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Clinical Trials

Effect of Repeated Low-Level Red Light Versus 0.01% Topical Atropine on Myopia Progression: A Randomized Crossover-Controlled Trial

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Received: August 20, 2024
Accepted: February 26, 2025
Published: April 23, 2025

Keywords: repeated low-level red light (RLRL); 0.01% atropine; axial length (AL); choroidal thickness; choroidal vessel volume

Citation: Pang X, Jin X, Fu A, Wang W, Zhao B, Shang L, Chang M, Ma N, Zheng G. Effect of repeated low-level red light versus 0.01% topical atropine on myopia progression: A randomized crossover-controlled trial. Transl Vis Sci Technol. 2025;14(4):22, https://doi.org/10.1167/tvst.14.4.22

Purpose: The purpose of this study was to compare the efficacy of repeated low-level red light (RLRL) and 0.01% atropine in controlling the progression of myopia children.

Methods: This randomized, single-blind, crossover-controlled trial recruited 91 myopic children aged 6 to 12 years. Participants were randomly allocated to the RLRL-atropine group ($n = 46$) and the atropine-RLRL group ($n = 45$), with intermediate washout for 1 month. Primary outcomes included changes in spherical equivalent refraction (SER) and axial length (AL), whereas the secondary outcomes included changes in subfoveal choroidal thickness (SFCT) and subfoveal choroidal vessel volume (SFCVV).

Results: The 13-month data analysis involved 45 (97.8%) and 42 (93.3%) children in the RLRL-atropine and the atropine-RLRL groups, respectively. RLRL was more effective than 0.01% atropine, with a mean difference in SER of 0.54 diopter (D; 0.24 ± 0.30 D vs. −0.29 ± 0.38 D, $P < 0.001$) and a mean difference in AL of 0.24 mm (−0.09 ± 0.14 mm vs. 0.15 ± 0.16 mm, $P < 0.001$) in period 1, whereas the mean differences in SER and AL were 0.55 D (0.22 ± 0.27 D vs. −0.33 ± 0.27 D, $P < 0.001$) and 0.22 mm (−0.06 ± 0.13 mm vs. 0.16 ± 0.11 mm, $P < 0.001$) in period 2, respectively. RLRL showed increased SFCT and SFCVV than 0.01% atropine (all $P < 0.001$). The change in SFCT from baseline to 3 months was the crucial predictor for the growth in AL at 6 months ($P < 0.05$).

Conclusions: Compared to 0.01% atropine, RLRL demonstrated superior effectiveness in slowing myopic progression and axial elongation in myopia children. Changes in SFCT may predict the retarding effects of RLRL on axial elongation.

Translational Relevance: RLRL is an effective alternative treatment for controlling myopia in schoolchildren.

Introduction

Recent years have witnessed a steep increase in the prevalence of myopia in children and adolescents.[1,2] By 2050, approximately 4.758 billion people—nearly half of the global population—will be affected, with a substantial 9.8% of people struggling with high myopia.[3] Importantly, myopia in a child typically emerges during the school years and progresses rapidly into early adulthood.[1,4] Even though time spent outdoors effectively controls myopia onset, it does not stop the progression[5] and sufficient time for outdoor activities is impractical in modern societies with high educational demand.[6] Therefore, the development of effective and safe strategies is urgently needed to control the progression of myopia in children.

Low-concentration atropine (0.01%) eye drops have become the standard choice for controlling the development and progression of myopia in children and adolescents.[7–9] Several clinical randomized controlled trials (RCTs) within the Asian population have reported the efficacy of 0.01% atropine eye drops in retarding the progression of myopia.[10–18] The Atropine for the Treatment of Myopia 2 (ATOM 2) and Low-Concentration Atropine for Myopia Progression

(LAMP) trials found minimal adverse effects and a reduced rebound effect of 0.01% atropine in comparison with higher concentrations.[10–14,19] Studies in other ethnicities have also revealed the efficacy of 0.01% atropine eye drops in controlling myopia, with a favorable safety profile.[20–24]

Repeated low-level red light (RLRL) therapy has recently emerged as an effective approach for slowing the progression of myopia, with no reported functional or structural harm.[25–34] Besides controlling refractive error and axial length (AL), the use of RLRL could increase choroidal thickness.[26,27,29–31] The increasing popularity of RLRL as a myopia treatment prompts a comparative evaluation against low-concentration atropine. An RCT of RLRL versus low-dose atropine demonstrated that RLRL was more effective than low-dose atropine for myopia control.[28] However, it used a parallel control method, and it did not measure the relevant parameters of the choroid. The crossover design is a self-controlled trial method that can eliminate individual differences and fully considers the interests of the subjects, more in line with the ethical requirements. The crossover design allows every child to receive the same intervention, only at different stages. It is more acceptable to parents and easier to find enrolled participants, while also reducing the sample size. Current studies show that choroid changes are particularly important in preventing the progression of myopia,[35,36] so the measurement of choroidal thickness and choroidal blood flow is particularly important to explore the mechanism of myopia prevention. The present study optimized the design with a randomized crossover-controlled design, and measured subfoveal choroidal thickness (SFCT) and subfoveal choroidal vessel volume (SFCVV) using swept-source optical coherence tomography (SS-OCT) to assess RLRL and 0.01% atropine for the control of myopia in children while exploring the potential mechanisms in terms of choroidal thickness and choroidal blood flow.

