

# Effect of Repeated Low-Level Red-Light Therapy for Myopia Control in Children

## A Multicenter Randomized Controlled Trial

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**Purpose:** To assess the efficacy and safety of repeated low-level red-light (RLRL) therapy in myopia control in children.

**Design:** Multicenter, randomized, parallel-group, single-blind clinical trial.

**Participants:** Two hundred sixty-four eligible children 8 to 13 years of age with myopia of cycloplegic spherical equivalent refraction (SER) of  $-1.00$  to  $-5.00$  diopters (D), astigmatism of 2.50 D or less, anisometropia of 1.50 D or less, and best-corrected visual acuity (BCVA) of 0.0 logarithm of the minimum angle of resolution or more were enrolled in July and August 2019. Follow-up was completed in September 2020.

**Methods:** Children were assigned randomly to the intervention group (RLRL treatment plus single-vision spectacle [SVS]) and the control group (SVS). The RLRL treatment was provided by a desktop light therapy device that emits red light of 650-nm wavelength at an illuminance level of approximately 1600 lux and a power of 0.29 mW for a 4-mm pupil (class I classification) and was administered at home under supervision of parents for 3 minutes per session, twice daily with a minimum interval of 4 hours, 5 days per week.

**Main Outcome Measures:** The primary outcome and a key secondary outcome were changes in axial length and SER measured at baseline and the 1-, 3-, 6-, and 12-month follow-up visits. Participants who had at least 1 postrandomization follow-up visit were analyzed for treatment efficacy based on a longitudinal mixed model.

**Results:** Among 264 randomized participants, 246 children (93.2%) were included in the analysis (117 in the RLRL group and 129 in the SVS group). Adjusted 12-month axial elongation and SER progression were 0.13 mm (95% confidence interval [CI], 0.09–0.17 mm) and  $-0.20$  D (95% CI,  $-0.29$  to  $-0.11$  D) for RLRL treatment and 0.38 mm (95% CI, 0.34–0.42 mm) and  $-0.79$  D (95% CI,  $-0.88$  to  $-0.69$  D) for SVS treatment. The differences in axial elongation and SER progression were 0.26 mm (95% CI, 0.20–0.31 mm) and  $-0.59$  D (95% CI,  $-0.72$  to  $-0.46$  D) between the RLRL and SVS groups. No severe adverse events (sudden vision loss  $\geq 2$  lines or scotoma), functional visual loss indicated by BCVA, or structural damage seen on OCT scans were observed.

**Conclusions:** Repeated low-level red-light therapy is a promising alternative treatment for myopia control in children with good user acceptability and no documented functional or structural damage. *Ophthalmology* 2022;129:509-519 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



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Myopia, also known as shortsightedness or nearsightedness, is a common condition that develops primarily during childhood.<sup>1</sup> Progressive myopia is nearsightedness that continues to worsen over time, leading to high myopia, often defined as  $-5$  or  $-6$  diopters (D) or more, which is associated with increased risk of developing conditions that cause irreversible visual impairment, including myopic maculopathy, glaucoma, or even retinal detachment.<sup>2</sup> An effective treatment to control the progression of myopia, therefore, is critically important for preserving eye health and quality of life.

In the past decade, increased time spent outdoors in bright light has been established as an effective protective factor for

myopia development.<sup>3,4</sup> A 3-year cluster-randomized trial conducted by our research group in Guangzhou, China, demonstrated that an additional 40 minutes of outdoor time every day reduced myopia incidence by at least 20%.<sup>5</sup> The protective effect of exposure to outdoor bright light and its dose-response relationship were confirmed by a trial in Taiwan and animal model research.<sup>6–8</sup> Since then, researchers have proposed renovating classrooms and installing glass walls and ceilings<sup>9,10</sup> as a means to increase the intensity and duration of protective bright light exposure for students, although these strategies often are expensive and pragmatically challenging.

As an alternative to increasing bright light exposure, we propose to deliver light on the retina directly at a much shorter duration of exposure but repeatedly for myopia control. We intend to use a device that emits red light at 650 nm in wavelength based on the fact that this was already approved and is used widely for amblyopia treatment in China so that the safety of the participants can be potentially maximized. The selection of treatment method is also based on unpublished anecdotal findings from children who used the device for the purpose of amblyopia treatment, where increased choroidal thickness and blood flow and stabilization of axial elongation were observed. By the time of this manuscript's preparation, a published report also demonstrated that this strategy, carried out using a similar device, significantly reduced the rate of myopia progression and axial length (AL) elongation over 6 months, similar to orthokeratology compared with single-vision spectacle (SVS) wear.<sup>11</sup> Herein, we report the results of a prospective, multicenter, randomized clinical trial to assess the efficacy and safety of repeated low-level red-light (RLRL) therapy in myopia control in children.

## Methods

### Study Design and Setting

We conducted a 12-month, multicenter, randomized, parallel-group, single-blind clinical trial to assess the efficacy and safety of RLRL therapy for myopia control at 5 study centers from 4 tertiary hospitals in China. The study protocol is available in the [Supplemental Methods](#) (available at [www.aojournal.org](http://www.aojournal.org)). Poster advertisements were used to inform and recruit participants at each study site. Children were enrolled between July 2019 and August 2019. All examinations at baseline and follow-up visits were performed by the same examiners using the same protocol and equipment throughout. This trial was completed in September 2020. Investigators and key personnel at each site involved in the present study were trained and certified before study commencement. No changes in the protocol or methods occurred after trial commencement. This trial is registered with [ClinicalTrials.gov](#) (identifier, NCT04073238).

### Eligibility Criteria

The inclusion and exclusion criteria adopted were the same as for most myopia control trials conducted for low-dose atropine eyedrops<sup>12</sup> and defocus incorporated multiple segments spectacle lens<sup>13</sup> to ensure that outcomes were comparable across studies. Eligible participants were children 8 to 13 years of age with myopia of cycloplegic spherical equivalent refraction (SER) of  $-1.00$  to  $-5.00$  D, astigmatism of 2.50 D or less, anisometropia of 1.50 D or less, and best-corrected visual acuity (BCVA) of 0.0 logarithm of the minimum angle of resolution or more (Snellen equivalent, 1.0 or 20/20) in either eye, and participants were willing to participate in the study and accept random allocation in grouping.

