Efficacy and Safety of 0.01% Atropine Eye Drops and Novel Lenslet-ARray-Integrated Spectacle Lenses for the Prevention of Myopia Progression among Children with Premyopia: A Randomized Clinical Trial.

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Trial Protocol

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Protocol Summary

Study Title	Efficacy and Safety of 0.01% Atropine Eye Drops and Novel Lenslet-ARray-Integrated Spectacle Lenses for the Prevention of Myopia Progression among Children with Premyopia
Study Type	A Randomized Clinical Trial
Study Objective	To investigate the efficacy and safety of 0.01% atropine eyedrops and novel Lenslet-ARray-Integrated spectacle lenses in decelerating myopia progression among children with premyopia in China.
Study Endpoint	After enrollment, the patients were treated for 12 months according to the treatment standard
Study Object	6-12 years old children with premyopia
Sample size	400
Inclusion criteria	1) age 6-12 years; 2) cycloplegic spherical equivalent refraction ≤ +0.75 D and > −0.50 D D in both eyes; 3) astigmatism < 1.00 D; 4) uncorrected visual acuity 0.20 logMAR or better in both eyes; 5) intraocular pressures ≤ 21 mmHg; and 6) cycloplegic spherical equivalent refraction of at least one parent ≥ −3.00D.
Exclusion criteria	1) anisometropia ≥ 1.00 D in both eyes; 2) have other eye conditions (strabismus, amblyopia, cloudy refractive media, severe inflammation, or eye tumors); 3) previous or current treatment for controlling myopia progression; 4) allergy to atropine; and 5) inability to complete the research visit plan.
Study Design	In total, 400 participants with premyopia who met the inclusion and exclusion criteria were enrolled and randomly assigned to the following 4 groups in a 1:1:1:1 ratio using a spreadsheet generator (Excel; Microsoft): 0.01% atropine eye drops group (group A), the novel Lenslet-ARray-Integrated spectacle lenses group (group S), the combination group (group AS) and the control group (group E). Measurements were conducted at baseline and at 3, 6, and 12 months of follow-up.
Outcomes	The primary outcomes were the cumulative incidence of myopia (defined as the cycloplegic spherical equivalent of at least -0.50 D) and the percentage of participants with fast myopic shift (defined as a spherical equivalent myopic shift of at least 0.50 D) over one year. Secondary outcomes included changes in spherical equivalent refraction (SER) and axial length (AL). Changes in uncorrected visual activity (UCVA), corneal curvature (CC), and subfoveal choroidal thickness (SFCT) were the exploratory outcomes. Intraocular pressure (IOP) and adverse events were recorded to assess the safety of 0.01% atropine eye drops. The safety of H.O.R.I. was measured by collecting the wearing experiences.
Statistical Analysis	SPSS, version 27.0 (IBM), R statistical software, version 4.2.3 (R Foundation for Statistical Computing) and GraphPad Prism 7 (GraphPad Software) will be employed for data processing and visualization. The Shapiro-Wilk test is adopted to assess the normality of continuous variables, and normally distributed variables are expressed as ($\bar{x}\pm s$). One-way analysis of variance (ANOVA) or independent sample t-tests are used for inter-group comparison. Non-normally distributed variables will be expressed as median (quartile) and compared using the Kruskal-Wallis H test. (n/%) is used to

	represent count data, and the χ^2 test is employed for comparing groups. The analysis focused on data only from the right eye to avoid potential correlation problems between the two eyes. $P < 0.05$ is deemed statistically significant.
Baseline and Follow-up	The baseline examination is in November 2023 to February 2024. The follow-up visits are 3, 6 and 12 months after enrollment..

1 Introduction

1.1 Background

For decades, several studies have been conducted to understand the development of myopia and decipher how to prevent its progression. The number of people affected by myopia is increasing worldwide, and it is estimated that by 2050, nearly 5 billion people worldwide will be nearsighted, nearly 1 billion people will have high myopia, and myopia will become the leading cause of permanent blindness worldwide [1].

Myopia is harmful to students' eyesight and imposes a heavy economic burden on society. It is one of the most common health problems among children and adolescents in China [2]. Myopia often causes problems, such as dry eye, fatigue, and swollen eyes, and high myopia can increase the risk of vision loss due to glaucoma, cataracts and retinal detachment [3]. Earlier onset of myopia is associated with faster progression of myopia and a higher final degree of myopia in adults [4, 5]. Therefore, early prevention and control of myopia among young children is crucial to minimize the risk of myopia-associated complications in later life.