Materials and Methods

Study Design and Population

In this crossover RCT, children with myopia were enrolled at the First Affiliated Hospital, Zhengzhou University, from November 2021 to March 2022. Inclusion criteria were children aged 6 to 12 years, exhibiting cycloplegic spherical equivalent refraction (SER) in the range of ≥ -5.00 diopter (D) to ≤ -0.75 D in both eyes, astigmatism < 2.00 D, anisometropia ≤ 2.00 D, monocular best-corrected visual acuity (BCVA) of 20/20 or better, and intraocular pressure (IOP) < 21 millimeters of mercury (mm Hg). Children with any of the following conditions were excluded: the usage of alternative prevention methods for myopia or medications, a history of amblyopia or strabismus, other ocular diseases or prior surgical interventions, and unable to adhere to the designated study visit schedule. This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhengzhou University (2021-KY-0399-003). The study was registered with the Chinese Clinical Trials Registry (ChiCTR2100052964). Written informed consent was obtained from the parents or legal guardians of the participants before initiating the study.

Randomization and Masking

This RCT was performed in two distinct periods. During the initial 6 months (period 1), children were randomly allocated (1:1 ratio) to receive either RLRL or 0.01% atropine treatment. This was followed by a subsequent, 1-month washout period with no other treatment apart from single-vision glasses. Then, children who initially received RLRL switched to 0.01% atropine treatment (the RLRL-atropine group), those who initially received 0.01% atropine switched to RLRL treatment (the atropine-RLRL group) for the following 6 months. Standardized examination protocols were consistently applied at baseline and during each visit, and the participants were instructed to wear single-vision glasses throughout the study.

A statistician independently conducted the simple randomization. In this process, eligible children were assigned to their respective groups according to a randomized sequence generated on an Excel spreadsheet (Microsoft Office 2007). The children were aware of their group assignments due to the nature of the interventions. However, throughout the study, the outcome assessors, comprising technicians, optometrists, and statisticians, remained blinded to the group allocations.

Interventions (RLRL and 0.01% Atropine Eye Drops)

The RLRL treatment was performed using a table-mountable commercially available device (Eyerising; Suzhou Xuanjia Photoelectric Technology, Jiangsu, China). The device was given free of charge to the children, and the children were instructed to use the RLRL therapy for 3 minutes twice daily, with at least 4 hours between sessions, for 7 days a week until the last follow-up visit. This RLRL instrument uses a semicon-

ductor laser diode emitting light of 650 ± 10 nm wavelength and an illuminance of 1600 Lux, directed through the pupil to the fundus.

Preparation of 0.01% atropine eye drops involved diluting atropine sulfate powder (Shaoxing Minsheng Medical Co., Ltd., Zhejiang, China) with normal saline under sterile conditions, in addition to a preservative (0.3 mg/mL ethylparaben). Atropine's performance is relatively stable, these eye drops had a pH value in the range of 5.4 to 5.6, were stored in sealed 3 mL bottles at 15°C to 25°C, and were discarded 1 month after opening the bottle. If the room temperature is high in summer, it can be stored in a refrigerator of approximately 2°C to 8°C. Children received one drop of 0.01% atropine eye drops in each eye before bedtime every night until the last follow-up visit. After the initial examination and a 3-month follow-up, 3 bottles of 0.01% atropine eye drops were provided to them.

Treatment Compliance

In the RLRL group, the equipment facilitated supervised treatment administered by the parents at home and was connected to the internet with an automated diary function to log treatment dates and times. Treatment compliance was defined as the percentage of completed sessions relative to the total assigned treatment sessions throughout the treatment period; the compliance was deemed inadequate if the usage proportion of the RLRL instrument was $< 80\%$.

In the 0.01% atropine group, the record calendar was distributed to the parents, on re-examination, the children were required to return the record calendar and 3 bottles. Treatment compliance was calculated as the percentage of the recorded number to the total number of treatments specified throughout the treatment period; the compliance was deemed inadequate if the usage proportion of the 0.01% atropine $< 80\%$.

Follow-Up Visits

Follow-up assessments of the participants were performed at 3, 6, 7, 10, and 13 months. AL measurements were obtained before cycloplegia using a non-contact partial coherent interferometer (IOLMaster-500; Carl Zeiss Meditec AG, Germany).

Both eyes were measured 5 times in each examination, only the data for signal-to-noise ratio (SNR) $\geq$ 5.0 were kept and their mean value was used for analysis. The repeatability of AL measurements using the IOLMaster-500 was well within ± 0.05 mm.[37] Cycloplegic autorefraction was performed after the administration of 4 drops of tropicamide eye drops (0.5% tropicamide and 0.5% neo-synephrine; Santen, Japan) to both eyes at 10-minute intervals.[38,39] After 10 minutes of the last drop, triple cycloplegic autorefraction was measured using an autorefractor (NIDEK, AR-1, Japan). The SER was calculated as the sum of the sphere value and one-half of the cylindrical power.

The SFCT (diameter 0–1 mm) and SFCVV (diameter 0–1 mm) measurements, taken before cycloplegia, were obtained by an SS-OCT (VG200S; SVision Imaging, Ltd., Henan, China[40,41]; Supplementary Fig. S1). All images were captured between 8:30 AM and 10:00 Am in a dark room environment by the same experienced examiner to avoid potential diurnal variations in choroidal thickness. Choroidal parameters were acquired by a raster scan protocol of 512 (horizontal) × 512 (vertical) B-scans, covering an area of 6 × 6 mm^2 centered on the macular fovea. The SFCT and SFCVV were measured and computed automatically using instrument software (software version V2.1.016). The SFCT was defined as the vertical distance between Bruch's membrane and the choroid−sclera interface in the diameter of 0–1 mm in the macular zone. The SFCVV was defined as the volume of the large and medium choroidal vessels in the diameter of 0–1 mm in the macular zone. Cycloplegic was not used before the examination, the examination room had a constant light brightness, the whole scan process requires the subject to have good fixation ability and to be examined by the same skilled physician. Each eye was examined three times, the best image of the right eye was selected for data collection and analysis, only high-quality scans with a signal intensity of not less than eight were adopted.

