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ORIGINAL RESEARCH

The Effect of Repeated Low-Level Red Light Versus 0.01% Atropine Treatment on Axial Length and Choroidal Parameters in Children with Myopia

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ABSTRACT

Introduction: This research was designed to compare the effectiveness of repeated low-level red light (RLRL) and 0.01% atropine on axial length (AL), spherical equivalent refraction (SER), and choroidal parameters in children with myopia.

Methods: We conducted a prospective, randomized, and single-blind controlled trial. Ninety-one children aged 6–12 years old were selected, with cycloplegic SER ≥ − 5.00 D and ≤ − 0.75 D. Participants were randomly assigned to the RLRL group and 0.01% atropine group. The primary outcomes included changes in AL, SER, and choroidal parameters after a duration of 6 months. Choroidal parameters specifically including the foveal, parafoveal, and perifoveal choroidal thickness (ChT) and the foveal, parafoveal, and perifoveal choroidal vessel volume (CVV).

Results: At 6-month follow-up, the AL and SER changes were − 0.09 mm (− 0.18, 0.01) compared to 0.13 mm (0.05, 0.24) ($p<0.001$) and 0.25 D (0, 0.50) compared to − 0.25 D (− 0.53, 0) ($p<0.001$) in the RLRL and 0.01% atropine groups. The foveal, parafoveal and perifoveal ChT changes were 36.38 μm (14.05, 65.39), 31.04 μm (4.09, 59.35), and 28.48 μm (5.35, 55.15), compared to 0.94 μm (− 9.20, 9.36), 3.52 μm (− 10.24, 14.45), and 6.14 μm (− 5.21, 15.69) (all $p<0.001$) in the RLRL and 0.01% atropine groups. The foveal, parafoveal, and perifoveal CVV changes were 0.01 μm^3 (0.00, 0.02), 0.05 μm^3 (0.02, 0.09), and 0.20 μm^3 (0.05, 0.30) compared to 0.00 μm^3 (− 0.00, 0.01), 0.01 μm^3 (− 0.02, 0.03), and 0.01 μm^3 (− 0.06, 0.09) ($p<0.001$) in the corresponding two groups.

Conclusions: After 6 months of treatment, RLRL was more effective than 0.01% atropine in controlling axial elongation and myopic progression among children with myopia. The foveal, parafoveal, and perifoveal ChT and foveal, parafoveal, and perifoveal CVV changes in the RLRL group were significantly higher than those in the 0.01% atropine group.

Keywords: Myopia; Repeated low-level red light (RLRL); 0.01% Atropine; Axial length; Choroidal thickness; Choroidal vessel volume

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Key Summary Points

Why carry out this study?

Myopia has emerged as a significant public health concern impacting the visual well-being of children and adolescents worldwide. The global prevalence of myopia is presently growing at an accelerated rate.

0.01% Atropine is a reasonable concentration to delay myopia progression in children, but the control effect is limited. The effectiveness of repeated low-level red light (RLRL) in delaying the development of myopia among children has been clinically certified.

This research aimed to evaluate the impact of RLRL and 0.01% atropine, and explored the potential mechanism of RLRL and 0.01% atropine in delaying myopia progression in choroidal thickness (ChT) and choroidal vessel volume (CVV).

What was learned from the study?

RLRL was more effective than 0.01% atropine in controlling axial elongation and myopic progression among children with myopia. The ChT and CVV changes in the RLRL group were significantly higher than those in the 0.01% atropine group.

INTRODUCTION

Myopia has emerged as a significant public health concern impacting the visual well-being of children and adolescents worldwide [1–3]. The global prevalence of myopia is presently growing at an accelerated rate. The prevalence of myopia is expected to reach 49.8% by 2050, totaling 4.8 billion people [4]. Myopia is more than just a common refractive error; it constitutes a vision-threatening condition. Myopia usually develops rapidly during childhood and, if left unmanaged, may further evolve into other serious eye conditions [5–7]. It is vital to find an efficacious treatment for myopia to control its development, given that the condition is associated with an upward trend in prevalence, younger age, and severity [4–8].

Atropine is the most commonly utilized medication for myopia control, and its effectiveness is highly correlated with concentration. Researchers demonstrated that a high concentration of atropine significantly retards the progression of myopia clinically; however, there are severe side effects, including rebound effects after drug withdrawal [9–23]. Thus, researchers found 0.01% atropine is a reasonable concentration to delay myopia progression in children and adolescents [24, 25].

Increasing exposure time under bright natural light outdoors is considered an effective protective factor against the onset of myopia [26–29], but its effectiveness in slowing myopia progression remains more controversial [30–32]. Furthermore, a substantial amount of extracurricular outdoor time is required to make the process effective, which is not practically feasible. As a result, researchers in China have proposed a new approach as a substitute for increasing light, involving low-intensity red light with a 650 nm wavelength in a concentrated beam. The effectiveness of repeated low-level red light (RLRL) in delaying the development of myopia among children has been clinically certified [33–42]. Only one randomized controlled trial of atropine vs. RLRL has been performed, by Chen et al. [36], which showed that RLRL was a better intervention than 0.01% atropine for myopia control. However, it did not measure the choroidal parameters. This research aimed to evaluate the impact of RLRL on managing children with myopia by examining the effectiveness disparity between RLRL and 0.01% atropine over 6 months, and explored the potential mechanism of RLRL and 0.01% atropine in delaying myopia progression in choroidal thickness and choroidal blood flow.

METHODS

Study Population

This study recruited Chinese schoolchildren with myopia who visited the First Affiliated Hospital of Zhengzhou University from November 2021 to March 2022. Inclusion criteria were

6–12 years of age with a spherical equivalent refraction (SER) ≥ − 5.00 D and ≤ − 0.75 D after cycloplegia in both eyes, astigmatism < 2.00 D, best-corrected visual acuity of 20/20 or better in monocular vision, and intraocular pressure ≤ 21 mmHg. The exclusion criteria were use of alternative medications or techniques for myopia prevention, past/current amblyopia or strabismus, and conflict with the research schedule. The Human Ethics Committee of the First Affiliated Hospital of Zhengzhou University approved this study (No. 2021-KY-0399-003), and it was subsequently registered in the Chinese Clinical Trial Registry (Registration number ChiCTR2100052964, registration date 2021-11-06). Before treatment commenced, the guardians were provided with a comprehensive explanation of the potential hazards involved and their consent was obtained.

Study Design, Randomization, and Masking

This research was carried out in two periods. During period 1, participants were randomly distributed equally to the 0.01% atropine or RLRL groups for 6 months, after which there was a 1-month recovery period with no therapy. Subsequently, participants from the 0.01% atropine group underwent a crossover to the RLRL group, while the participants in the RLRL group underwent a crossover to the 0.01% atropine group during the second 6 months of period 2. This study presents the findings of the initial 6-month investigation, often known as the period 1 study. All participants had the same medical examination procedure at the initial and the 3-month and 6-month visits. Participants were instructed to wear monofocal glasses during class if their uncorrected visual acuity activity was less than 0.8 in both eyes, which interfered with their learning.