Children were excluded if they had strabismus, binocular vision abnormalities, other ocular abnormalities in either eye, or systemic diseases. Children who underwent previous myopia control treatment, including but not limited to atropine therapy and orthokeratology, were excluded further. We also excluded children if investigators believed they had contraindications that made them unsuitable for participation.

The protocol was approved by the institutional review board of Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China (identifier, 2019KYPJ093), and subsequently was approved by all study sites, including Shenzhen Children's Hospital, The Second People's Hospital of Foshan, and Xiangya Hospital of Central South University. The trial was conducted in accordance with Good Clinical Practice guidelines, the tenets of the Declaration of Helsinki, and all applicable regulations. An independent data safety monitoring committee (DSMC) periodically oversaw the trial and reviewed safety data from the study. A parent or legal guardian provided written informed consent before their child's participation. All study participants were covered by a 2-year research insurance indemnity scheme that included up to Renminbi 200,000 in compensation for each foreseeable and unforeseeable severe adverse event.

### Randomization and Masking

Immediately after verifying participant eligibility and obtaining written informed consent, eligible children were allocated randomly to either the RLRL treatment as the intervention arm or SVS correction as the control arm. Site staff obtained a participant's randomization number by logging into a centralized web-based randomization service (Solomon electronic data capture system; Vision Tech Medical Technology) set up at the Zhongshan Ophthalmic Center. The randomization list in the system was pre-generated by a statistician who had no contact with any study investigators using a simple random sampling package (Seedrandom.js version 3.0.5; Node package manager for JavaScript). The random allocation sequence is available in the [Supplemental Methods](#). The study identification, name of the participant, and group allocation assigned were frozen in the system where further changes were not allowed.

Because of the nature of the intervention, children were aware of the study allocation. Outcome assessors including technicians, optometrists, and statisticians were masked to the treatment allocation.

### Intervention

As the standard treatment for optical correction of myopia, all children wore SVSs throughout the study and updated their spectacles if needed. In addition to SVS, children in the intervention group additionally received RLRL therapy. This treatment was provided by a desktop light therapy device (Eyerising [Suzhou Xuanjia Optoelectronics Technology]; [Fig S1](#), available at [www.aojournal.org](http://www.aojournal.org)), which has been on the market and used widely for amblyopia treatment for the past decade in China. This device is certified as a class IIa device by the China National Medical Products Administration (register number, 170808-01039). It consists of semiconductor laser diodes, which deliver low-level red light with a wavelength of  $650 \pm 10$  nm at an illuminance level of approximately 1600 lux through the pupil to the fundus. Based on calculations completed by an independent lab, the light power going through a 4-mm pupil is 0.29 mW and is classified as class I under the International Electrotechnical Commission 60825-1:2014 standard, which is at a level considered safe for direct ocular exposure that would not create retinal thermal hazard.<sup>14</sup> Children in the RLRL group brought the device home, where they were instructed to complete treatment under supervision of their parents twice daily with an interval of at least 4 hours, with each treatment lasting 3 minutes, during weekdays (5 days per week). This treatment was repeated daily during weekdays until the last follow-up visit at 12 months.

## Intervention Compliance Monitoring

The device was connected to the internet with an automated diary function to record the date and time of treatment sessions, as well as to control light emission as per the predefined treatment schedule (3 minutes per session, 2 sessions per weekday, with a minimum 4-hour interval). Children, their parents, or legal guardians logged in the system using assigned accounts to initiate and complete the treatment sessions. Data on the date and time of each login were used to build an online automated diary function, thus providing an accurate measure of compliance with the treatment. If a child was completing fewer than 8 sessions per week, the manufacturer system alerted the trial manager and automatically sent the parent or legal guardian a short mobile reminder message to facilitate improvements in treatment compliance. Treatment compliance was calculated based on data from the automated diary function in the device system. Treatment compliance was calculated as a percentage of completed sessions divided by the total number of assigned treatment sessions (2 sessions per day, 5 days per week) during the entire treatment period.

## Study Outcomes

The outcomes of interest included efficacy in myopia control and safety of the light treatment. The primary outcome was changes in AL measured at the 1-, 3-, 6-, and 12-month follow-up visits compared with baseline. Five measures of AL were conducted on each eye before cycloplegia using partial coherence interferometry with the IOLMaster (Carl Zeiss 500, Meditec) and averaged until the desired precision (i.e.,  $\leq 0.05$  mm) was achieved. The examiner otherwise deleted measurements with signal-to-noise ratios of  $< 10$  and repeated the measurement.

Secondary outcomes in this trial included changes in cycloplegic SER (myopia progression). Other ocular biometric parameters included anterior chamber depth (ACD), corneal curvature (CC), and white-to-white (WTW) corneal diameter, as well as visual acuity measured at baseline compared with that obtained at the 1-, 3-, 6-, and 12-month follow-up visits.

Refraction data were measured at each eye using an autorefractor (KR-8800; Topcon) 3 times and averaged until the desired precision (i.e., spherical and cylindrical power,  $\leq 0.25$  D; axis,  $\leq 5^\circ$ ) was achieved; otherwise, the entire measurement was repeated. Cycloplegia was achieved using 1 drop of 0.5% Alcaine (Alcon) followed by 3 drops of 1% cyclopentolate (Alcon) to each eye at 0, 5, and 20 minutes. Pupil light reflex and pupil diameter were checked to confirm full cycloplegia after an additional 15 minutes. Dilation and light reflex status were recorded, and full cycloplegia was justified if the pupil dilated to 6 mm or more and the light reflex was absent. The SER was calculated by using the sum of the spherical power and half of the cylindrical power. Other ocular biometric parameters (ACD, CC, and WTW corneal diameter) were measured at the same session as AL measurement on each eye before cycloplegia by IOLMaster and were averaged if their desired precisions were achieved.