Safety analysis was performed in children who received at least one treatment. All children underwent IOP, BCVA, and OCT examinations at each follow-up visit. In addition, symptoms of discomfort in both groups were evaluated through a standardized questionnaire. The questionnaire of the RLRL group included inquiries about flash blindness, short-term glare, afterimages, sudden visual loss within seconds to a few days, or development of scotoma in the center of the visual field.[30] The questionnaire for children using 0.01% atropine included: (1) whether photophobia and photophobia scene (indoor normal light, daily outdoor light, or strong sunlight) and duration; (2) near blurred vision, the degree of blurred vision (mild, moderate, or severe) and duration; (3) redness, itchy eyes, eye swelling, and other uncomfortable symptoms and duration; and (4) systemic discomfort, including dry mouth, dry nose, fever, palpitation, skin flushing, and other symptoms.[15]

Statistical Analysis

The sample size was calculated based on the results of previous studies.[12,28] The sample size calculation took into account a significance level (alpha) of 0.05 for the atropine group, a statistical power of 90%, with an expected 6-month AL elongation of 0.18 mm (a standard deviation [SD] of 0.23 mm) in this group. For the RLRL group, the expected outcome was a reduction of 0.09 mm in AL elongation (with an SD of 0.13 mm). Thus, this crossover trial required a minimum of 68 participants per group. To accommodate an estimated 25% dropout rate, it was imperative to enroll a total of 91 participants.

All statistical analyses followed an intention-to-treat (ITT) principle. For the analysis, data from all children who attended at least one subsequent follow-up visit were included regardless of compliance with treatment or with attending follow-up visits. For analysis, data for the right eye were utilized.

Continuous variables with normally distribution were expressed as mean ± SD and assessed using the Student's *t*-test. Categorical variables, such as gender, were presented as a percentage (%) and evaluated through the chi-square test. The efficacy and trends of choroid parameters in both groups, considering covariates, were evaluated using the generalized estimating equation (GEE) model. This model incorporated a within-subject factor (periods 1 and 2) and a between-subject factor (RLRL or 0.01% atropine). Univariate analysis and multivariable linear regression analyses, adjusting for covariates, were conducted to identify associated risk factors for AL elongation. Compliance and treatment efficacy between RLRL and 0.01% atropine was evaluated by Pearson correlation analysis. All statistical analyses were performed using SPSS software (version 20.0). A P value < 0.05 indicated statistical significance.

Results

From the initial pool of 91 participants, 87 (95.6%) successfully completed their visits during period 1, and 82 (90.1%) during period 2. In period 1, four participants withdrew (1 from the RLRL-atropine group and 3 from the atropine-RLRL group), whereas in period 2, three participants withdrew (1 from the RLRL-atropine group and 2 from the atropine-RLRL group), meanwhile 2 children from the RLRL-atropine group changed their treatment regimen midway. Finally, this analysis comprised 87 children who had completed at least one follow-up visit (Fig. 1). Baseline parameters showed similar characteristics between the two groups (all $P > 0.05$; Table 1).

Changes in SER and AL

Significant differences in SER and AL changes between children undergoing RLRL or 0.01% atropine treatment emerged after adjustments for age and baseline SER using the GEE model (F-SER = 6.85, $P < 0.001$; and F-AL = −6.54, $P < 0.001$).

The SER of children treated with RLRL showed hyperopia drift from baseline, and the SER of children treated with 0.01% atropine showed myopia drift. In period 1, the difference in mean SER change between the RLRL-atropine and atropine-RLRL groups was 0.54 D (0.24 ± 0.30 D vs. −0.29 ± 0.38 D, $P < 0.001$). In period 2, the SER of children treated with RLRL showed hyperopia drift from baseline, and the SER of children treated with 0.01% atropine showed myopia drift; the difference in mean SER change between the atropine-RLRL and RLRL-atropine groups was 0.60 D (0.22 ± 0.27 D vs. −0.33 ± 0.27 D, $P < 0.001$; Table 2, Fig. 2A). Neither order effects nor period effects reached statistical significance (all $P > 0.05$).

Children receiving RLRL showed a shorter AL than the baseline, and those receiving 0.01% atropine showed a longer AL than the baseline. In period 1, the difference in the mean change in AL between the RLRL-atropine and atropine-RLRL groups was 0.24 mm (−0.09 ± 0.14 mm vs. 0.15 ± 0.16 mm, $P < 0.001$). In period 2, the AL of children treated with RLRL showed shorted from baseline, and the AL of children treated with 0.01% atropine showed increased; the difference in the mean change in SER between the atropine-RLRL and RLRL-atropine groups was 0.22 mm (−0.06 ± 0.13 mm vs. 0.16 ± 0.11 mm, $P < 0.001$; see Table 2, Fig. 2B). Neither order effects nor period effects reached statistical significance (all $P > 0.05$).

During the 1-month washout period, both groups displayed statistically significant differences in SER and AL when comparing the seventh month to the sixth month (Supplementary Table S1). However, there were no significant differences in SER and AL changes between the two groups. The SER and AL changes for the RLRL-atropine group and the atropine-RLRL group were −0.09 ± 0.12 D versus −0.07 ± 0.11 D and 0.06 ± 0.04 mm versus 0.05 ± 0.04 mm (all $P > 0.05$).