A statistician performed simple randomization independently, and the randomization methods are in Supplementary File 1. As a result of the nature of the intervention, the participants themselves were aware of the grouping results, while outcome evaluators, including technicians, optometrists, and statisticians, were blinded to the two groups.

Intervention (0.01% Atropine Eye Drops and RLRL)

Supplementary File 2 presents the preparation of 0.01% atropine eye drops. Each child was given a single drop of 0.01% atropine to put in their eyes before going to sleep each night. A record calendar was distributed to the parents; at each follow-up visit, the children were asked to return the record calendar and three bottles. Treatment compliance was calculated as a percentage of the number recorded over the total treatment course specified for the entire treatment period; compliance was considered inadequate if the proportion of 0.01% atropine was less than 80%.

The RLRL device was obtained from Eyerising (Suzhou Xuanjia Photoelectric Technology, Jiangsu, China), which employs a semiconductor laser diode to emit red light with a 650 ± 10 nm wavelength, illuminating from pupil to fundus at an illuminance level of 1600 lx, including a light spot diameter of 10 ± 3 mm at the exit peephole and mean energy of the light source is 2.0 ± 0.5 mW. The device was used with the supervision of the participant's guardian, and the time of treatment could be recorded; additionally, it could control the luminescence according to the scheduled treatment arrangements (3 min each time, twice a day, at least 4 h apart, repeated once a day). Treatment adherence was derived by dividing the total number of completed sessions by the total number of designated therapy sessions throughout the treatment duration. A percentage of RLRL instrument usage below 80% was deemed poor compliance.

Study Procedures

Before cycloplegia, a non-touch partial correlation interferometric instrument (IOLMaster 500; Carl Zeiss Meditec AG, Germany) was used to assess the axial length (AL), corneal power, and anterior chamber depth (ACD). Each occasion involved five consecutive measurements, and the mean value of the SNR ≥ 5 was used for the analysis. The IOLMaster 500 demonstrated a repeatability of ± 0.05 mm in AL measurements [43]; AL shortening was defined as decrease of

AL more than 0.05 mm from baseline. Both eyes received four drops of tropicamide eye solution (0.5% tropicamide and 0.5% neo-synephrine) (Santen, Japan) with a 10-min interval between administrations to perform cycloplegic autorefraction. Circumferential autorefraction was determined thrice using an automatic refractometer (NIDEK, AR-1, Japan) 10 min after the last drop. The analysis involved averaging three readings, each differing by 0.25 D. The SER was determined by adding sphere power to 1/2 of cylinder power.

In the state of cycloplegia, the choroidal thickness (ChT) and choroidal vessel volume (CVV) were obtained using scanning frequency swept-source optical coherence tomography (SS-OCTA, VG200S; SVision Imaging, Ltd., Henan, China). CVV stands for volume of large and medium vascularized choroidal vessels. Meanwhile, in the Early Treatment Diabetic Retinopathy Study (ETDRS), the entire macular zone (6 mm × 6 mm range) was divided into three concentric circles (0–1 mm diameter foveal, 1–3 mm diameter parafoveal and 3–6 mm diameter perifoveal) (Fig. 1). Details of the measuring method of ChT and CVV are provided in Supplementary File 3. The right eye was examined first, and only high-quality scans (signal strength ≥ 8) were selected.

At each trial, participants in both groups were administered a questionnaire on symptoms of discomfort. Details of the discomfort symptoms for the RLRL group and 0.01% atropine group can be viewed in Supplementary File 4.

Data Analysis

The sample size was determined using data from previous studies [15, 37]. Our assumptions are as follows: an alpha value of 0.05, 90% power, a 0.18 mm axial elongation with a standard deviation (SD) of 0.13 mm over 6 months in the atropine group, and a 50% treatment effect (reducing axial elongation by 0.09 mm in the RLRL group). Therefore, this crossover trial necessitated the inclusion of 72 participants. Considering a 25% withdrawal ratio, a minimum of 90 children was needed.

All measurements from the right eye of those who accomplished the 6-month examination were incorporated into the outcome analysis. The Shapiro–Wilk test was used to check for the normality of continuous variables. Normally distributed parameters were characterized as mean ± SD and were assessed using Student's *t* test. Non-normally distributed continuous variables are presented as medians and interquartile range (median [Q1, Q3]) and evaluated using the non-parametric rank-sum test. Categorical parameters like gender were represented as percentages (%) and analyzed by the chi-squared test. The Mann–Whitney *U* test was used to compare the differences in AL, SER, and choroid parameters between the two groups. A generalized additive mixed model was employed to examine the temporal variations in AL and SER of the two groups, considering potential confounders. The levels of statistical significance set at $p < 0.05$ and Empower (*R*) software was employed for analysis.

RESULTS

Baseline Characteristics

Out of the initial sample of 100 children, 91 children fulfilled the inclusion criteria in the study. Among them, 46 were randomly assigned to the RLRL group, and 45 were randomly assigned to the 0.01% atropine group. Among the participants, 87 children (95.6%) completed the 6-month visit. This included 45 children (97.8%) from the RLRL group and 42 children (93.3%) from the 0.01% atropine group (Fig. 2). The mean treatment compliance in children using RLRL and 0.01% atropine was 83.2% and 83.5%, respectively. No significant differences in baseline values were observed between the two groups (all $p > 0.05$; Table 1). There were no significant differences in the age, gender, baseline SER, baseline AL between the dropout children and those who completed the study (all $p > 0.05$).

Changes in AL and SER

During a period of 6 months, distinct differences in the variations of AL and SER between the two groups were observed. The change in