Uncorrected visual acuity (UCVA) and BCVA were assessed at 4 m by trained optometrists using the Early Treatment Diabetic Retinopathy Study visual acuity chart (Precision Vision). The examination protocol was the same as the protocol used in the Refractive Error Study in Children (which was a multicountry population-based study in children organized by the World Health Organization).

Choroidal thickness was an optional outcome for the study centers where an OCT device was available. For this outcome measure, a subset of participants ( $N = 162$ ; RLRL group,  $n = 72$ ; SVS group,  $n = 90$ ) enrolled from Zhongshan Ophthalmic Center in Guangzhou underwent swept-source OCT (DRI-OCT Triton;

Topcon) with pupil dilation and under standardized mesopic light conditions. The DRI-OCT system uses an axial scan rate of 100 000 Hz at a laser wavelength of 1050 nm, yielding an 8- $\mu$ m axial resolution and transverse resolution of 20  $\mu$ m. Children underwent 12.0 mm radial scans (resolution,  $1024 \times 12$ ) centered at the fovea. The quality of the scans was indicated by an automated display mode. The choroidal thickness (the distance between outer choroid–scleral margin and retinal pigment epithelium–Bruch's complex) was obtained automatically with the assistance of the swept-source OCT software.

Data from the IOLMaster and autorefractor were extracted automatically into the electronic data capture system, whereas data from other secondary outcomes initially were recorded on paper case report forms and then entered into the electronic data capture system on the same day of examination. Study coordinators supervised the completeness and integrity of data every week and reported to the independent DSMC.

## Adverse Events

Those who underwent at least 1 session of treatment were analyzed for safety. A questionnaire on adverse events, including but not limited to dazzling, short-term glare, flash blindness, and afterimages, was collected from children, parents, or legal guardians at each follow-up and at any unplanned visits if needed. These were recorded in the case report forms and sent to the DSMC. As per the protocol, the treatment was censored if children experienced unexpected severe adverse events, including sudden visual loss of  $> 2$  lines occurring over a period of a few seconds or minutes to a few days or a scotoma perceived to develop in the center of the visual field. At the end of the study, investigators contacted each participant who discontinued RLRL treatment to clarify possible side effects.

## Sample Size

The sample size estimation was conducted based on the assumption of an  $\alpha$  level of 0.05, 80% power, annual axial elongation of 0.30 mm (standard deviation, 0.40 mm) over 12 months, and a 50% treatment effect (reducing axial elongation by 0.15 mm). The sample size required was 112 participants per group or a total sample size of 224 participants. Adjusting for 15% loss to follow-up yielded a total sample size of 264 participants.

## Interim Analyses

To ensure safety of the treatment, an interim analysis at 3 months was planned. Based on the data collected, the independent DSMC concluded that the study could be continued until 12 months. Given this interim analysis, we adjusted the significance threshold to a  $P$  value of 0.048 after O'Brien–Fleming  $\alpha$ -spending adjustment for the primary outcome.<sup>15</sup>

## Statistical Analyses

All statistical analyses strictly followed a prespecified analysis plan, which was endorsed by the independent DSMC. All outcomes were analyzed in all randomly assigned children by means of an intention-to-treat method. Data from all children who attended at least 1 subsequent follow-up visit were included in the analysis regardless of compliance with treatment or compliance with attending follow-up visits. Missing data on outcomes were not imputed. Individuals who were switched to other myopia treatment methods, including orthokeratology or atropine eye drops, or those who discontinued RLRL treatment were considered to be censored. They were included in the analysis, but only the data at the last visit before censoring were used. Right eyes that met the enrollment

criteria were used as the outcome data representing the participant. If the right eye did not meet inclusion criteria or if right eye data were missing, left eyes were used instead ( $n = 6$ ).

Longitudinal mixed models were used to demonstrate treatment efficacy in terms of the primary outcome (changes in AL) and secondary outcomes (changes in SER, ACD, CC and WTW corneal diameter) on multiple follow-up visit time points. Treatment efficacy was calculated by dividing the between arm difference in values by the control arm value. An unstructured covariance matrix was used along with a restricted maximum likelihood method, where the group, visit, and group-by-visit interaction were added as fixed effects together with baseline age, sex, and baseline AL as covariates. The participants were included as a random factor. The estimated mean treatment differences, corresponding 95% confidence intervals (CIs), and 2-sided  $P$  values were calculated. Only the SER data with full cycloplegia were used for the analysis to ensure accuracy on refraction measurement. To measure associations between treatment efficacy and treatment compliance in the intervention group, we carried out a further longitudinal mixed model where treatment compliance in the intervention group was estimated as a percentage to the total number of assigned treatment sessions.

Changes in UCVA (an ordinal variable) were categorized into 3 groups: worsening of 2 lines or more, no change (within 1 line), and improvement of 2 lines or more. Best-corrected visual acuity at 12 months was categorized into meeting a 20/20 threshold and not meeting the threshold.

All adverse events were reported individually in detail. Two ophthalmologists (Y.J. and Z.Z.) independently reviewed all OCT scans to identify possible structural damages.

We conducted sensitivity analyses based on the protocol strategy to investigate the efficacy of the RLRL therapy on the primary outcome (axial elongation) and secondary outcome (SER progression). The protocol strategy analysis included only children who completed the treatment (SVS wear and RLRL treatment scheduled as 3 minutes per session, twice daily with a minimum interval of 4 hours, 5 days per week) and control (SVS wear) as originally allocated and who did not commit any major protocol violation. Subgroup analyses were performed to assess treatment effects of RLRL therapy in controlling myopia progression (axial elongation and SER progression) across different SER groups and age groups.

We used Stata Statistical Software release 14 (StataCorp) for statistical analyses. All statistical tests were 2-sided and were performed at the 5% significance level except where noted otherwise.