To provide a framework for research into the prevention of myopia, International Myopia Institute (IMI) White Papers published in 2019 defined the condition of premyopia as a refractive state of an eye of $\leq +0.75$ D and > -0.50 D in children where a combination of baseline refraction, age, and other quantifiable risk factors provide a sufficient likelihood of the future development of myopia to merit preventative interventions [6]. Studies have found that the refraction and axial length (AL) change faster among children with pre-myopic, and their rate of change gradually decelerates after the development of myopia [7, 8]. Premyopia is the first early warning sign, which can help find high-risk children, and reduce the

incidence of myopia and the final degree of myopia, which is crucial for the prevention and control of myopia [9,10].

There are three effective interventions for myopia control in premyopia children, including environmental, pharmacological, and optical approaches [11,12,13].

Increased outdoor time and light exposure can lower the incidence of myopia. Clinical studies have found that increased outdoor time was an effective preventive measure in children with high hyperfarsightedness reserve. But paradoxically, outdoor time was not effective in decelerating the progression of myopia among those who were already affected [14]. Therefore, the effect of behavioral intervention is limited among children with premyopia, and clinical intervention may be needed to prevent or delay the onset of myopia.

Currently, low-concentration atropine eye drops play a dominant role in the pharmacological treatment of myopia. ATOM2 has been shown to be effective and safe when different concentrations of atropine are compared, indicating that 0.01% atropine is the optimal concentration for clinical use [15,16]. Its effectiveness and safety in children with premyopia need further studies [17-19].

Optical correction modalities, such as orthokeratology, multifocal myopia control contact lenses, and peripheral defocus spectacles, are the most commonly employed methods and can effectively control myopia [20-23]. However, the efficacy of optical therapies in preventing myopia progression among premyopic children remains inconclusive. The novel Lenslet-ARray-Integrated spectacle lenses was employed in this study, and the lens degree was from +1.00 to -12.00D, which made the optical intervention in premyopia possible. In addition, previous studiy has reported the efficacy of optical intervention in combination with 0.01% atropine for controlling myopia [24]. Further research is

warranted to investigate both the clinical necessity of combination therapies for children with premyopia and the potential synergistic effects that may arise from such combined interventions.

1.2 Study purpose

Therefore, this prospective, randomized, controlled trial was conducted to investigate the efficacy and safety of 0.01% atropine, novel Lenslet-ARray-Integrated spectacle lenses, and their combination in decelerating the progression of myopia among Chinese children with premyopia and provide clinical evidence for the development of individualized treatment of premyopia.

2 Methods

2.1 Sample size

The sample size was calculated based on previous research [19, 30-31]. We assumed that clinical interventions reduced the myopia shift by at least −0.36 D ($\delta = 0.36$) with a standard deviation of 0.70D ($\sigma = 0.70$), assuming a power of 90% ($\beta = 0.10$) with a two-sided test of 5% ($\alpha = 0.05$). The formula for calculating the sample size is as follows:

$$n = \frac{2\sigma^2(Z1 - \alpha/2 + Z1 - \beta)^2}{\delta^2}$$

Considering a dropout rate of 20%, 100 participants were considered sufficient for each group.

2.2 Inclusion criteria

1) age 6-12 years;

2) cycloplegic spherical equivalent refraction ≤ +0.75 D and > −0.50 D in both eyes;

3) astigmatism < 1.00 D;

4) uncorrected visual acuity 0.20 logMAR or better in both eyes;

5) intraocular pressures ≤ 21 mmHg;

6) cycloplegic spherical equivalent refraction of at least one parent ≥ −3.00D.

2.3 Exclusion criteria

1) anisometropia ≥ 1.00 D in both eyes;

2) have other eye conditions (strabismus, amblyopia, cloudy refractive media, severe inflammation, or eye tumors);

3) previous or current treatment for controlling myopia progression;

4) allergy to atropine;

5) inability to complete the research visit plan.

2.4 Withdrawal criteria

1) Participants enrolled per inclusion/exclusion criteria who fail to initiate the clinically prescribed conventional treatment regimen specified in the study protocol;

2) Participants who voluntarily withdraw informed consent and discontinue study participation during the clinical trial.

2.5 Study termination criteria

1) The study may be terminated if unacceptably severe safety concerns emerge, such as serious adverse events;

2) The study may be prematurely terminated if statistically significant efficacy is conclusively demonstrated, rendering further research unlikely to alter established conclusions;

3) Early termination may occur if the study fails to achieve anticipated therapeutic outcomes, with sufficient evidence indicating continued investigation would not modify this conclusion;

4) The study may be discontinued due to insufficient participant enrollment, where inadequate sample size would compromise statistical validity and result interpretation.