SFCT and SFCVV Changes

Significant differences were observed in the SFCT and SFCVV changes between children receiving RLRL or 0.01% atropine, as determined by the GEE model

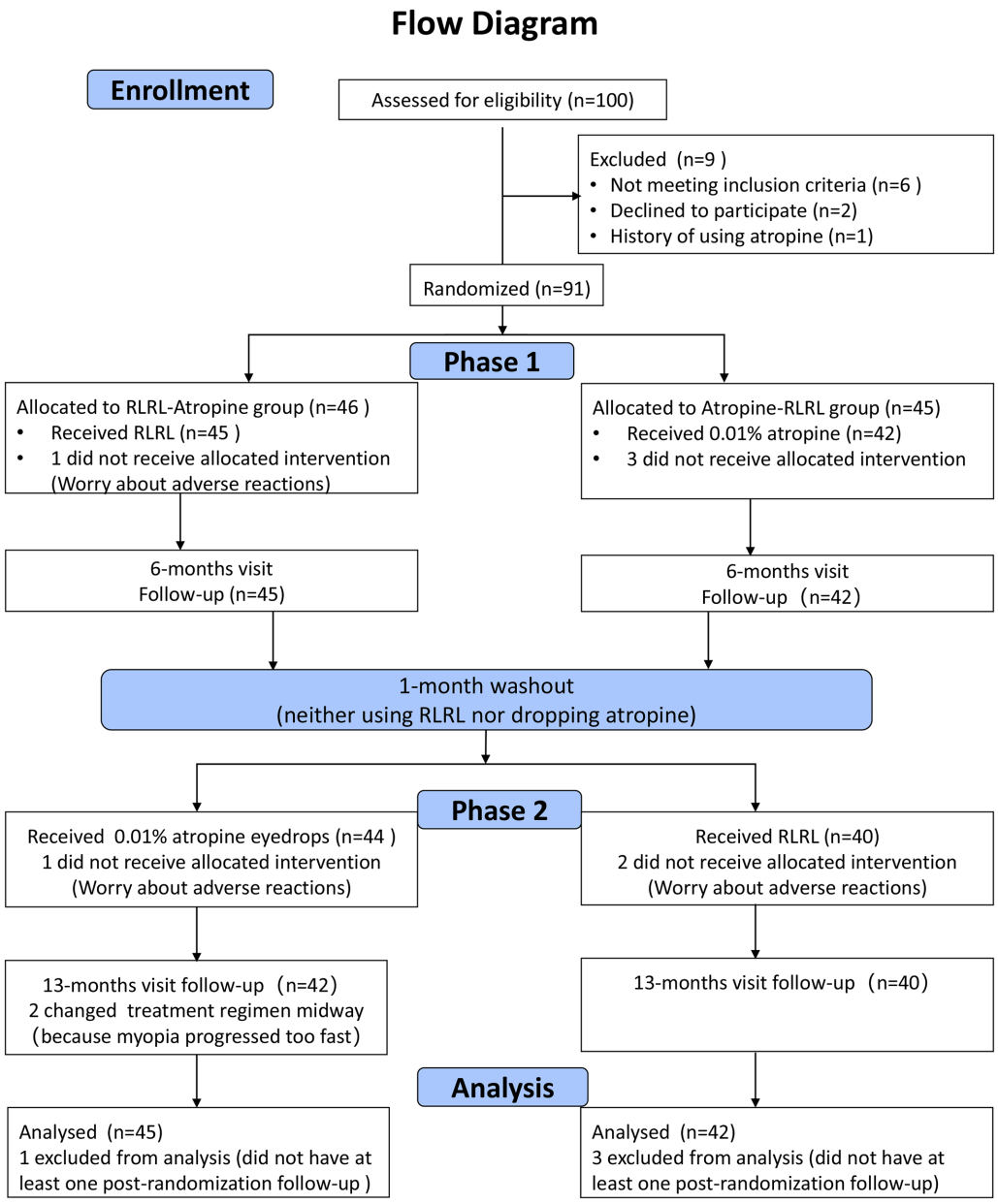

Figure 1. A flow diagram of the study design.

and adjusted for age, baseline AL, and SFCT (F-SFCT = 9.91, $P < 0.001$) and (F-SFCVV = 9.14, $P < 0.001$). In period 1, the RLRL-atropine group exhibited a mean SFCT change of 41.47 ± 34.27 µm, whereas the atropine-RLRL group showed 2.38 ± 16.69 µm ($P < 0.001$). In period 2, the respective figures were −1.69 ± 17.01 µm and 33.33 ± 28.54 µm ($P < 0.001$; see Table 2, Fig. 3A). Considering SFCVV, in period 1, the RLRL-atropine group had a mean change in SFCVV of 0.009 ± 0.007 μm^3, and the atropine-RLRL group had 0.002 ± 0.006 μm^3. In period 2, these values were 0.001 ± 0.005 μm^3 and 0.008 ± 0.006 μm^3, respectively ($P < 0.001$; see Table 2, Fig. 3B). Neither order effects nor period effects were statistically significant (all $P > 0.05$).

In period 1, SFCT and SFCVV in the RLRL-atropine group increased from baseline to 6 months and then returned to baseline during 6 to 7 months. In period 2, similar to the trends seen in period 1, SFCT and SFCVV in the atropine-RLRL group increased from 7 to 13 months. SFCT and SFCVV remained stable in children treated with 0.01% atropine in periods 1 as well as 2. During the 1-month recovery period, from 6 to 7 months, the SFCT and SFCVV changes for the RLRL-atropine group and the atropine-RLRL group were −32.63 ± 19.85 µm versus −7.01

Table 1. Baseline Characteristics of Study Participants That Complect the Trial

	RLRL-Atropine Group ($n = 45$)	Atropine-RLRL Group ($n = 42$)	*P* Value
Sex, male, *n* (%)	21 (46.7)	23 (54.8)	0.45
Age, y	9.27 ± 1.45	8.98 ± 1.27	0.32
Body mass index	17.20 ± 2.96	17.60 ± 3.05	0.53
SER, D	−2.43 ± 1.13	−2.28 ± 1.04	0.51
Axial length, mm	24.33 ± 0.81	24.52 ± 0.82	0.29
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
Anterior chamber depth, mm	3.73 ± 0.21	3.70 ± 0.26	0.48
Intraocular pressure, mm Hg	18.16 ± 2.39	18.11 ± 2.36	0.93
Accommodative amplitude, D	14.28 ± 1.42	14.76 ± 1.81	0.17
Pupil diameter, mm	5.98 ± 0.81	6.12 ± 0.68	0.39
SFCT, µm	297.89 ± 51.04	286.62 ± 38.93	0.25
SFCVV, μm^3	0.08 ± 0.02	0.08 ± 0.01	0.13
Parental myopia			0.71
0 (neither parent myopic)	4 (8.89%)	4 (11.11%)	
1 (one parent myopic)	19 (42.22%)	12 (33.33%)	
2 (both parents myopic)	22 (48.89%)	20 (55.56%)	

RLRL, repeated low-level red-light; SD, standard deviation; SER, spherical equivalent refraction; SFCT, subfoveal choroidal thickness; SFCVV, macular choroidal vessel volume.

