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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], 0.09–0.17mm) and −0.20 D (95% CI, −0.29 to −0.11D) 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 −0.59D (95% CI, −0.72 to −0.46 D) between the RLRL and SVS groups. No severe adverse events (sudden vision loss ≥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*

Supplemental material available at www.aaojournal.org.

Myopia, also known as shortsightedness or nearsightedness, is a common condition that develops primarily during childhood.[1] 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.[2] 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.[3,4] 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%.[5] 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.[6–8] Since then, researchers have proposed renovating classrooms and installing glass walls and ceilings[9,10] 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.

https://doi.org/10.1016/j.ophtha.2021.11.023
ISSN 0161-6420/21

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.[11] 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.aaojournal.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[12] and defocus incorporated multiple segments spectacle lens[13] 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.aaojournal.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 ± 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 1 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.[14] 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°) 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-µm axial resolution and transverse resolution of 20 µm. Children underwent 12.0 mm radial scans (resolution, 1024 × 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 DMSC. 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 α 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 α-spending adjustment for the primary outcome.[15]

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). 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).

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), 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).

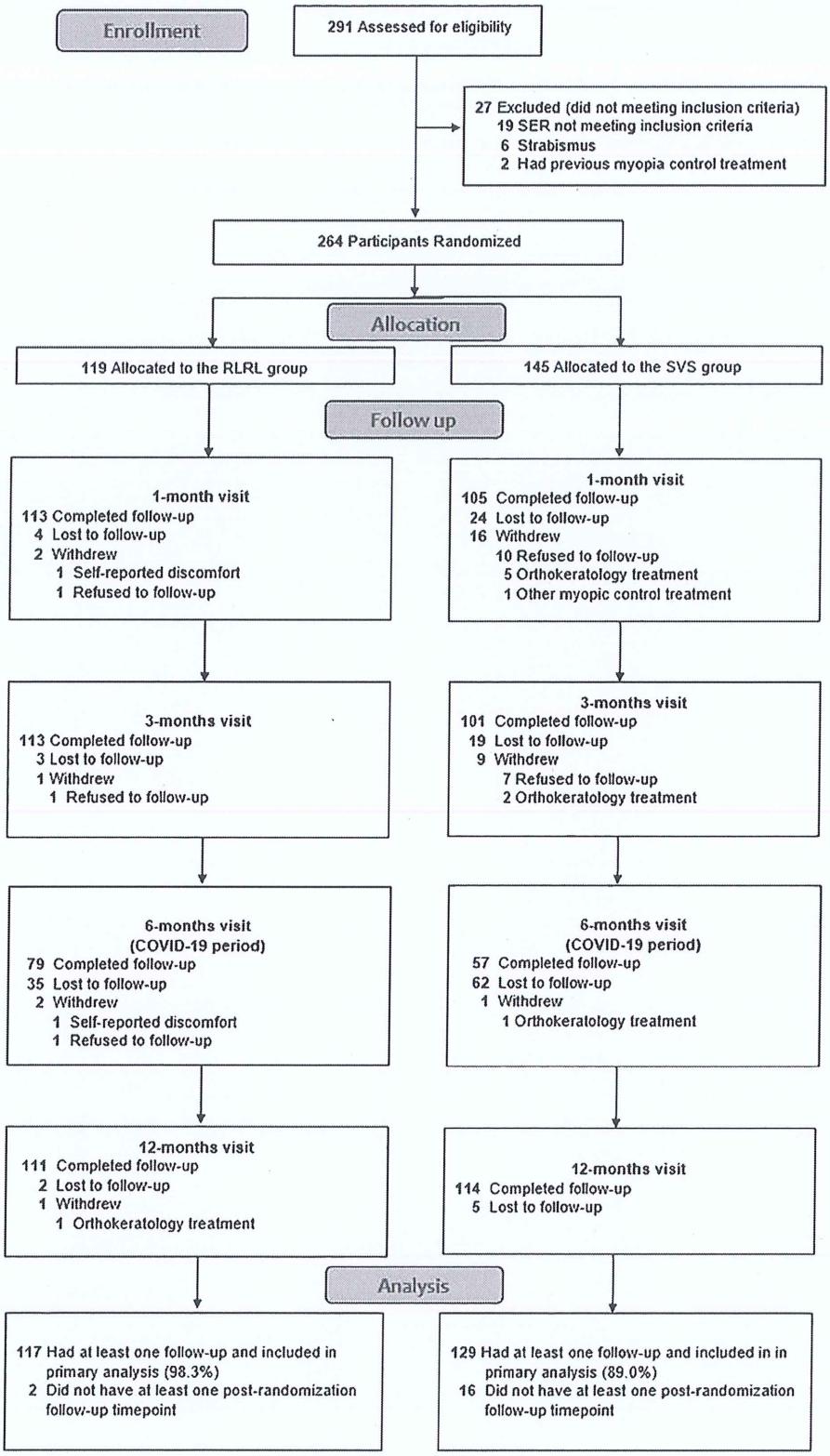

Figure 1. Consolidated standards of reporting trials flow diagram showing the trial profile. COVID-19 = coronavirus disease 2019; RLRL = repeated low-level red-light; SER = spherical equivalent refraction; SVS = single-vision spectacle.

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.[16] 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).

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.[17]

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).

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). 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) in the adjusted linear mixed models, indicating that

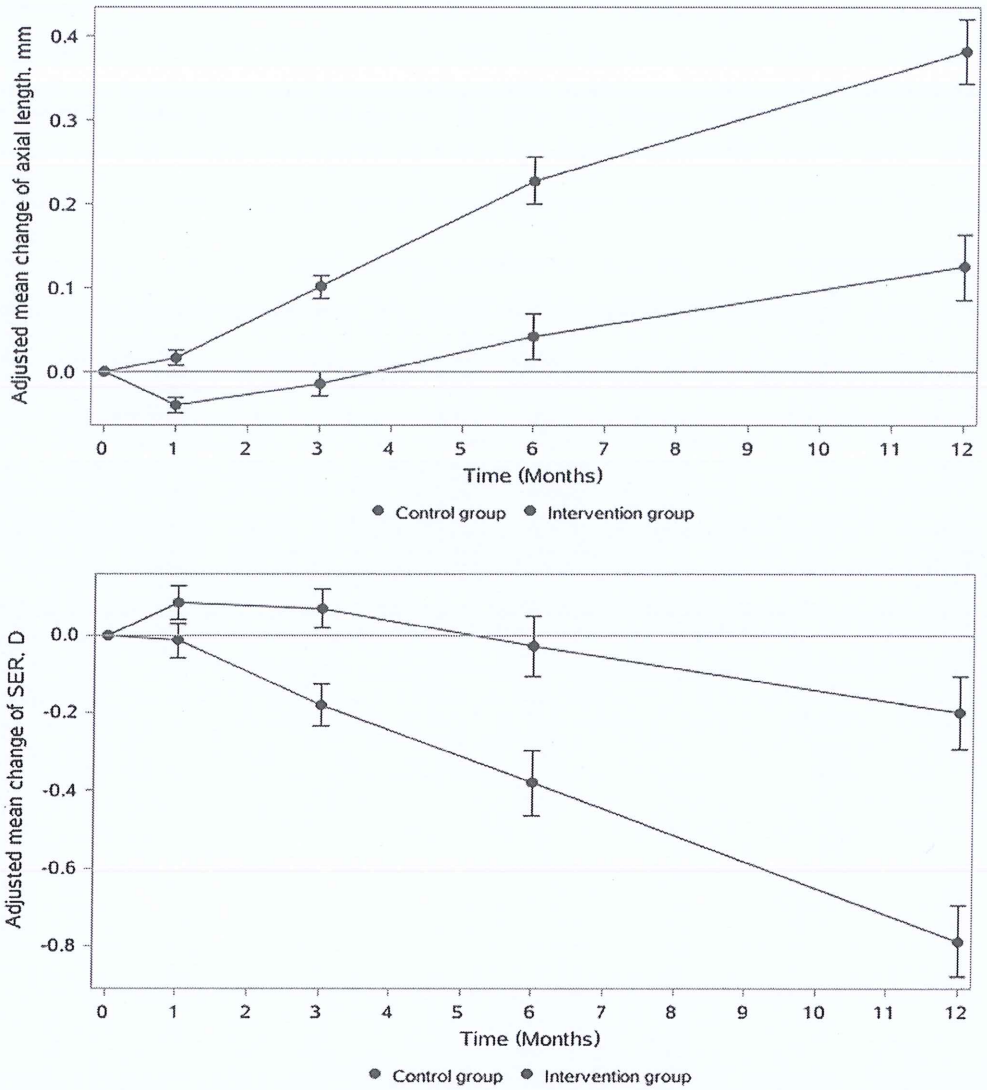

Figure 2. Line graphs showing the adjusted mean changes in (**A**) axial length and (**B**) cycloplegic spherical equivalent refractions (SERs) from baseline to 12 months at each time point between the repeated low-level red-light group and single vision spectacle group. D = diopter.