## Role of the Funding Source

The funder had no role in study conception and design, confirming data and statistical analyses, or conducting the study. The device manufacturer provided devices on a free-of-charge basis but did not provide research funding. All authors had full access to all the data in the study and were involved in data interpretation and writing of the report. The corresponding author had final responsibility for the decision to submit for publication.

## Results

Between July 23, 2019, and August 23, 2019, children with myopia ( $n = 291$ ) were recruited and assessed for eligibility at 5 study sites. A total of 264 children (90.7%) were included in the study, with 119 children with myopia randomly assigned to the RLRL group and 145 children

randomly assigned to the SVS group by simple random sampling (Fig 1). Enrollment was ceased when the predefined sample size was achieved. The number of participants enrolled at the 5 study sites is available in Table S1 (available at [www.aaojournal.org](http://www.aaojournal.org)). Figure 1 summarizes the number of the participants who completed enrollment, baseline examination, and intervention at each of the follow-up visits. Some participants did not complete all follow-up visits. Because of the coronavirus disease 2019 pandemic and associated lockdown, the number of participants at the 6-month visit was affected significantly. As per instructions from the advisory committee, we decided to continue the trial and strived to maximize attendance at the 12-month visit. Of 264 included children, 225 (85.2%) completed the 12-month study, consisting of 111 children (93.3%) in the RLRL group and 114 children (78.6%) in the SVS group.

A total of 117 children in the RLRL and 129 children in the SVS group were included in the analysis. This cohort for analysis was determined after excluding 2 children in the RLRL group and 16 children in the SVS group who did not attend any of follow-up visit appointments. Baseline characteristics of those included and excluded in the analysis were not statistically significantly different in the SVS group, except for SER ( $-2.61$  D vs.  $-3.23$  D;  $P = 0.03$ ; Table S2, available at [www.aaojournal.org](http://www.aaojournal.org)).

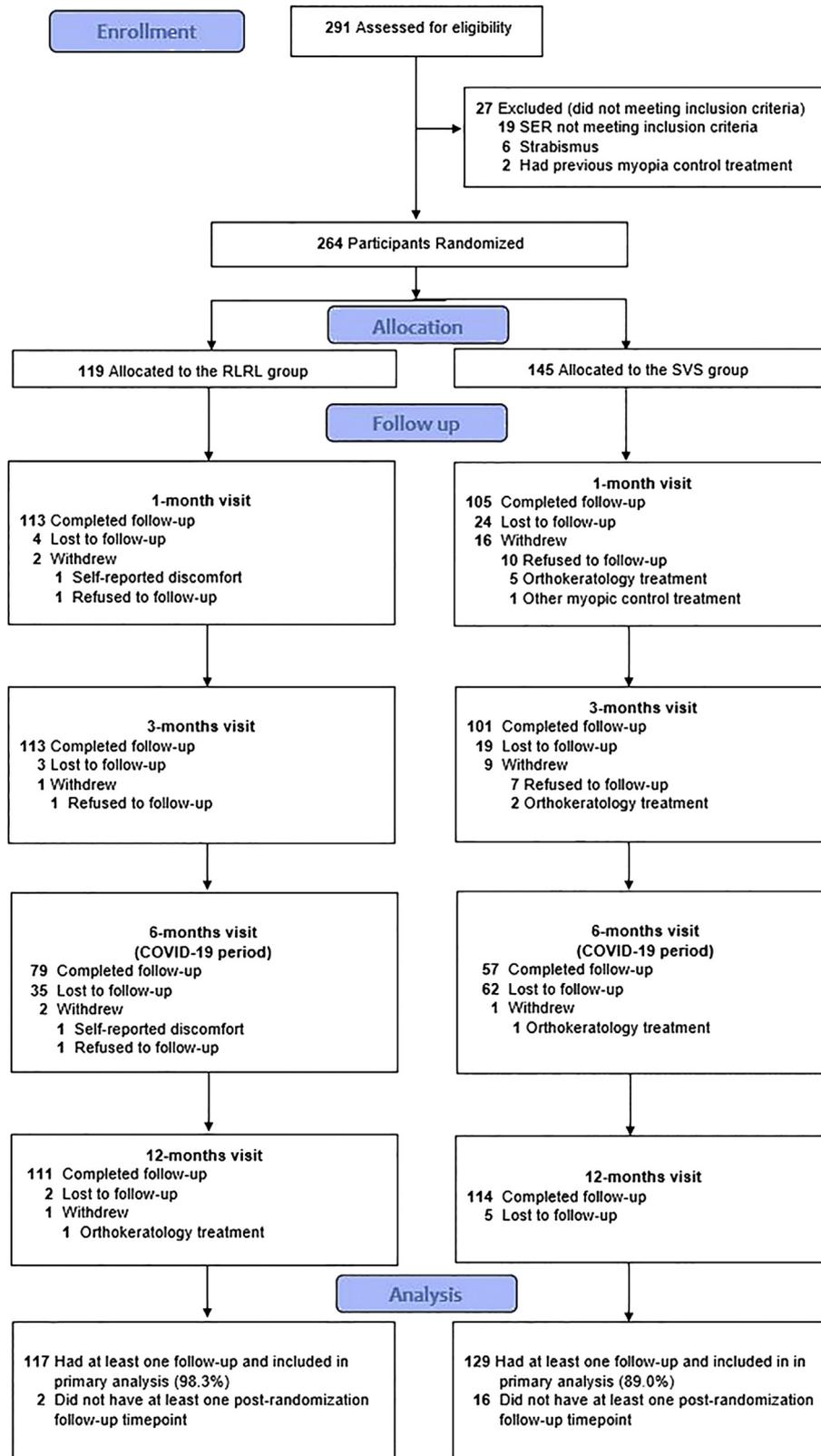
A total of 6 children in the RLRL group discontinued the RLRL treatment. One child in the RLRL group and 8 children in the SVS group switched to orthokeratology treatment, and 1 child in the SVS group switched to other treatments. They were considered censored, where data from their last visit before censoring were used for analysis.