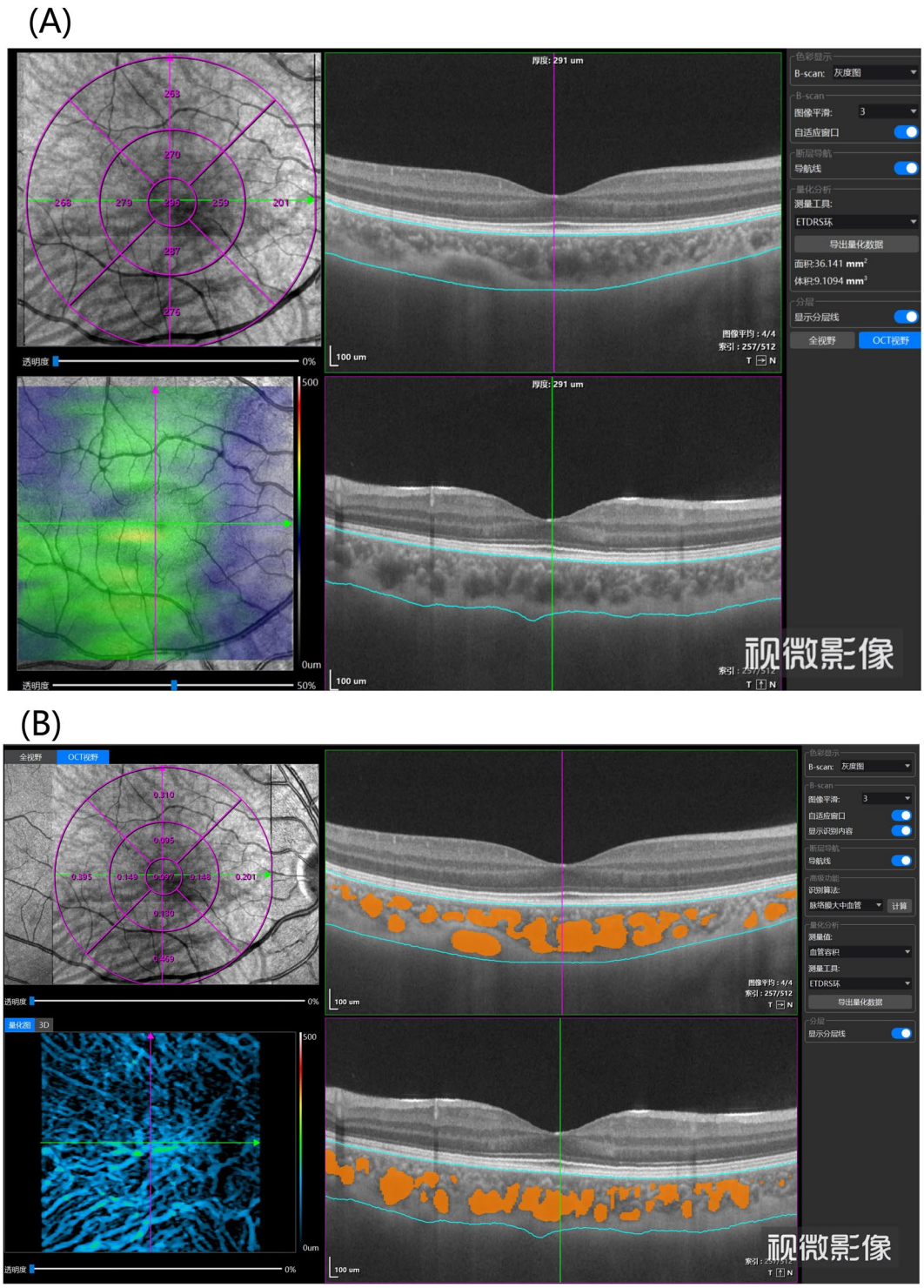

Fig. 1 Illustration of SS-OCT imaging. The entire macular zone was divided into three concentric circles (0–1 mm diameter foveal, 1–3 mm diameter parafoveal, and 3–6 mm diameter perifoveal). **a** Measurement of ChT by SS-OCT. **b** Measurement of CVV by SS-OCT