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). 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).

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[18–21]; 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.[22] 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),[23,24] has approximately 50% efficacy in myopia control.[12,25] 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.[12,26] 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.[13,27] 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.[16] 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,[28,29] 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,[30] with a similar effect also observed in the Atropine in the Treatment of Myopia study.[26] 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[31] and International Myopia Institute workshops.[32] 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.[27]

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.

Acknowledgment

The authors thank the participants who were involved in this trial, without whom the trial would not have been possible, and members of the DSMC, who provided valuable input throughout the study: Leon B. Ellwein, Robert Chang, and Lei Zhang.

Footnotes and Disclosures

Originally received: July 28, 2021.
Final revision: November 23, 2021.
Accepted: November 24, 2021.
Available online: December 1, 2021. Manuscript no. D-21-01511.

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Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): Z.Z.: Patent — "A method to increase retinal blood flow and metabolism" (CN201910490186.6)

M.H.: Patent — "A method to increase retinal blood flow and metabolism" (CN201910490186.6)

Supported in part by the Fundamental Research Funds of the State Key Laboratory of Ophthalmology, National Natural Science Foundation of China (grant no.: 81420108008 and 81271037).

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.

Author Contributions:

Conception and design: Jiang, Zhu, Tan, Kong, Zhong, Zhang, Zeng, Morgan, He

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Obtained funding: N/A

Overall responsibility: Jiang, Zhu, Tan, Kong, Zhong, He

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.

Keywords:
Axial length, Myopia control, Randomized clinical trial, Repeated low-level red-light therapy, Spherical equivalent refraction.

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重复低强度红光治疗对控制儿童近视进展的作用：多中心随机对照试验

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目的：评估重复低强度红光（RLRL）治疗对控制儿童近视进展的有效性和安全性。

设计：多中心、随机、平行、单盲临床试验。

受试者：2019 年 7-8 月，将 264 名睫状肌麻痹散瞳后等效球镜（SER）为-1.00 D 到-5.00 D、散光≤2.50 D、屈光参差≤1.50 D、且最佳矫正视力（BCVA）≥0.0 logMAR 的 8-13 岁儿童纳入研究。2020 年 9 月完成随访。

方法：将纳入研究的儿童随机分配至干预组（RLRL 治疗+框架眼镜[SVS]）和对照组（SVS）。重复低强度红光治疗由一台式设备完成，该设备所发出的红光波长为 650nm、照度约 1600lux、经 4 mm 直径瞳孔的功率为 0.29mW（一类光）。此过程在家中由父母监督进行，每周照射治疗 5 天、每天 2 次，两次之间需间隔 4 个小时以上。

主要观察指标：主要结局指标和其中一项关键的次要结局指标为，相较于基线，第 1，3，6 及 12 月随访中，眼轴长度和散瞳后等效球镜的变化。纳入至少完成一次随机分组后随访的受试者进行有效性分析，分析基于纵向混合效应模型完成。

结果：在 264 名随机分组的受试者中，246 名（93.2%）儿童被纳入分析（其中 117 名儿童随机分配至 RLRL 组，129 名随机分配至 SVS 组）。经过 12 个月随访，RLRL 治疗组校正后的眼轴增长和散瞳后等效球镜进展分别为 0.13 mm（95%置信区间[CI]：0.09 至 0.17 mm）和-0.20 D（95% CI：-0.29 至-0.11 D）。SVS 组校正后的眼轴增长和散瞳后等效球镜进展分别为 0.38 mm（95% CI：0.34 至 0.42 mm）和-0.79 D（95% CI，-0.88 至-0.69 D）。RLRL 组和 SVS 组的眼轴增长和散瞳后等效球镜进展的差值分别为 0.26 mm（95% CI：0.20 至 0.31 mm）和-0.59 D（95% CI：-0.72 至-0.46 D）。研究过程中未观察到严重的不良事件，即视力突然下降（2 行及以上）或出现视野中心暗点，由 BCVA 提示的功能性损伤或由光学相干断层（OCT）扫描提示的结构损伤等。

结论：重复低强度红光治疗可有效控制儿童近视进展。作为一种新的替代疗法，该疗法具有良好的用户接受性且未观察到其对眼睛造成功能性或结构性损伤。眼科学（2022；129：509-519©2021 年获美国眼科学会批准。本篇论文是一篇获 CC BY-NC-ND 许可的开放获取文章（http://creativecommons.org/licenses/by-nc-nd/4.0/）。