## Baseline Characteristics

The median age and genders were similar between the RLRL and SVS groups (10.4 years [interquartile range, 8.0–13.0 years] vs. 10.5 years [interquartile range, 8.1–13.0 years]; male sex, 47.9% [ $n = 57$ ] vs. 50.3% [ $n = 73$ ]). Ocular characteristics, including UCVA, AL, and SER, were well balanced in the 2 groups (Table 1).

## Primary Outcome

For the RLRL group, the 12-month adjusted (for age at randomization, sex, baseline AL, treatment, visit, and treatment-by-visit interaction) mean axial elongation was 0.13 mm (95% CI, 0.09–0.17 mm). Corresponding mean axial elongation was 0.38 mm (95% CI, 0.34–0.42 mm) in the SVS group. The mean difference in axial elongation between the SVS and RLRL groups was 0.26 mm (95% CI, 0.20–0.31 mm;  $P < 0.001$ ; prespecified primary outcome; Fig 2; Table S3, available at [www.aaojournal.org](http://www.aaojournal.org)), representing a 69.4% reduction in myopia progression. The 1-, 3-, and 6-month adjusted axial elongation values for each group and mean differences between the 2 groups are presented in Figure 2 and Table S3. The adjusted mixed model for the primary outcome showed that age, group, visits, and group-by-visit interaction were statistically significant (Table S4, available at [www.aaojournal.org](http://www.aaojournal.org)).



**Figure 1.** Consolidated standards of reporting trials flow diagram showing the trial profile. COVID-19 = coronavirus disease 2019; RLRL = repeated low-level red-light; SER = spherical equivalent refraction; SVS = single-vision spectacle.

Table 1. Demographics and Baseline Ocular Characteristics between the Repeated Low-Level Red-Light Group and Single-Vision Spectacle Group

Characteristic	All Patients Randomly Assigned	
	Repeated Low-Level Red-Light Group (n = 119)	Single-Vision Spectacle Group (n = 145)
Age (yrs)		
8–10	49 (41.2)	58 (40.0)
11–13	70 (58.8)	87 (60.0)
Median	10.4 (8.0–13.0)	10.5 (8.1–13.0)
Sex		
Male	57 (47.9)	73 (50.3)
Female	62 (52.1)	72 (49.7)
UCVA (logMAR)		
Mean	0.25 ± 0.13	0.25 ± 0.15
Median	0.20 (0.10–0.50)	0.20 (0.05–0.63)
AL (mm)		
Mean	24.54 ± 0.67	24.62 ± 0.86
Median	24.52 (23.41–25.79)	24.63 (23.18–26.17)
SER (D)		
Mean	−2.49 ± 0.92	−2.67 ± 1.06
Median	−2.38 (−4.38 to −1.00)	−2.63 (−4.75 to −1.13)

AL = axial length; D = diopter; logMAR = logarithm of the minimum angle of resolution; SER = spherical equivalent refraction; UCVA = uncorrected visual acuity.

Data are presented as mean ± standard deviation, number (%), or median (interquartile range).

Of note, 39.8% of myopic children in the RLRL group at the 1-month follow-up achieved AL shortening of > 0.05 mm; exceeding that was possible as a result of AL measurement error using the IOLMaster.<sup>16</sup> The corresponding proportions of clinically significant AL shortening at the 3-, 6-, and 12-month follow-up were 29.2%, 32.9%, and 21.6%, respectively.

## Secondary Outcomes

For the RLRL group, the adjusted mean SER progression over 12 months was −0.20 D (95% CI, −0.29 to −0.11 D). For the SVS group, the adjusted mean SER progression over 12 months was −0.79 D (95% CI, −0.88 to −0.69 D). The mean difference in SER progression between the SVS and RLRL groups was 0.59 D (95% CI, −0.72 to −0.46 D;  $P < 0.001$ ; Fig 2; Table S3), representing a 76.6% reduction in myopia progression. The 1-, 3-, and 6-month adjusted SER progression values for each group and mean differences between the 2 groups are presented in Figure 2 and Table S3. Baseline SER, group, visits, and group-by-visit interaction were statistically significant in the adjusted mixed model (Table S4). The percentages of myopic children showing SER regression (worsened myopia of >0.25 D and to account for errors in refraction measurement) in the RLRL group were 15.1%, 17.9%, 15.8%, and 18.9% at the 1-, 3-, 6-, and 12-month follow-up visits, respectively.