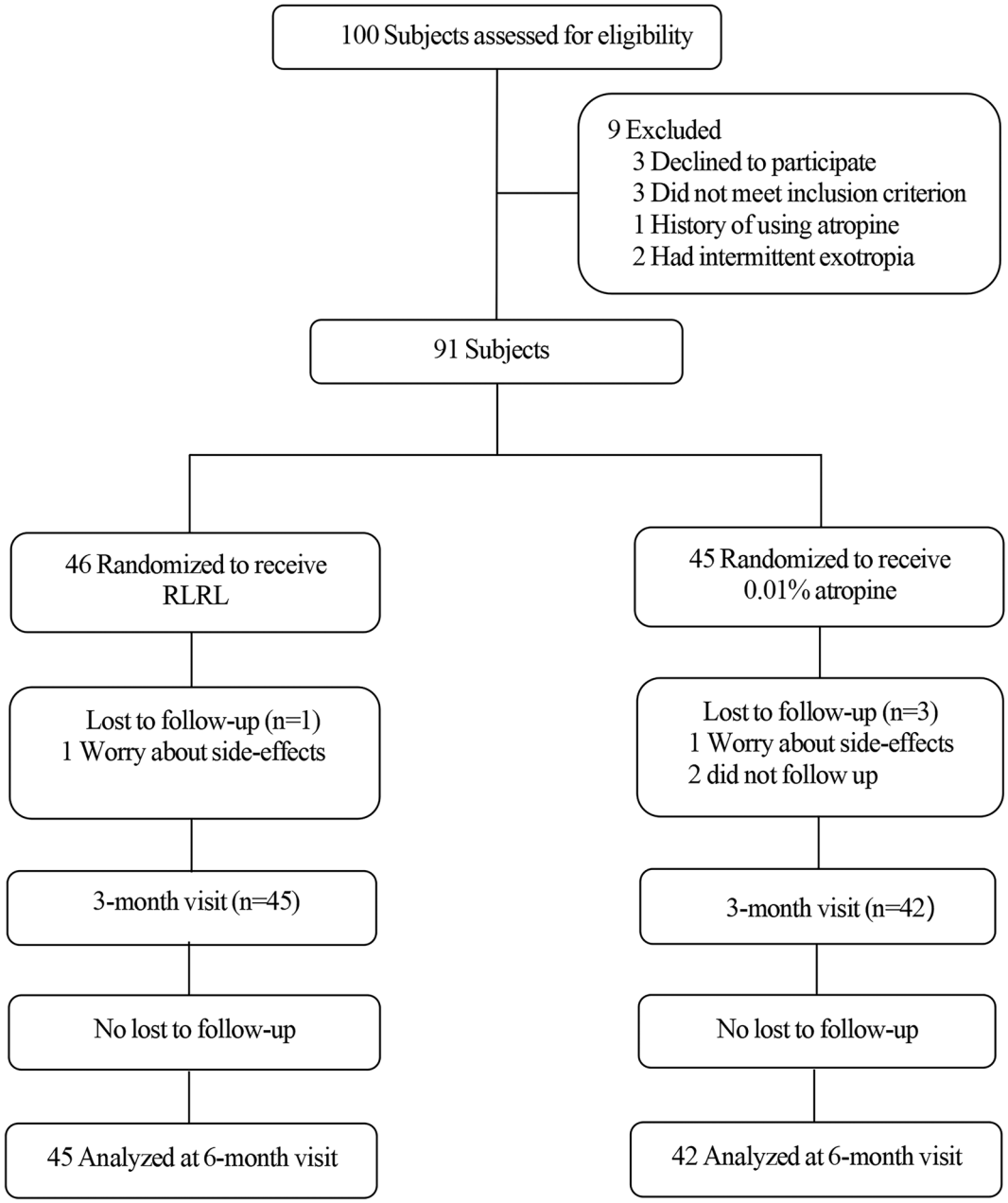

Fig. 2 Flowchart of subject recruitment and group allocation

AL was −0.09 mm (−0.18, 0.01) compared to 0.13 mm (0.05, 0.24) in the RLRL group and 0.01% atropine group ($Z = -6.12$, $p < 0.001$), and the change in SER was 0.25 D (IQR 0, 0.50) compared to −0.25 D (IQR −0.53, 0) ($Z = -6.02$, $p < 0.001$) in the corresponding two groups (Table 2, Fig. 3). RLRL performed better than 0.01% atropine. The generalized additive mixed model (adjusted for age, baseline SER, and baseline AL) showed that the difference in AL (β = −0.21, 95% CI 0.77 to 0.86, $p_{time \times group} < 0.001$) and SER (β = 0.47, 95% CI 1.41 to 1.80, $p_{time \times group} < 0.001$) between the two groups increased over time.

Table 1 Baseline characteristics of study participants

	RLRL group ($N=45$)	0.01% Atropine group ($N=42$)	p value
Sex			
Male, *n*	21 (46.7%)	23 (54.8%)	0.45
Female, *n*	24 (53.3%)	19 (45.2%)	
Age (year)	9.27 ± 1.45	8.98 ± 1.27	0.32
BMI	17.20 ± 2.96	17.60 ± 3.05	0.53
Flat corneal curvature (D)	42.96 ± 1.42	42.49 ± 1.27	0.11
Corneal astigmatism (D)	− 1.03 ± 0.49	− 1.18 ± 0.49	0.16
Pupil diameter (mm)	5.98 ± 0.81	6.12 ± 0.68	0.39
Accommodative amplitude (D)	14.28 ± 1.42	14.76 ± 1.81	0.17
Anterior chamber depth (mm)	3.73 ± 0.21	3.70 ± 0.26	0.48
Intraocular pressure (mmHg)	18.16 ± 2.39	18.11 ± 2.36	0.93
Spherical equivalent refractive error (D)	− 2.43 ± 1.13	− 2.28 ± 1.04	0.51
Axial length (mm)	24.33 ± 0.81	24.52 ± 0.82	0.29
Choroidal thickness (μm)			
Foveal choroidal thickness	297.89 ± 51.04	286.62 ± 38.93	0.25
Parafoveal choroidal thickness	292.55 ± 54.62	278.09 ± 45.70	0.13
Perifoveal choroidal thickness	285.74 ± 48.62	268.05 ± 39.61	0.07
Choroidal vessel volume (μm^3)			
Foveal choroidal vessel volume	0.08 ± 0.02	0.08 ± 0.01	0.13
Parafoveal choroidal vessel volume	0.64 ± 0.14	0.60 ± 0.13	0.27
Perifoveal choroidal vessel volume	1.99 ± 0.37	1.92 ± 0.34	0.37
Heredity			
−− (neither parent myopic)	4 (8.9%)	4 (11.1%)	0.71
+− (one parent myopic)	19 (42.2%)	12 (33.3%)	
++ (both parents myopic)	22 (48.9%)	20 (55.6%)	

Data are presented as mean ± SD or *N* (%)

SD standard deviation, *RLRL* repeated low-level red light, *BMI* body mass index, *foveal* 0–1 mm diameter, *parafoveal* 1–3 mm diameter, *perifoveal* 3–6 mm diameter

Changes in Choroidal Parameters

The ChT changes were significantly different between the two groups compared to the baseline at 3 months and 6 months (Table 3). The foveal, parafoveal, and perifoveal ChT changes were 36.38 μm (14.05, 65.39), 31.04 μm (4.09, 59.35), and 28.48 μm (5.35, 55.15), compared to 0.94 μm (− 9.20, 9.36),

Table 2 Changes in AL and SER after treatment in the two groups

	RLRL group $N=45$	0.01% Atropine group $N=42$	*p* value
AL, mm			
Baseline to 3 months	−0.07 (−0.17, 0.01)	0.07 (−0.03, 0.12)	< 0.001
Baseline to 6 months	−0.09 (−0.18, 0.01)	0.13 (0.05, 0.24)	< 0.001
SER, D			
Baseline to 3 months	0.25 (0, 0.37)	0 (−0.37, 0)	< 0.001
Baseline to 6 months	0.25 (0, 0.50)	−0.25 (−0.53, 0)	< 0.001

RLRL repeated low-intensity red light, *AL* axial length, *SER* spherical equivalent refraction

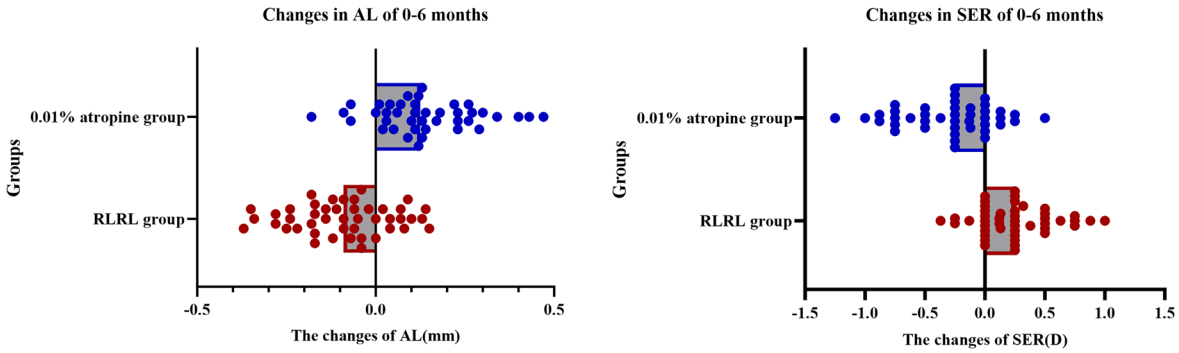

Fig. 3 Changes in AL and SER from 0 to 6 months

3.52 μm (−10.24, 14.45), and 6.14 μm (−5.21, 15.69) (all $p<0.001$) in the RLRL and 0.01% atropine groups at 6 months.

The CVV changes were significantly different between the two groups compared to the baseline at 3 months and 6 months (Table 4). The foveal, parafoveal, and perifoveal CVV changes were 0.01 μm^3 (0.00, 0.02), 0.05 μm^3 (0.02, 0.09), and 0.20 μm^3 (0.05, 0.30) compared to 0.00 μm^3 (−0.00, 0.01), 0.01 μm^3 (−0.02, 0.03), and 0.01 μm^3 (−0.06, 0.09) ($p<0.001$) in the RLRL and 0.01% atropine groups at 6 months.