Table 2. Change in Primary and Secondary Outcomes in Two Groups

	Study Period	RLRL - Atropine Group ($n = 45$)	Atropine - RLRL Group ($n = 42$)	*P* Value
SER, D	0–6 mo	0.24 ± 0.30	−0.29 ± 0.38	<0.001
	Reg	−0.09 ± 0.12	−0.07 ± 0.11	0.47
	Reg to 13 mo	−0.33 ± 0.27	0.22 ± 0.27	<0.001
AL, mm	0–6 mo	−0.09 ± 0.14	0.15 ± 0.16	<0.001
	Reg	0.06 ± 0.04	0.05 ± 0.04	0.32
	Reg to 13 mo	0.16 ± 0.11	−0.06 ± 0.13	<0.001
SFCT, µm	0–6 mo	41.47 ± 34.27	2.38 ± 16.69	<0.001
	Reg	−32.63 ± 19.85	−7.01 ± 11.51	<0.001
	Reg-13months	−1.69 ± 17.01	33.33 ± 28.54	<0.001
SFCVV, μm^3	0–6 mo	0.009 ± 0.007	0.002 ± 0.006	<0.001
	Reg	−0.007 ± 0.006	−0.002 ± 0.004	<0.001
	Reg to 13 mo	0.001 ± 0.005	0.008 ± 0.006	<0.001

AL, axial length; RLRL, repeated low-level red light; SER, spherical equivalent refraction; SFCT, subfoveal choroidal thickness; SFCVV, subfoveal choroidal vessel volume.

Reg: 1-month recovery period without using 0.01% atropine and RLRL from 6 to 7 months.

± 11.51 µm and −0.007 ± 0.006 μm^3 versus −0.002 ± 0.004 μm^3 (all $P < 0.001$).

The Proportion of SER Regression and AL Shortening

SER regression was defined as the SER hyperopic shift over 0.25 D from baseline, which could not account for errors in refraction measurement.[30] After adjusting for age and baseline SER, in period 1, the RLRL-atropine group exhibited an SER regression rate of 31.1% (14/45), whereas that of the atropine-RLRL group was only 2.4% (1/42). In period 2, these proportions were 4.4% (2/45) for the RLRL-atropine group and 33.3% (14/42) for the atropine-RLRL group (Supplementary Table S2, Fig. 4A). AL shortening was defined as a decrease of AL more than 0.05 mm from baseline, which exceeded the possible AL measurement error using the IOLMaster.[37] In period 1, the RLRL-

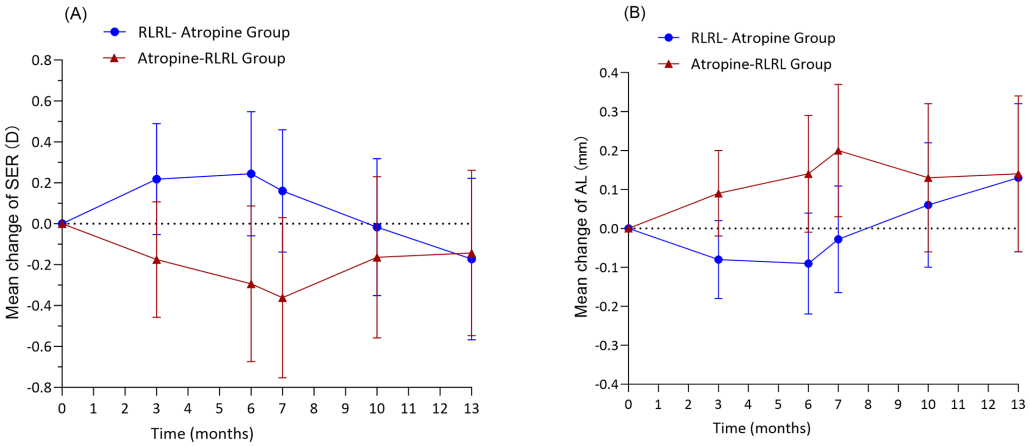

Figure 2. Effectiveness of RLRL and 0.01% atropine for controlling myopia and axial progression. (**A**) Trend chart of spherical equivalent refraction (SER) from baseline to 13 months in 2 groups. (**B**) Trend chart of axial length (AL) from baseline to 13 months in 2 groups.