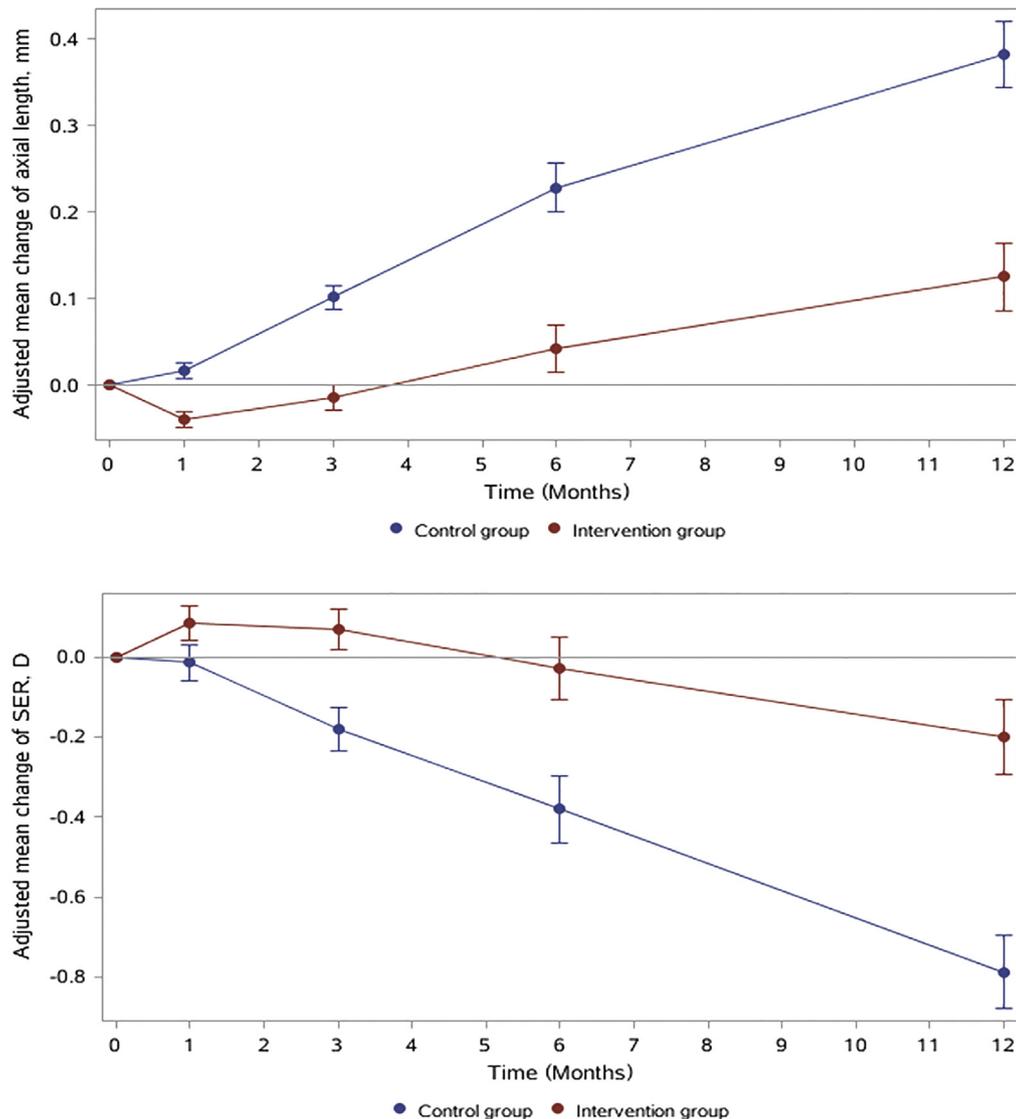
Repeated low-level red-light treatment was similar to SVS for mean changes in other ocular biometric parameters (ACD, CC, and WTW corneal diameter). The 1-, 3-, 6-, and 12-month adjusted mean changes of these ocular parameters for each group and mean differences between the RLRL and SVS groups are presented in Table S5 (available at [www.aaojournal.org](http://www.aaojournal.org)).

At the 12-month follow-up visit, the proportion of children whose UCVA improved by at least 2 lines was significantly greater in children with myopia in the RLRL group than those in the SVS group (21.8% vs. 7.9%;  $P < 0.001$ ). The proportion of children achieving a BCVA of at least 20/20 was similar between the RLRL and SVS groups (97.3% vs. 92.9%;  $P > 0.05$ ; Table 2). Children who did not achieve 20/20 both in the RLRL and SVS groups had BCVA of 20/25, which was likely a result of measurement errors.<sup>17</sup>

For the RLRL group, the adjusted mean change in choroidal thickness over 12 months was 12.1 μm (95% CI, 6.1–18.1 μm). For the SVS group, the adjusted mean change in choroidal thickness over 12 months was −9.5 μm (95% CI, −15.6 to −3.5 μm; Table S6, available at [www.aaojournal.org](http://www.aaojournal.org)).

## Treatment Compliance and Treatment Efficacy

Median treatment compliance in the RLRL group was 75% (interquartile range, 14.1%–112.1%; Fig S2A, available at [www.aaojournal.org](http://www.aaojournal.org)). Participants with a treatment compliance rate of > 100% carried out the treatment >5 days per week on average. The dose-response relationship between treatment compliance with RLRL and efficacy in controlling myopia progression and AL reduction are shown in Table 3 and Figure S2B. With improvements in treatment compliance from < 50% to > 75%, efficacy increased from 44.6% to 76.8% in reducing axial elongation and from 41.7% to 87.7% in controlling SER progression (Table 3). The association between treatment compliance and myopia progression (axial elongation and SER progression) was statistically significant (all  $P < 0.001$ ; Table S7, available at [www.aaojournal.org](http://www.aaojournal.org)) in the adjusted linear mixed models, indicating that



**Figure 2.** Line graphs showing the adjusted mean changes in (A) axial length and (B) cycloplegic spherical equivalent refractions (SERs) from baseline to 12 months at each time point between the repeated low-level red-light group and single vision spectacle group. D = diopter.

improved treatment compliance enhanced the effect of RLRL therapy.

### Adverse Events

No severe adverse events, including sudden vision loss by 2 lines occurring in a period of a few seconds or minutes to a few days or scotoma, developed during the trial. Among 6 participants who discontinued RLRL treatment, the reasons were “feeling that the light is too bright” (n = 2), lack of cooperation with the instructed treatment (n = 3), and conversion to orthokeratology treatment (n = 1). A total of 3 participants (2.7%) did not achieve 20/20 BCVA at 12 months of follow-up, but their BCVAs all were 20/25. This proportion of compromised BCVA was 8 of 112 (7.1%) in the control arm. None reported to have glare, flash blindness, or afterimages after treatment. For participants with available OCT data (RLRL group, n = 72), no structural damage was seen on the photosensory layer.

### Sensitivity and Subgroup Analyses

Sensitivity analyses using per-protocol strategy were performed to verify the robustness of the main findings. Similar results were observed (Table S8, available at [www.aaojournal.org](http://www.aaojournal.org)). Subgroup analyses compared efficacy in myopia control (axial elongation and SER progression) by different baseline SER groups and age groups. Children with greater baseline myopic SER (−3.00 to −5.00 D vs. −1.00 to −2.99 D) or with older age (11–13 years) showed better efficacy in myopia control (Tables S9 and S10, available at [www.aaojournal.org](http://www.aaojournal.org)).