Changes in Internal Axial Length

The internal axial length (IAL), which refers to the length from the anterior corneal surface to the anterior sclera, was obtained by summing the foveal ChT measured by SS-OCT with the AL determined by IOLMaster. The change in IAL was −0.04 mm (−0.12, 0.04) and 0.13 mm (0.05, 0.24) ($Z=-5.78$, $p<0.001$) in the RLRL and 0.01% atropine groups (Table 5), respectively.

Proportion of AL Shortening and IAL Shortening

The proportion of AL shortening accounted for 28 cases (62.22%) and 4 cases (9.52%) in the RLRL group and 0.01% atropine group, respectively, with a statistically significant difference ($p<0.001$) (Table 6). Similarly, IAL shortening (corresponding changes in IAL were less than −0.05 mm). The proportion of the two groups with IAL shortening accounted for 21 cases (46.67%) and 2 cases (4.76%) in the two groups, respectively, with a statistically significant difference ($p<0.001$) (Table 6).

Table 3 Changes in the foveal, parafoveal, and perifoveal ChT in the two groups

	RLRL group $N=45$	0.01% Atropine group N = 42	*p* value
Foveal ChT, μm			
Baseline to 3 months	38.00 (7.87, 60.97)	− 0.88 (− 9.20, 10.61)	< 0.001
Baseline to 6 months	36.38 (14.05, 65.39)	0.94 (− 9.20, 9.36)	< 0.001
Parafoveal ChT, μm			
Baseline to 3 months	39.53 (3.45, 56.52)	− 2.05 (− 8.17,14.60)	< 0.001
Baseline to 6 months	31.04 (4.09, 59.35)	3.52 (− 10.24, 14.45)	< 0.001
Perifoveal ChT, μm			
Baseline to 3 months	33.06 (2.53, 53.06)	− 1.35 (− 5.40, 10.24)	< 0.001
Baseline to 6 months	28.48 (5.35, 55.15)	6.14 (− 5.21, 15.69)	< 0.001

RLRL repeated low-intensity red light, *ChT* choroidal thickness, *foveal* 0–1 mm diameter, *parafoveal* 1–3 mm diameter, *perifoveal* 3–6 mm diameter

Table 4 Changes in the foveal, parafoveal, and perifoveal CVV in the two groups

	RLRL group $N=45$	0.01% Atropine group $N=42$	*p* value
Foveal CVV, μm^3			
Baseline to 3 months	0.01 (0.00, 0.01)	0.00 (− 0.00, 0.00)	< 0.001
Baseline to 6 months	0.01 (0.00, 0.02)	0.00 (− 0.00, 0.01)	< 0.001
Parafoveal CVV, μm^3			
Baseline to 3 months	0.05 (− 0.02, 0.08)	0.00 (− 0.02, 0.05)	< 0.001
Baseline to 6 months	0.05 (0.02, 0.09)	0.01 (− 0.02, 0.03)	< 0.001
Perifoveal CVV, μm^3			
Baseline to 3 months	0.17 (0.05, 0.29)	0.04 (− 0.05, 0.14)	< 0.001
Baseline to 6 months	0.20 (0.05, 0.30)	0.01 (− 0.06, 0.09)	< 0.001

RLRL repeated low-intensity red light, *CVV* choroidal vessel volume, *foveal* 0–1 mm diameter, *parafoveal* 1–3 mm diameter, *perifoveal* 3–6 mm diameter

Change of Pupil Diameter and Accommodative Amplitude

During a period of 6 months, distinct differences in the variations of pupil diameter (PD) and accommodative amplitude (AMP) between the two groups were observed. The change in PD was 0 mm (−0.60, 0.20) compared to 0.30 mm (0, 0.70) in the RLRL group and 0.01% atropine group ($Z=-3.20$, $p=0.001$), and the change in AMP was 0 D (−0.80, 0.60) compared to −1.00 D (−1.80, 0) ($Z=-3.18$, $p=0.001$) in the corresponding two groups (Table 7).

Table 5 Changes in AL and IAL at 6 months in the two groups

	RLRL group $N = 45$	0.01% Atropine group $N = 42$	*p* value
AL change at 6 months (mm)	− 0.09 (− 0.18, 0.01)	0.13 (0.05, 0.24)	< 0.001
Foveal ChT change at 6 months (mm)	0.04 (0.01, 0.07)	0.00 (− 0.01, 0.01)	< 0.001
IAL change at 6 months (mm)	− 0.04 (− 0.12, 0.04)	0.13 (0.05, 0.24)	< 0.001

RLRL repeated low-intensity red light, *ChT* choroidal thickness, *AL* axial length, *IAL* internal axial length

Table 6 Proportion of AL shortening and IAL shortening in the two groups

	RLRL group	0.01% Atropine group	*p* value
AL shortening (mm)	28 (62.22%)	4 (9.52%)	< 0.001
IAL shortening (mm)	21 (46.67%)	2 (4.76%)	< 0.001

RLRL repeated low-level red light, *AL* axial length, *IAL* internal axial length

Adverse Events

No severe adverse events occurred during the trial, including sudden vision loss or scotoma. Five children (5.74%) in the 0.01% atropine group had mild photophobia under bright lights; however, they did not report any additional distress when exposed to regular indoor or outdoor light. Four children experienced the disappearance of photophobia following a 2- to 4-week course (the remaining one child lost these symptoms during the 1-month recovery period) of treatment involving 0.01% atropine. Sunglasses or a sun hat can resolve the problem of photophobia when outdoors. None of the children in either group exhibited any other symptoms of discomfort. The SS-OCTA data revealed no discernible structural injury in the choroid and retina across all participants.

DISCUSSION

This prospective, randomized, single-blind, controlled 6-month clinical trial showed RLRL was more effective than 0.01% atropine in delaying the axial growth among schoolchildren after 6 months of treatment. The foveal, parafoveal, and perifoveal ChT and foveal, parafoveal, and perifoveal CVV changes in the RLRL group were significantly higher than those in the 0.01% atropine group.

