA levels in patients using overnight OK lenses. Studying the alteration of D.E. parameters and inflammatory markers after wearing OK lenses or spectacles will provide new insights into detecting ocular effects and the most suitable OK lenses wearing time.

In summary, the side effects of OK lenses on the eyes have attracted vast attention. This study aims to investigate the symptoms and signs of dry eyes in children or adolescents caused by wearing OK lenses or spectacles. The results will have instructive significance for the clinical use of OK lenses in the future.

Trial status

The experiment was recruited starting from January 2023 to December 2023.

Funding {4}

This study was funded entirely by He Eye Specialist Hospital, Shenyang, China. There was no support for the publication of this article.

Availability of data and materials {29}

All data analyses and manuscripts produced will be available on request.

Ethics approval consent, and assent to participate {24}

The research registration number is NCT06023108, and it was conducted following the principles outlined in the Declaration of Helsinki and the ethics committee of the He Eye Specialist Hospital, Shenyang, China (IRB (2023) K024.01). All participant's parents or guardians will be required to sign informed consent forms and the minor's assent. In this study, any component of the dataset containing identifiable information was removed if it contained any graphic elements.

Consent for publication {32}

Not applicable.

Competing interests {28}

None.

Data and code availability statement

Data will be made available upon reasonable request.

CRediT authorship contribution statement

Yilin Song: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Jiayan Chen:** Writing – review & editing, Methodology, Conceptualization. **Guanghao Qin:** Writing – review & editing, Methodology, Conceptualization. **Ling Xu:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Wei He:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Sile Yu:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Emmanuel Eric Pazo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Xingru He:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations:

OK	Orthokeratology
DED	Dry eye disease
CRF	Case report form

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