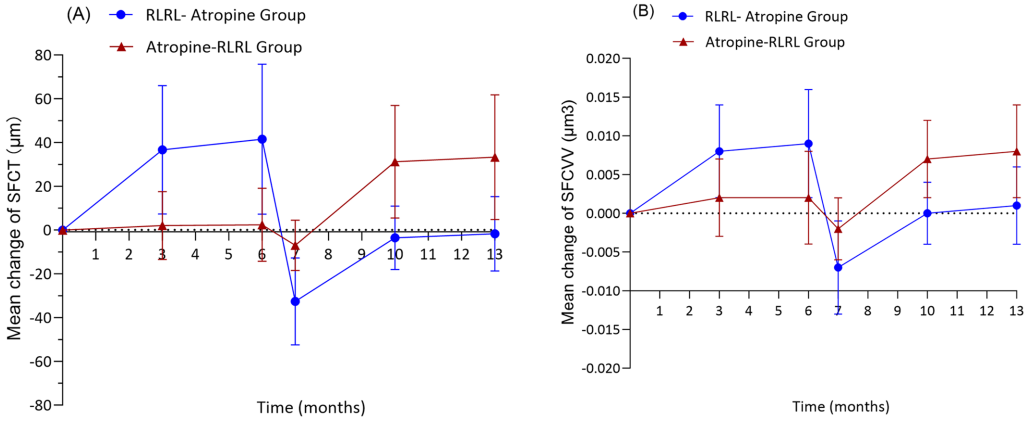

Figure 3. The SFCT and SFCVV changes between children receiving RLRL or 0.01% atropine. (**A**) Trend chart of SFCT from baseline to 13 months in 2 groups. (**B**) Trend chart of SFCVV from baseline to 13 months in 2 groups.

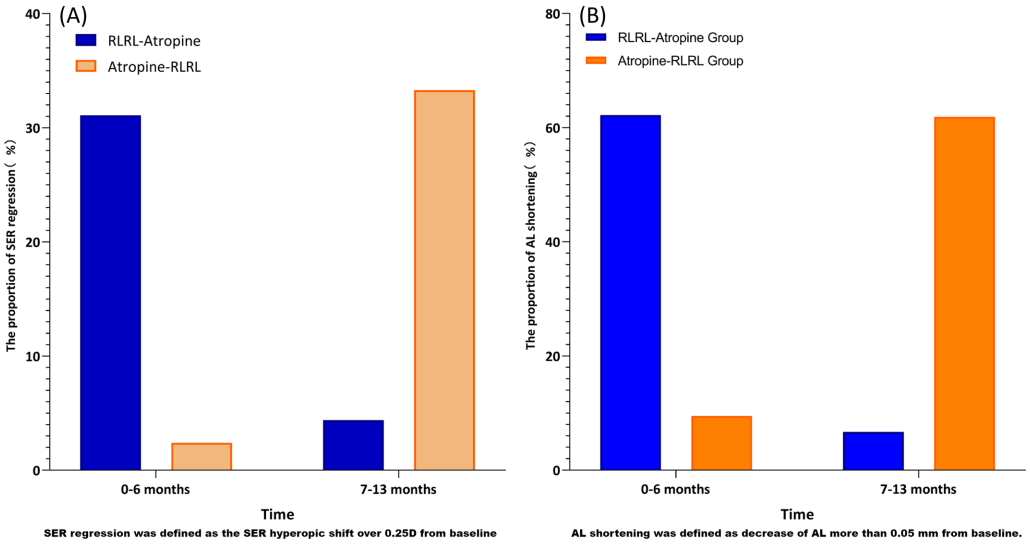

Figure 4. Incidence of SER regression or AL shortening after RLRL or 0.01% atropine eye drops. (**A**) SER regression. (**B**) AL shortening. SER regression was defined as the SER hyperopic shift over 0.25 D from baseline. AL shortening was defined as decrease of AL more than 0.05 mm from baseline.

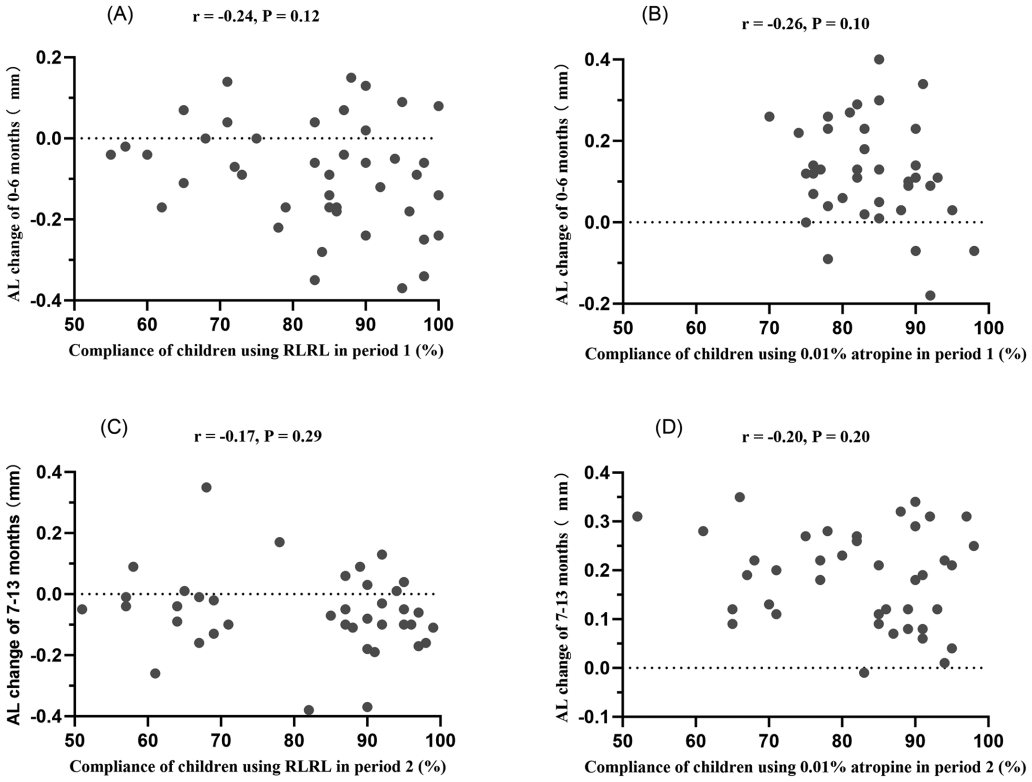

Figure 5. Distribution of treatment compliance and its association with the AL change of children using RLRL and 0.01% atropine. (**A**) Zero to 6 months in the RLRL-atropine group. (**B**) Zero to 6 months in the atropine-RLRL group. (**C**) Seven to 13 months in the atropine-RLRL group. (**D**) Seven to 13 months in the RLRL-atropine group.

atropine group exhibited a 62.2% (28/45) proportion of AL shortening, whereas that of the atropine-RLRL group was only 9.5% (4/42). In period 2, these proportions were 6.7% (3/45) for the RLRL-atropine group and 61.9% (26/42) for the atropine-RLRL group (see Supplementary Table S2, Fig. 4B).