### Discussion

In this 12-month, multicenter, randomized clinical trial, RLRL treatment slowed axial elongation by 0.26 mm and

Table 2. Changes in Uncorrected Visual Acuity and Best-Corrected Visual Acuity from Baseline to 12 Months between the Repeated Low-Level Red-Light Group and Single-Vision Spectacle Group

Visual Acuity	No. (%)	
	Repeated Low-Level Red-Light Group	Single-Vision Spectacle Group
Change of UCVA	110	114
≥2 lines worsening	21 (19.1)	36 (31.6)
±1 line	65 (59.1)	69 (60.5)
≥2 lines improvement	24 (21.8)	9 (7.9)
BCVA		
20/25	3 (2.7)	8 (7.1)
≥20/20	108 (97.3)	104 (92.9)

BCVA = best-corrected visual acuity; UCVA = uncorrected visual acuity. Uncorrected visual acuity was missing in 1 participant from the repeated low-level red-light group, and BCVA was missing in 2 participants from the single-vision spectacle group at the 12-month follow-up visit.

SER progression by 0.59 D compared with SVS, respectively, representing a 69.4% and 76.6% slowing of axial elongation and myopic refraction progression, respectively.

### Efficacy in Comparison with Other Treatments

Orthokeratology, specially designed spectacles, and atropine eye drops are the most common optical and pharmacologic interventions for myopia control. Orthokeratology lenses are worn overnight to flatten the cornea and are used primarily to correct myopia temporarily such that children do not need to wear spectacles during the day to achieve good vision. Evidence from randomized controlled trials demonstrates that this treatment is able to achieve 30% to 59% efficacy in the control of myopia progression among children, probably because of reduced hyperopic defocus on the peripheral retina<sup>18–21</sup>; however, this treatment is associated with a small but significant risk of developing sight-threatening corneal infection, and compliance with wearing a tight contact lens every night can be challenging.<sup>22</sup> Likewise, atropine is the most widely used eye drop for myopia control. Atropine, used at a 0.01% to 0.05% concentration for optimal tradeoff of efficacy, rebound effects, and side effects (such as pupil dilation, photophobia, and near blur),<sup>23,24</sup> has approximately 50% efficacy in myopia control.<sup>12,25</sup> In both the Atropine in the Treatment of Myopia and Low-Concentration Atropine for Myopia Progression studies, it was noted that, although 0.01% atropine demonstrates decreased SER changes, no statistical difference was found in AL compared with the placebo, suggesting that this low concentration of atropine does not control myopia fully.<sup>12,26</sup> In addition to orthokeratology and atropine eye drops, 2 recent innovatively designed spectacle lenses that impose myopic defocus on the retina, the defocus incorporated multiple segments lens and highly aspherical lenslet target lens, have shown strong myopia-controlling effects of 52% and reduced axial elongation by 62% when compared over 2 years with SVS wear. A further report showed that this myopia control effect is sustained in the

third year.<sup>13,27</sup> Although study design differences make direct comparison difficult, the RLRL efficacy results reported here seem at least competitive with these other treatment methods.

### Axial Shortening and Reversal of Spherical Equivalent Refraction Myopia Progression

Myopia traditionally is recognized as an eye disease that is progressive and irreversible. In this study, we demonstrated that RLRL treatment was able to achieve > 0.05 mm AL shortening in 39.8% of the participants at 1 month and in 21.6% of the participants at 12 months. Axial length measurement as measured by the IOLMaster generally is accepted to be accurate with measurement error within 0.05 mm, and, thus, the observed axial shortening cannot be explained fully by measurement error alone.<sup>16</sup> In this study, we also measured choroidal thickness change at 2 study sites. Choroidal thickness increased on average by 16.1 μm (95% CI, 12.0–20.2 μm) at the 1-month visit (Table S6), whereas axial shortening was measured as –0.04 mm (95% CI, –0.05 to –0.03 mm) at this visit; axial shortening, therefore, cannot be explained fully by choroidal thickening, either. Because recent evidence confirmed scleral hypoxia as a promoter for scleral remodeling and myopia development,<sup>28,29</sup> we hypothesized the RLRL treatment might increase blood flow and metabolism of the fundus, thus ameliorating scleral hypoxia and restoration of scleral collagen levels.

### Treatment Methods and Treatment Compliance

Repeated low-level red-light intervention in this study required repeated treatment twice daily, 3 minutes per session, 5 days per week. This treatment protocol follows exactly the same one as in amblyopia treatment. To enable this daily treatment schedule, we provided the device to parents so that they could implement this treatment at home. The device is connected to the internet, requiring users to log in to the system using a designated username and password provided to initiate treatment. By doing so, the research coordinator can observe, document, and monitor treatment compliance in device use. Our study further demonstrated that treatment efficacy increased significantly with improved treatment compliance. This strong dose-response effect may support further the efficacy of RLRL on myopia control and, more importantly, highlight the imperative of setting up a proper incentive system to encourage children to use the device and to maximize treatment efficacy. This strong dose-response effect also may imply that an extension of the treatment duration from 3 minutes to a longer treatment time per session may result in improved treatment efficacy. Of note, the current 3 minutes per session protocol was chosen intentionally to be consistent with the protocol adopted for amblyopia treatment, the original treatment indication for the device, as per instruction from the ethics committee. No evidence was found to suggest that further extension of the treatment duration would not be feasible or safe.