Table 7 Changes in PD and AMP after treatment in the two groups

	RLRL group	0.01% Atropine group	*p* value
PD, mm			
0–3 months	0.01 (− 0.50, 0.30)	0.45 (0, 0.80)	< 0.001
0–6 months	0 (− 0.60, 0.20)	0.30 (0, 0.70)	0.001
AMP, D			
0–3 months	0.03 (− 0.51, 0.83)	− 1.24 (− 2.54, − 0.49)	< 0.001
0–6 months	0 (− 0.80, 0.60)	− 1.00 (− 1.80, 0)	0.001

RLRL repeated low-intensity red light, *PD* pupil diameter, *AMP* accommodative amplitude

Comparison of Efficacy of 0.01% Atropine with RLRL

Wei et al. [10] conducted a randomized, controlled, double-blind study involving children aged 6–12 years with myopia in the range of − 1.00 D to − 6.00 D. At the 6-month follow-up, the children had mean AL increases of 0.16 mm and 0.21 mm, and the mean SER changes of − 0.21 D and − 0.36 D for the 0.01% atropine group and placebo group. Consistent with the findings of this research, the incorporation criteria of this investigation yielded similar results: an AL change of 0.13 mm (0.05, 0.24) and a SER change of − 0.25 D (− 0.53, 0) at 6 months when 0.01% atropine was administered, suggesting that the administration of 0.01% atropine was better than the placebo in controlling myopia. Consistent with previous research, the effectiveness of 0.01% atropine therapy in this investigation provided a dependable benchmark to evaluate the efficacy of RLRL therapy. However, the physiological growth rate of the AL of children for this age group is 0.09 mm/year [44], and the amount of AL growth in 6 months is about 0.05 mm. In this study, the amount of AL increase in the 0.01% atropine group is 0.13 mm, which exceeded the physiological growth of AL, indicating that myopia was still progressing.

RLRL has recently been revealed to be an effective treatment for controlling the progression of myopia in children [33–40]. Multiple randomized controlled clinical trial studies have demonstrated a progression range of − 0.08 mm to 0.04 mm for AL and − 0.03 D to 0.29 D for SER after using RLRL for 6 months [34–39]. In this study, the variation of AL and SER in the RLRL group was − 0.09 mm (− 0.18, 0.01) and 0.25 D (0, 0.50), respectively, in accordance with the previous findings. The differences in AL and SER changes following RLRL treatment may be attributed to different participant baseline characteristics (such as baseline AL, SER) and different laser power intensities of RLRL devices that reach the fundus. Our findings indicate that RLRL is a more effective therapy technique compared to 0.01% atropine.

Reversal of AL and IAL

In this research, a reduction in AL was found, which has a clinical significance. At 6 months of follow-up, 62.22% of children in the RLRL group exhibited an AL reduction exceeding 0.05 mm, and the corresponding proportion is 9.52% in the 0.01% atropine group. The AL results of the IOLMaster measurements are generally regarded as precise, the measurements are associated with a margin of error within 0.05 mm. Therefore, the AL reduction is not attributable to the measurement error. In previous research on red-light exposure, a decrease in AL was also detected, with the proportion of ocular axis shortening over 0.05 mm at 6 months from 23.2% to 63.74% [36–39]. A retrospective study conducted by Wang et al. [45] also found AL shortening in children following RLRL therapy at 12 months.

Anatomically, the choroid is located adjacent to the retina. The thickened choroid pushes the retina forward, resulting in a mechanical shortening of the AL. Since variations in foveal ChT can affect AL, IAL was used in this research to reveal the true nature of axial growth. IAL, which is the length between the anterior sclera and the anterior surface of the cornea, was obtained by summing the foveal ChT measured by SS-OCT with the AL determined by IOLMaster. No statistically significant variation in IAL was found in the 0.01% atropine group after a 6-month treatment period. Nevertheless, participants who received RLRL exhibited a noteworthy reduction in IAL by 46.67%, which was considerably greater than the 4.76% reduction observed in the 0.01% atropine group. As a result, choroidal thickening could not provide a complete explanation for ocular axial shortening. The mechanism of AL shortening is unclear, and we speculate that RLRL may affect the synthesis of the molecular signal and transfer capacity of the choroid, or enhance scleral oxygenation by increasing the choroid blood flow.

Changes in Choroidal Parameters

This study found that the RLRL group induced a substantial upsurge of the foveal, parafoveal,

and perifoveal ChT and foveal, parafoveal, and perifoveal CVV, whereas these parameters remained stable in the 0.01% atropine group. Xiong et al. [34] revealed that variations in foveal ChT in the SVS, OK lens, and RLRL groups were − 16.84 µm, 14.98 µm, and 35.30 µm, respectively. The LAMP study showed no significant change in foveal ChT from baseline after 1 year of follow-up (− 3.96 ± 23.11 µm, $p > 0.05$). In the present study, a significant increase in foveal ChT was observed in the RLRL group at 6-month follow-up (36.38 µm [14.05, 65.39]), whereas no notable change was found in the 0.01% atropine group (0.94 µm [− 9.20, 9.36]), consistent with previous studies. Only one retrospective study, conducted by Zhou et al. [46] on a cohort in eastern China, has examined choroidal blood flow. The total choroidal area (TCA) and luminal area (LA) increased substantially after RLRL at 9 months. In this study, at the 6-month follow-up, the CVV increased in the RLRL group, consistent with the findings of the previous study; no notable change was found in the 0.01% atropine group.

The choroidal tissue exhibits the most substantial blood circulation within the eye and is crucial in transmitting the signal from the retina to the sclera. Throughout the process of visual development, the choroid generates substances that control the metabolism of the sclera, which in turn influences the restructuring of the scleral extracellular matrix (ECM). This active involvement of the choroid in the development of emmetropization or myopia is a significant factor in the pathogenesis [47]. Research conducted on both animals and humans has demonstrated a clear correlation between alterations in choroidal thickness and choroidal blood flow [48]. The decline in choroidal blood flow can lead to less oxygen and nutrition delivery to the avascular sclera, impacting the progression of myopia [47–49]. This study suggests that RLRL therapy can be accomplished by enhancing the blood flow in the choroid, which improves the oxygen supply and nutrient availability to the scleral hypoxia and delays axial growth. Further studies are required to comprehend the exact mechanisms of RLRL therapy.

Safety

No severe adverse events and structural damage to the choroid and retina were found in both groups, except for the most common ocular photophobia in the 0.01% atropine group; however, the photophobia of most children disappeared with prolonged medication time. Our study also found that there was no significant change in PD and AMP in the RLRL group (0 mm [− 0.60, 0.20] and 0 D [− 0.80, 0.60]), while the PD increased 0.30 mm (0, 0.70) and AMP decreased − 1.00 D (− 1.80, 0) in the 0.01% atropine group, which was consistent with previous studies; the effect on children's learning was not significant [9, 50].

Study Limitations

The study has several limitations. First, the double-blind method, such as using a low-illumination "light therapy simulator" as a placebo, was not adopted. As a result of the different interventional methods, we were unable to achieve a double-blind control. Second, the current study lacked a placebo-control set. Considering that a lot of previous studies have shown that both 0.01% atropine and RLRL have certain effects in controlling myopia progression, it is appropriate to directly compare the effects of the two intervention methods, and it is unethical to enroll children in a non-intervention control group at the age of rapid progression of myopia. Third, the observed therapeutic effect for preventing the development of myopia was exclusively applicable to the devices used in this study. It is yet to be shown whether other wavelengths, power intensity, duration of each exposure, or treatment frequency have comparable or better efficacy. Fourth, the trial duration was designed to last for a duration of 6 months, which may not have provided sufficient time to thoroughly investigate the myopia control impact and subsequent rebound following the discontinuation of the medication. Extended follow-up is needed to confirm if RLRL continues to yield benefits over a more prolonged duration of use. Fifth, we have not established the uniformity of efficacy in ethnic groups beyond Chinese children.