Predictors for Change in AL During Follow-Up

After univariate analysis, changes in SFCT at 3 months were the only factors related to AL increase at 6 months in the 2 groups, and other factors, such as sex, age, baseline AL, SFCT, SFCVV, changes in SFCT at 6 months, and changes in SFCVV at 3 and 6 months were not related to the AL increase at 6 months. In the multivariate linear regression analysis, after adjusting for potential confounders (age and SFCT at baseline), the change in SFCT during the 0 to 3 months exhibited a significantly negative effect on the change in AL over the subsequent 0 to 6 months ($\beta_{\text{RLRL-Atropine}} = -0.004$, $P < 0.001$; $\beta_{\text{Atropine-RLRL}} = -0.001$, $P = 0.03$). Similarly, change in SFCT during the period of 7 to 10 months had a significantly negative influence on AL during the subsequent months 7 to 13 ($\beta_{\text{RLRL-Atropine}} = -0.001$, $P = 0.03$; $\beta_{\text{Atropine-RLRL}} = -0.005$, $P < 0.001$). In other words, changes in SFCT at 3 months after using RLRL or 0.01% atropine were negatively associated with the AL changes after 6 months.

Compliance and Treatment Effect

In period 1, the mean treatment compliance rate of children using RLRL was 83.2% (range = approximately 55.1%–100%), and the mean treatment compliance rate of children using 0.01% atropine was 83.5% (range = approximately 70.2%–97.9%). There was no significant correlation between the compliance and the AL change of 0 to 6 months in the RLRL-atropine group ($r = -0.24$, $P = 0.12$) or the atropine-RLRL group ($r = -0.26$, $P = 0.10$; Figs. 5A, 5B). In period 2, the mean compliance rate of children using RLRL was 81.4% (range = approximately 50.9%–99.3%), and the mean compliance rate of children using 0.01% atropine was 81.3% (range = approximately 41.4%–97.8%). There was no significant correlation between the compliance and the AL change of 7 to 13 months in the atropine-RLRL group ($r = -0.17$, $P = 0.29$)

or the RLRL-atropine group ($r = -0.20$, $P = 0.20$; Figs. 5C, 5D).

Adverse Events

Serious adverse events of abnormal IOP, a decrease in BCVA by two or more lines, or structural damage identified by OCT were not observed in both groups throughout the study period. In the RLRL-atropine group, one child experienced discomfort initially due to excessive brightness, which subsided by the follow-up at 3 months. Among participants in the 0.01% atropine group during periods 1 and 2, five (11.9%) and six (13.3%) children, respectively, reported mild photophobia upon exposure to intense sunlight. This photophobia was effectively corrected by wearing hats or sunglasses during outdoor activities. There were no other discomfort-related symptoms reported by any child in either study group.

Discussion

This study demonstrated the superior efficacy of RLRL over 0.01% atropine in reducing the progression of myopia and AL elongation in children with myopia during 2 consecutive 6-month follow-up periods. Significant improvements in SFCT and SFCVV were noted in the RLRL group compared to the 0.01% atropine group.

Previous studies have reported the efficacy of treatment with 0.01% atropine. The LAMP study[12] showed that in children aged 4 to 12 years with SER ≤ -1.00 D, after 12 months of follow-up, the mean SER changes for treatment with 0.01% atropine and placebo were -0.59 D and -0.81 D ($P < 0.001$), whereas the mean AL changes were 0.36 mm and 0.41 mm, respectively ($P < 0.001$). A previous study evaluating the efficacy of 0.01% atropine found that in children aged 6 to 12 years with SER approximately 1.00 D to -6.00 D, the SER change was -0.49 D versus -0.76 D for placebo after 1-year follow-up, whereas the AL change was 0.32 mm versus 0.41 mm for placebo.[16] In the present study, the 6-month SER changes in children treated with 0.01% atropine were -0.29 ± 0.38 D and -0.33 ± 0.27 D in period 1 and period 2, whereas the AL changes were 0.15 ± 0.16 mm and 0.16 ± 0.11 mm in 2 periods, respectively, consistent with previous studies (converted to 1 year) and were superior to the blank control group, providing a reliable comparison for assessing the efficacy of RLRL.

Increasing evidence has demonstrated the effectiveness of RLRL in slowing the progression of SER and AL growth in children with myopia.[26–30,33] Previous studies showed that after 6 months of RLRL treatment, AL progression was in the range of -0.09 mm to 0.04 mm, whereas that of SER progression spanned from -0.03 D to 0.29 D (Supplementary Table S3). In the present trial, children receiving RLRL treatment led to AL changes of -0.09 ± 0.14 mm and -0.06 ± 0.13 mm in periods 1 and 2, respectively. Simultaneously, the children also displayed changes in SER of 0.24 ± 0.30 D and 0.22 ± 0.27 D, aligning closely with previous reports.[13] In a recent 12-month RCT with 62 participants, RLRL demonstrated greater effectiveness in controlling AL and myopia progression compared with 0.01% atropine.[28] This study had the advantage over the aforementioned studies by its use of a crossover design, resulting in less bias, showing that RLRL was more effective in delaying the progression of AL and SER in children with myopia when compared to the 0.01% atropine.