2.6 Study design, randomization and interventions

Participants with premyopia who meet the inclusion and exclusion criteria will be enrolled and randomly assigned to the following 4 groups in a 1:1:1:1 ratio using a spreadsheet generator (Excel; Microsoft): 0.01% atropine eye drops group (group A), the novel Lenslet-ARray-Integrated spectacle lenses group (group S), the combination group (group AS) and the control group (group E). In addition to the clinical routine knowledge education on the prevention of myopia (including no less than 10 hours of outdoor activities per week) in the four groups, group A will be given 0.01% atropine (daily, one drop at a time) eye drops packed with unit dose and without preservatives (Sinqi Pharmaceutical, Shenyang, China; approved by the National Medicine H20240320). Group S will be given novel Lenslet-ARray-Integrated spectacle lenses (manufacturer: Vision Eye Care Technology, Guangdong, China; registration number: 68736330), which was worn for 12 hours per day. The combination group will be given both treatments. No clinical intervention will be given in the control group.

2.7 Outcomes

The primary outcomes are the cumulative incidence of myopia (defined as the cycloplegic spherical equivalent of at least -0.50 D) and the percentage of participants with fast myopic shift (defined as a spherical equivalent myopic shift of at least 0.50 D) over one year. Secondary outcomes includes changes in spherical equivalent refraction (SE) and axial length (AL). Changes in uncorrected visual activity (UCVA), corneal curvature (CC), and subfoveal choroidal thickness (SFCT) are the exploratory outcomes. Intraocular pressure (IOP) and adverse events were recorded to assess the safety of 0.01% atropine eye drops. The safety of the novel Lenslet-ARray-Integrated spectacle lenses will be measured by collecting the wearing experiences.

2.8 Statistical analysis

SPSS, version 27.0 (IBM), R statistical software, version 4.2.3 (R Foundation for Statistical Computing) and GraphPad Prism 7 (GraphPad Software) will be employed for data processing and visualization. The Shapiro-Wilk test is adopted to assess the normality of continuous variables, and normally distributed variables are expressed as ($\bar{x} \pm s$). One-way analysis of variance (ANOVA) or independent sample t-tests are used for inter-group comparison. Non-normally distributed variables will be expressed as median (quartile) and compared using the Kruskal-Wallis H test. (n/%) is used to represent count data, and the χ^2 test is employed for comparing groups. The analysis focused on data only from the right eye to avoid potential correlation problems between the two eyes. $P < 0.05$ is deemed statistically significant. The analysis was conducted on complete case data without imputing missing data and dropouts. The analysis focused on data only from the right eye to avoid potential correlation problems between the two eyes. $P < 0.05$ was deemed statistically significant.

3. Adverse events and serious adverse events

For 0.01% atropine eye drops: Possible AEs include conjunctivitis/keratitis (manifesting as ocular pain, blurred vision, conjunctival hyperemia, corneal lesions, or eyelid edema) and glaucoma (manifesting as ocular pain, blurred vision, conjunctival hyperemia, shallow anterior chamber, or elevated intraocular pressure).

For novel myopia-control spectacles: AEs may include ocular discomfort or blurred vision due to improper wear.

Recurrent AEs in the same participant after recovery should be documented as separate events.

Onset Date: Date of first AE occurrence or symptom presentation.

Resolution Date: Date of AE/symptom resolution.

Severity: Graded as mild, moderate, or severe.

Causality Assessment: Relationship to study intervention.

Actions Taken: No intervention required, pharmacological treatment based on ocular status, observation after reassurance, immediate discontinuation of intervention, or other measures.

Outcome: Resolved, improved, or unresolved.

4 Study feasibility analysis

The principal investigator possesses the qualifications, expertise, and technical capacity to conduct this trial, with dedicated time for study execution.

The research team and required equipment meet trial specifications, including:

Standard logarithmic distance visual acuity charts

Auto-refractometer

Slit-lamp biomicroscope

Zeiss HD-OCT 5000

Lenstar LS 900 (HAAG-STREIT AG, Koeniz, Switzerland).

5 Ethical Principles

5.1 Ethical compliance

This study adheres to the Declaration of Helsinki, China's Ethical Review Measures for Life Sciences and Medical Research Involving Human Subjects, and relevant international regulations. Prior to commencement, the protocol and informed consent documents were approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University.

Protocol or consent form modifications require ethics committee reapproval.

All SAEs must be reported to the ethics committee within 24 hours.

Protocol deviations increasing participant risk require immediate ethics committee notification.

Confidentiality of participant data is maintained, with regulatory authorities retaining audit rights.

Participants are entitled to compensation for study-related injuries.

5.2 Informed consent

Written informed consent must be obtained from all participants (or legal guardians for minors/incapacitated individuals) prior to enrollment. The consent form, presented in comprehensible language/multimedia formats, includes:

Study objectives, procedures, risks, and benefits;

Right to withdraw without penalty;

Data confidentiality provisions.

For participants unable to provide written consent, oral consent with audio/video documentation is permissible.