CONCLUSION

Among children with myopia aged 6–12 years in the Central Plains of China, RLRL was found to be more effective than 0.01% atropine in preventing the axial elongation and myopia progresses. Furthermore, RLRL does not result in any functional or structural damage to the eyes. The foveal, parafoveal, and perifoveal ChT and foveal, parafoveal, and perifoveal CVV increases in the RLRL group were significantly higher than those in the 0.01% atropine group. Nevertheless, additional research is necessary to comprehend the effectiveness and safety of prolonged usage, the rebound phenomenon, the most effective treatment approach, and the potential underlying mechanisms.

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Data Availability. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of Interest. Xuena Pang, Aicun Fu, Guangying Zheng, Weiqun Wang, Mei Zhong, Lili Shang, Minghang Chang, Xuemin Jin have no conflicts of interest to declare.

Ethical approval. The study was approved by the Ethics Committee of the Human Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2021-KY-0399-003) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the parents of each subject.

REFERENCES

1. Morgan IG, French AN, Ashby RS, et al. The epidemics of myopia: aetiology and prevention. Prog Retin Eye Res. 2018;62:134–49. https://doi.org/10.1016/j.preteyeres.2017.09.004.

2. Pan CW, Ramamurthy D, Saw SM. Worldwide prevalence and risk factors for myopia. Ophthalm Physiol Opt. 2012;32(1):3–16. https://doi.org/10.1111/j.1475-1313.2011.00884.x.

3. Wu PC, Huang HM, Yu HJ, Fang PC, Chen CT. Epidemiology of myopia. Asia Pac J Ophthalmol (Phila). 2016;5(6):386–93. https://doi.org/10.1097/APO.0000000000000236.

4. 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):1036–42. https://doi.org/10.1016/j.ophtha.2016.01.006.

5. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. Lancet. 2012;379(9827):1739–48. https://doi.org/10.1016/S0140-6736(12)60272-4.

6. Haarman AEG, Enthoven CA, Tideman JWL, Tedja MS, Verhoeven VJM, Klaver CCW. The complications of myopia: a review and meta-analysis. Invest Ophthalmol Vis Sci. 2020;61(4):49. https://doi.org/10.1167/iovs.61.4.49.

7. Ohno-Matsui K, Wu PC, Yamashiro K, et al. IMI pathologic myopia. Invest Ophthalmol Vis Sci. 2021;62(5):5. https://doi.org/10.1167/iovs.62.5.5.

8. Fricke TR, Jong M, Naidoo KS, et al. Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: systematic review, meta-analysis and modelling. Br J Ophthalmol. 2018;102(7):855–62. https://doi.org/10.1136/bjophthalmol-2017-311266.

9. Fu A, Stapleton F, Wei L, et al. Effect of low-dose atropine on myopia progression, pupil diameter and accommodative amplitude: low-dose atropine and myopia progression. Br J Ophthalmol. 2020;104(11):1535–41. https://doi.org/10.1136/bjophthalmol-2019-315440.

10. 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):1178–84. https://doi.org/10.1001/jamaophthalmol.2020.3820.

11. Zadnik K, Schulman E, Flitcroft I, et al. Efficacy and safety of 0.01% and 0.02% atropine for the treatment of pediatric myopia progression over 3 years: a randomized clinical trial. JAMA Ophthalmol. 2023;141(10):990–9. https://doi.org/10.1001/jamaophthalmol.2023.2097.

12. Zhu X, Wang Y, Liu Y, Ye C, Zhou X, Qu X. Effects of atropine 0.01% on refractive errors in children with myopia. Heliyon. 2023;9(8):e18743. https://doi.org/10.1016/j.heliyon.2023.e18743.

13. Chia A, Lu QS, Tan D. Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eyedrops. Ophthalmology. 2016;123(2):391–9. https://doi.org/10.1016/j.ophtha.2015.07.004.

14. Clark TY, Clark RA. Atropine 0.01% eyedrops significantly reduce the progression of childhood myopia. J Ocul Pharmacol Ther. 2015;31(9):541–5. https://doi.org/10.1089/jop.2015.0043.

15. Yam JC, Jiang Y, Tang SM, et al. Low-concentration atropine for myopia progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. Ophthalmology. 2019;126(1):113–24. https://doi.org/10.1016/j.ophtha.2018.05.029.

16. Cui C, Li X, Lyu Y, et al. Safety and efficacy of 0.02% and 0.01% atropine on controlling myopia progression: a 2-year clinical trial. Sci Rep. 2021;11(1):22267. https://doi.org/10.1038/s41598-021-01708-2.

17. Joachimsen L, Bohringer D, Gross NJ, et al. A pilot study on the efficacy and safety of 0.01% atropine in German schoolchildren with progressive myopia. Ophthalmol Ther. 2019;8(3):427–33. https://doi.org/10.1007/s40123-019-0194-6.

18. Pineles SL, Kraker RT, VanderVeen DK, et al. Atropine for the prevention of myopia progression in children: a report by the American Academy of Ophthalmology. Ophthalmology. 2017;124(12):1857–66. https://doi.org/10.1016/j.ophtha.2017.05.032.

19. Larkin GL, Tahir A, Epley KD, Beauchamp CL, Tong JT, Clark RA. Atropine 0.01% eye drops for myopia control in american children: a multiethnic sample across three US sites. Ophthalmol Ther. 2019;8(4):589–98. https://doi.org/10.1007/s40123-019-00217-w.

20. Li FF, Kam KW, Zhang Y, et al. Differential effects on ocular biometrics by 0.05%, 0.025%, and 0.01% atropine: low-concentration atropine for myopia progression study. Ophthalmology. 2020;127(12):1603–11. https://doi.org/10.1016/j.ophtha.2020.06.004.

21. Sacchi M, Serafino M, Villani E, et al. Efficacy of atropine 0.01% for the treatment of childhood myopia in European patients. Acta Ophthalmol. 2019;97(8):e1136–40. https://doi.org/10.1111/aos.14166.

22. Yam JC, Li FF, Zhang X, et al. Two-year clinical trial of the low-concentration atropine for myopia progression (LAMP) study. Ophthalmology. 2020;127(7):910–9. https://doi.org/10.1016/j.ophtha.2019.12.011.