Table 3. The Efficacy of Repeated Low-Level Red-Light Therapy in Controlling Axial Length and Cycloplegic Spherical Equivalent Refraction in Different Treatment Compliance Groups

Treatment Compliance Group (Repeated Low-Level Red-Light Group)	Repeated Low-Level Red-Light Group		Efficacy (%)
	No.	Mean ± Standard Deviation	
Primary outcome			
Change of AL (mm)			
Total	111	0.116 ± 0.225	69.4
<50%	17	0.210 ± 0.252	44.6
50%–75%	35	0.117 ± 0.223	69.1
>75%	59	0.088 ± 0.215	76.8
Secondary outcome			
Change of SER (D)			
Total	106	−0.184 ± 0.543	76.6
<50%	15	−0.459 ± 0.674	41.7
50%–75%	33	−0.212 ± 0.491	73.1
>75%	58	−0.097 ± 0.517	87.7

AL = axial length; D = diopter; SER = spherical equivalent refraction.

Treatment compliance was calculated based on data from the automated diary function in the device system as a percentage of completed sessions divided by the total number of assigned treatment sessions (2 sessions per day, 5 days per week) during the entire treatment period. For changes in AL, 114 patients with a mean ± standard deviation of 0.379 ± 0.192 mm in the single-vision spectacle group were used as the benchmark for efficacy. For changes in SER, 110 patients with a mean ± standard deviation of −0.787 ± 0.460 D in the single-vision spectacle group were used as the benchmark for efficacy. Treatment efficacy was calculated by dividing the between arm difference in values by the control arm value.

### Outcomes of Interest

Spherical equivalent refraction and AL are chosen commonly as the outcomes of interest for almost all clinical trials of myopia control. Although SER is chosen as the primary outcome in most myopia control trials, it is not uncommon to see a treatment have a statistically significant effect on SER but not on AL elongation. For example, no statistically significant difference was found in AL between the 0.01% atropine group and the placebo group (0.36 mm vs. 0.41 mm;  $P = 0.180$ ) in the Low-Concentration Atropine for Myopia Progression study,<sup>30</sup> with a similar effect also observed in the Atropine in the Treatment of Myopia study.<sup>26</sup> Given that refraction measurement is highly dependent on the completeness of cycloplegia and is subject to measurement error and variation from the autorefractor or examiners, we chose to use AL measured by the same IOLMaster as the primary outcome for the current study, as recommended by cosponsored Food and Drug Administration<sup>31</sup> and International Myopia Institute workshops.<sup>32</sup> Interestingly, as expected, we observed a better efficacy in myopia control on SER than AL. Similar to findings from many other clinical trials, we did not observe differences between the 2 groups in anterior segment biometric measurement changes as measured by the IOLMaster, such as ACD, CC, and corneal diameter, because most biometric changes for myopia progression are in the posterior segment of the eyes.<sup>27</sup>

### Safety

The treatment device used has been approved by the China National Medical Products Administration (equivalent to the Food and Drug Administration in the United States) as a

treatment method for amblyopia that involves multiple repeated treatment sessions over a long period. In the treatment initiation phase, very few (2 in total) patients believed that the light emitted was “too strong” and therefore discontinued treatment. In the further 12 months of treatment, no additional participants withdrew from the study because of intolerability or discomfort. No side effects were documented in terms of complaints, functional loss (BCVA), or anatomic changes (OCT scans) during the 12 months of follow-up.

### Study Limitations

This study had several limitations. First, because of pragmatic feasibility, we did not implement masking, such as using a light treatment simulator with a much lower illuminance, as a placebo. Second, the findings on improved efficacy with different levels of compliance should be understood in the context of the fact that the level of compliance was not assigned randomly. Third, because of the outbreak of coronavirus disease 2019, approximately 50% of children were lost to follow-up at 6 months, although we tried all efforts to maximize the follow-up retention rate for the 12-month visit (response rate, 93.3% in the intervention and 78.6% in the control groups). Sensitivity analyses using a per-protocol strategy yielded similar results as those using the intention-to-treat strategy in the main analyses. Fourth, the observed treatment efficacy in controlling myopic progression was generalizable only to the device used in the present study. It is unproven that other wavelengths, power intensities, exposure durations per session, or frequencies of treatment may have similar or even better efficacy. Fifth, the duration of the trial was designed as 1 year. This may not be long enough to observe full myopia control effects;

however, our data suggest that the cumulative treatment efficacy is very strong and that this treatment efficacy in fact increases over time. For example, the mean difference in SER between the 2 groups increased from  $-0.10$  D at 1 month to  $-0.25$  D at 3 months,  $-0.35$  D at 6 months, and  $-0.59$  D at 12 months, respectively. Similar increased efficacy over time was observed for AL, suggesting that we likely would have observed even better efficacy if follow-up had been extended. This was supported further by the statistically significant interaction identified between assignment groups and visits. Sixth, in the current study, we were unable to describe possible stop and rebound effects or carry-on effects when the treatment was stopped. Finally, we have yet to prove that efficacy is consistent in ethnic groups other than children of Chinese heritage. All of these require further investigation.

In conclusion, among Chinese children 8 to 13 years of age with myopia, RLRL therapy is an effective new alternative treatment for myopia control with good user acceptability and no documented functional or structural damage; however, further research with double-masking and placebo control is needed to understand its long-term efficacy and safety, rebound effects, optimal treatment strategies (wavelength, power, duration, and frequency of treatment), and potential underlying mechanisms.

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HUMAN SUBJECTS: Human subjects were included in this study. The protocol was approved by the Institutional Review Board of Zhongshan

Ophthalmic Center, Sun Yat-sen University, Guangzhou, China (2019KYPJ093) and subsequently approved by all study sites, including Shenzhen Children's Hospital, The Second People's Hospital of Foshan, and Xiangya Hospital of Central South University. The trial was done in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and all applicable regulations. A parent or legal guardian provided written informed consent prior to the child's participation.

No animal subjects were included in this study.

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Abbreviations and Acronyms:

ACD = anterior chamber depth; AL = axial length; BCVA = best-corrected visual acuity; CC = corneal curvature; CI = confidence interval; D = diopter; DSMC = data safety monitoring committee; RLRL = repeated low-level red-light; SER = spherical equivalent refraction; SVS = single-vision spectacle; UCVA = uncorrected visual acuity; WTW = white-to-white.

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