6 Dissemination of Research Outcomes

Study results are anticipated to be published in peer-reviewed journal articles by 2025.

References

1. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology. 2016;123(5):1036-1042.

2. Chinese Optometric Association, Chinese Ophthalmological Society; et al. Chinese Journal of Optometry Ophthalmology and Visual science, 2022, 24(9): 641-648.

3. Németh J, Tapasztó B, Aclimandos WA, et al. Update and guidance on management of myopia. European Society of Ophthalmology in cooperation with International Myopia Institute. Eur J Ophthalmol. 2021;31(3):853-883.

4. Hu Y, Ding XH, Guo XX, et al. Association of age at myopia onset with risk of high myopia in adulthood in a 12-year follow-up of a Chinese Cohort. JAMA Ophthalmol.2020;138:1129–1134.

5. Parssinen O, Kauppinen M. Risk factors for high myopia: a 22-year follow-up study from childhood to adulthood. Acta Ophthalmol.2019;97:510–518.

6. IMI - Defining and Classifying Myopia: A Proposed Set of Standards for Clinical and Epidemiologic Studies. Invest Ophthalmol Vis Sci. 2019;60(3):M20-M30.

7. Mutti DO, Hayes JR, Mitchell GL,et al. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. Invest Ophthalmol Vis Sci.2007;48:2510–2519.

8. Xiang F, He MG, Morgan IG. Annual changes in refractive errors and ocular components before and after the onset of myopia in Chinese children. Ophthalmology.2012;119:1478–1484.

9. Wu PC, Chuang MN, Choi J,et al.Update in myopia and treatment strategy of atropine use in myopia control. Eye.2019;33:3–13.

10. Modjtahedi BS, Abbott RL, Fong DS,et al. Reducing the global burden of myopia by delaying the onset of myopia and reducing myopic progression in children the academy's task force on myopia. Ophthalmology.2021;128:816–826.

11. Brennan NA, Toubouti YM, Cheng X, Bullimore MA. Efficacy in myopia control. Prog Retin Eye Res. 2021;83:100923.

12. He M, Xiang F, Zeng Y, et al. Effect of Time Spent Outdoors at School on the Development of Myopia Among Children in China: A Randomized Clinical Trial. JAMA. 2015;314(11):1142-1148.

13. Huang J, Wen D, Wang Q, et al. Efficacy Comparison of 16 Interventions for Myopia Control in Children: A Network Meta-analysis. Ophthalmology. 2016;123(4):697-708.

14. Xiong S, Sankaridurg P, Naduvilath T, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. Acta Ophthalmol. 2017;95(6):551-566.

15. Chia A, Chua WH, Cheung YB, et al. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). Ophthalmology. 2012;119(2):347-354.

16. Wei S, Li SM, An W, et al. Safety and Efficacy of Low-Dose Atropine Eyedrops for the Treatment of Myopia Progression in Chinese Children: A Randomized Clinical Trial. JAMA Ophthalmol. 2020;138(11):1178-1184.

17. Fang PC, Chung MY, Yu HJ, Wu PC. Prevention of myopia onset with 0.025% atropine in premyopic children. J Ocul Pharmacol Ther. 2010;26(4):341-345.

18. Jethani J. Efficacy of low-concentration atropine (0.01%) eye drops for prevention of axial myopic progression in premyopes. Indian J Ophthalmol. 2022;70(1):238-240.

19. Wang W, Zhang F, Yu S, et al. Prevention of myopia shift and myopia onset using 0.01% atropine in premyopic children - a prospective, randomized, double-masked, and crossover trial. Eur J Pediatr. 2023;182(6):2597-2606.

20. Bao J, Huang Y, Li X, et al. Spectacle Lenses With Aspherical Lenslets for Myopia Control vs Single-Vision Spectacle Lenses: A Randomized Clinical Trial. JAMA Ophthalmol. 2022;140(5):472-478.

21. Cho P, Cheung SW. Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. Invest Ophthalmol Vis Sci. 2012;53(11):7077-7085. Published 2012 Oct 11.

22. Lam CSY, Tang WC, Tse DY, et al. Defocus Incorporated Multiple Segments (DIMS) spectacle lenses slow myopia progression: a 2-year randomised clinical trial. Br J Ophthalmol. 2020;104(3):363-368.

23. Li SM, Kang MT, Wu SS, et al. Studies using concentric ring bifocal and peripheral add multifocal contact lenses to slow myopia progression in school-aged children: a meta-analysis. Ophthalmic Physiol Opt. 2017;37(1):51-59.

24. Wildsoet CF, Chia A, Cho P, et al. IMI - Interventions Myopia Institute: Interventions for Controlling Myopia Onset and Progression Report. Invest Ophthalmol Vis Sci. 2019;60(3):M106-M131.