23. Moriche-Carretero M, Revilla-Amores R, Gutierrez-Blanco A, et al. Five-year results of atropine 0.01% efficacy in the myopia control in a European population. Br J Ophthalmol. 2024;108(5):715–9. https://doi.org/10.1136/bjo-2022-322808.

24. Wu J, Lu AD, Zhang LP, Zuo YX, Jia YP. Study of clinical outcome and prognosis in pediatric core binding factor-acute myeloid leukemia. Zhonghua Xue Ye Xue Za Zhi. 2019;40(1):52–7. https://doi.org/10.3760/cma.j.issn.0253-2727.2019.01.010.

25. 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. https://doi.org/10.1016/j.ophtha.2015.11.010.

26. Rose KA, Morgan IG, Ip J, et al. Outdoor activity reduces the prevalence of myopia in children. Ophthalmology. 2008;115(8):1279–85. https://doi.org/10.1016/j.ophtha.2007.12.019.

27. French AN, Ashby RS, Morgan IG, Rose KA. Time outdoors and the prevention of myopia. Exp Eye Res. 2013;114:58–68. https://doi.org/10.1016/j.exer.2013.04.018.

28. 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):1142–8. https://doi.org/10.1001/jama.2015.10803.

29. Wu PC, Chen CT, Lin KK, et al. Myopia prevention and outdoor light intensity in a school-based cluster randomized trial. Ophthalmology. 2018;125(8):1239–50. https://doi.org/10.1016/j.ophtha.2017.12.011.

30. Sherwin JC, Reacher MH, Keogh RH, Khawaja AP, Mackey DA, Foster PJ. The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. Ophthalmology. 2012;119(10):2141–51. https://doi.org/10.1016/j.ophtha.2012.04.020.

31. Wu PC, Tsai CL, Wu HL, Yang YH, Kuo HK. Outdoor activity during class recess reduces myopia onset and progression in school children. Ophthalmology. 2013;120(5):1080–5. https://doi.org/10.1016/j.ophtha.2012.11.009.

32. 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):551–66. https://doi.org/10.1111/aos.13403.

33. Zhou L, Tong L, Li Y, Williams BT, Qiu K. Photobiomodulation therapy retarded axial length growth in children with myopia: evidence from a 12-month randomized controlled trial evidence. Sci Reports. 2023. https://doi.org/10.1038/s41598-023-30500-7.

34. Xiong F, Mao T, Liao H, et al. Orthokeratology and low-intensity laser therapy for slowing the progression of myopia in children. Biomed Res Int. 2021;2021:8915867. https://doi.org/10.1155/2021/8915867.

35. Chen H, Wang W, Liao Y, et al. Low-intensity red-light therapy in slowing myopic progression and the rebound effect after its cessation in Chinese children: a randomized controlled trial. Graefes Arch Clin Exp Ophthalmol. 2023;261(2):575–84. https://doi.org/10.1007/s00417-022-05794-4.

36. Chen Y, Xiong R, Chen X, et al. Efficacy comparison of repeated low-level red light and low-dose atropine for myopia control: a randomized controlled trial. Transl Vis Sci Technol. 2022;11(10):33. https://doi.org/10.1167/tvst.11.10.33.

37. Jiang Y, Zhu Z, Tan X, et al. Effect of repeated low-level red-light therapy for myopia control in children: a multicenter randomized controlled trial. Ophthalmology. 2022;129(5):509–19. https://doi.org/10.1016/j.ophtha.2021.11.023.

38. Tian L, Cao K, Ma D-L, et al. Investigation of the efficacy and safety of 650 nm low-level red light for myopia control in children: a randomized controlled trial. Ophthalmol Therapy. 2022;11(6):2259–70. https://doi.org/10.1007/s40123-022-00585-w.

39. Dong J, Zhu Z, Xu H, He M. Myopia control effect of repeated low-level red-light therapy in Chinese children: a randomized, double-blind, controlled clinical trial. Ophthalmology. 2023;130(2):198–204. https://doi.org/10.1016/j.ophtha.2022.08.024.

40. Xiong R, Zhu Z, Jiang Y, et al. Sustained and rebound effect of repeated low-level red-light therapy on myopia control: a 2-year post-trial follow-up study. Clin Exp Ophthalmol. 2022;50(9):1013–24. https://doi.org/10.1111/ceo.14149.

41. Zhou L, Xing C, Qiang W, Hua C, Tong L. Low-intensity, long-wavelength red light slows the progression of myopia in children: an Eastern China-based cohort. Ophthalm Physiol Opt. 2022;42(2):335–44. https://doi.org/10.1111/opo.12939.

42. Liu G, Liu L, Rong H, et al. Axial shortening effects of repeated low-level red-light therapy in children with high myopia: a multicenter randomized controlled trial. Am J Ophthalmol. 2025;270:203–15. https://doi.org/10.1016/j.ajo.2024.10.011.

43. Carkeet A, Saw SM, Gazzard G, Tang W, Tan DT. Repeatability of IOLMaster biometry in children. Optom Vis Sci. 2004;81(11):829–34. https://doi.org/10.1097/01.opx.0000145020.33250.c0.

44. Public Health Ophthalmology Branch of Chinese Preventive Medicine A. [Chinese expert consensus on the reference interval of ocular hyperopia reserve, axial length, corneal curvature and genetic factors in school-age children (2022)]. Zhonghua Yan Ke Za Zhi. 2022;58(2):96–102. https://doi.org/10.3760/cma.j.cn112142-20210603-00267.

45. Wang W, Jiang Y, Zhu Z, et al. Clinically significant axial shortening in myopic children after repeated low-level red light therapy: a retrospective multicenter analysis. Ophthalmol Ther. 2023;12(2):999–1011. https://doi.org/10.1007/s40123-022-00644-2.

46. Cooper J, Eisenberg N, Schulman E, Wang FM. Maximum atropine dose without clinical signs or symptoms. Optom Vis Sci. 2013;90(12):1467–72. https://doi.org/10.1097/OPX.0000000000000037.

47. Summers JA. The choroid as a sclera growth regulator. Exp Eye Res. 2013;114:120–7. https://doi.org/10.1016/j.exer.2013.03.008.

48. Zhang S, Zhang G, Zhou X, et al. Changes in choroidal thickness and choroidal blood perfusion in guinea pig myopia. Invest Ophthalmol Vis Sci. 2019;60(8):3074–83. https://doi.org/10.1167/iovs.18-26397.

49. Chhablani J, Barteselli G. Clinical applications of choroidal imaging technologies. Indian J Ophthalmol. 2015;63(5):384–90. https://doi.org/10.4103/0301-4738.159861.

50. Moon JS, Shin SY. The diluted atropine for inhibition of myopia progression in Korean children. Int J Ophthalmol. 2018;11(10):1657–62. https://doi.org/10.18240/ijo.2018.10.13.