In this study, the 6-month RLRL treatment led to a significant rise in SFCT, with respective changes measuring 41.47 ± 34.27 µm and 33.33 ± 28.54 µm, closely aligning with previous research findings.[26,29,30] In a retrospective study, Zhou et al.[27] found a substantial increase in SFCT at 45.32 µm following 9 months of RLRL treatment. Interestingly, the LAMP study demonstrated that after 1 year of using 0.01% atropine, there was no significant change in the SFCT compared to baseline (3.96 ± 23.11 µm, $P > 0.05$).[42] We also observed no significant changes in the SFCT in the 0.01% atropine group during the two 6-month follow-up periods. These findings indicate that the efficacy of RLRL can be partly associated with choroidal thickening.

During the two 6-month follow-up periods (1 and 2), RLRL treatment resulted in 62.2% and 61.9% of children experienced AL shortening exceeding 0.05 mm. The exact mechanism underlying the reversal in myopia as a result of RLRL treatment remains elusive. Three explanations are worth considering. First, AL measurements using IOL-Master span from the corneal surface to the retinal pigment epithelium. As thickened SFCT pushes the retinal pigment epithelium forward, it mechanically shortens the AL. However, Wang et al.[43] revealed that choroidal thickening accounted for less than 28% of reduction in AL following RLRL treatment, and suggested that factors other than SFCT influence AL growth. Second, we observed stable SFCVV in children receiving 0.01% atropine, whereas there was an increase in children treated with RLRL during both periods. The extent of choroidal vessel volume and blood flow increased was more in the RLRL group compared with the 0.01% atropine group.[44] Third, recent

evidence highlights the vital role of scleral hypoxia in scleral remodeling, leading to reduced supply of oxygen and nutrients to the avascular sclera, resulting in thinning and eventual progression of myopia.[45] Further investigation is needed to fully understand the precise mechanisms underlying the action of RLRL therapy.

This study found no significant association between AL progression and compliance with RLRL treatment, which was consistent with the findings of Chen et al.,[28] but in contrast to the findings of Jiang et al.[30] Moreover, the dose-response effect of RLRL was unknown in the current study due to insufficient follow-up. It should be noted that the participants in this study received RLRL treatment daily, which was similar to the study results of Xiong et al.,[26] Zhou et al.,[27] and Chen et al.,[28] which was better than the treatment effect of Jiang et al.[30] for 5 days per week. Furthermore, the study of Dong et al.[33] showed that children treatment with RLRL of 100% power reduced myopia progression compared with children treated with a sham device of 10% original power. Therefore, it is possible to infer a dose-response effect between myopia progression and RLRL treatment. Research on the treatment of RLRL is still in its infancy, and we will follow up to find the best treatment frequency and dose of 650 nm RLRL by changing the frequency of RLRL or the power of RLRL.

The SFCT changes noted at the 3-month interval were significantly associated with the increase in AL at 6 months in both study groups. Moreover, RLRL treatment significantly increased SFCT, which subsequently reverted to baseline levels after a withdrawal period of 1 month (7 months of follow-up). This suggests that alterations in SFCT during the initial period following RLRL or 0.01% atropine treatment may serve as predictive indicators of their long-term efficacy in retarding the progression of myopia, highlighting the clinical utility of SFCT in myopia management.

This study had notable strengths, including its randomized crossover-controlled design, as well as the adoption of SS-OCT for measuring SFCT and SFCVV, which facilitates exploring potential mechanisms underlying the delay in the progression of myopia and AL growth attributable to RLRL and 0.01% atropine.[35,36] Nonetheless, several limitations must be acknowledged. First, the absence of a placebo-control group in this study is noteworthy. Prior studies have consistently demonstrated the efficacy of RLRL treatment compared to a placebo, making the inclusion of such a group ethically untenable. Second, due to feasibility constraints, this study used a single-blind design. Although the study was randomized and specifically designed as a crossover study following 6 months of RLRL usage, the relatively short duration could not fully capture the long-term performance of RLRL. Third, adherence to the 0.01% atropine treatment was less reliable. Whereas the RLRL therapy had a built-in server that monitored compliance, compliance with atropine therapy was determined by the number of medications recorded by the parents on the calendar. We cannot avoid the possibility of false reports from parents; therefore, high compliance to atropine should be interpreted with caution. Fourth, we did not evaluate the effect of near work and outdoor activity time on the progression of myopia, which limited our ability to detect potential risk factors that led to poor responses to the RLRL or atropine therapy.

In conclusion, this crossover RCT demonstrated that RLRL was more effective as a treatment option compared to 0.01% atropine. Alterations in SFCT can potentially serve as predictive indicators of the decline in AL growth achieved by both RLRL and 0.01% atropine. Further study is needed to assess the long-term efficacy and safety of RLRL treatment across diverse racial and geographic populations.

Acknowledgments

The authors thank Suzhou Xuanjia Photoelectric Technology Co., Ltd for its support in operating the RLRL instrumentation technology, and the families and children who participated in this study.

Supported by new technology and a new project of the First Affiliated Hospital of Zhengzhou University (Grant No. 2022-C50).

Author Contributions: Conception and design: Zheng, Jin, and Fu; Software: Pang, Shang, and Chang; Analysis and interpretation: Pang and Ma; Data collection: Pang, Fu, Wang, and Zhao; Writing—original draft preparation: Pang and Fu; Writing—review and editing: All authors; All authors have read and agreed to the published version of the manuscript.

Data Availability Statements: The datasets used and analyzed during the current study are available from the corresponding authors upon reasonable request. The data are not publicly available due to patient privacy.

Disclosure: **X. Pang**, None; **X. Jin**, None; **A. Fu**, None; **W. Wang**, None; **B. Zhao**, None; **L. Shang**, None; **M. Chang**, None; **N. Ma**, None; **G. Zheng**, None

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