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近视眼，近视，是主要发生于儿童时期的一种常见疾病。[1]进行性近视是指随着时间的推移度数逐步加深的近视，会导致高度近视，高度近视通常指度数达到或超过-5.00 D 或-6.00 D。这可能会导致不可逆视力损害的风险增加，包括近视性黄斑病变、青光眼，甚至视网膜脱离。[2]因此有效控制近视进展的治疗方法对保持眼睛健康和生活质量至关重要。

在过去的十年中，增加户外明亮自然光线下的暴露时间被认为是控制近视进展的有效保护因素。[3,4]我们的研究小组在中国广州进行的一项为期 3 年的群组随机试验表明，每天额外的 40 分钟户外时间可以降低至少 20%的近视发病率。[5]台湾的一项试验和动物模型研究证实了户外强光照射的保护作用及其剂量-反应关系。[6,7,8]此后，研究人员提出了更新教室、建设玻璃墙和安装透明屋顶的方法，[9,10]以增加学生接受强光保护的强度和时间。但这些方法成本很高，实际操作上也颇具难度。

http://doi.org/10.1016/j.ophtha.2021.11.023
ISSN 0161-6420/21

我们提出了一种替代方法以增加强光暴露，即在很短的时间内用光重复地直接照射视网膜以达到控制近视的目的。我们使用一种波长为 650nm 红光的设备。在中国，这种设备已经获得医疗器械注册证并广泛用于弱视治疗，因此对于受试者是非常安全的。选择这一治疗方法是基于该设备治疗儿童弱视过程中，我们观察到了脉络膜厚度增加、血流增加和眼轴增长稳定。在撰写这份报告时，一份已发表的报告也表明，在 6 个月内，使用该设备进行近视控制，近视进展和眼轴增长（AL）的速度相比于框架眼镜（SVS）显著降低，而与角膜塑形镜类似。[11] 在此，本文报道了一项评估重复低强度红光（RLRL）治疗对控制儿童近视进展的有效性和安全性的前瞻性、多中心、随机临床试验的结果。

方法

研究设计和设置

我们在中国 4 家三级医院、5 个研究中心开展了一项为期 12 个月的，多中心、随机、平行、单盲的临床试验，以评估 RLRL 治疗控制近视进展的有效性和安全性。研究方案载于附录文件（可在 www.aaojournal.org 查阅）。在每个研究地点，通过招募海报来通知和招募受试者。2019 年 7 月至 8 月，所有儿童招募完成进入研究。所有基线检查和随访检查均由同一检查员全程使用相同的方案和设备进行。该试验已于 2020 年 9 月完成。本次研究涉及的每个现场的调查人员和关键人员在研究开始前都接受了培训和认证。试验开始后，试验方案和方法无变化。该试验已在 ClinicalTrials.gov 进行注册，编号 NCT04073238。

入排标准

采用的纳入和排除标准与对低浓度阿托品滴眼液研究 [12] 和多区正向光学离焦镜片研究 [13] 的大多数近视控制试验相同，以确保各个研究的结果具有可比性。符合条件的受试者为睫状肌麻痹散瞳后等效球镜（SER）为-1.0 D 到-5.0 D、散光≤2.50 D、屈光参差≤1.50 D、且最佳矫正视力（BCVA）≥0.0 logMAR（1.0 或 20/20Snellen decimal）、自愿参与研究，并接受随机分组分配的 8-13 岁儿童。

我们排除了有斜视、双眼视觉异常、任意一只眼的其他眼部异常或系统性疾病的儿童，同时排除既往接受过近视防控治疗（包括但不限于阿托品和角膜塑形镜）的儿童。调查人员认为有禁忌症不适合参与试验的儿童，我们也予以排除。

本方案经中国广州中山大学中山眼科中心批准（2019KYPJ093），以及所有研究中心的批准，包括深圳儿童医院、佛山市第二人民医院和中南大学湘雅医院。试验是在良好临床实践指南、赫尔辛基宣言以及所有适用的法规下进行的。独立的数据安全监查委员会（DSMC）对研究中的安全数据进行定期监督试验并审查。在儿童参与之前，其父母或法定监护人签署书面的知情同意书。所有研究受试者均享受为期两年的研究保险赔偿方案，对于任何可预见和不可预见的严重不良事件，最高可获得 20 万元赔偿金。

随机化和盲法

在核实受试者符合入组标准并征得书面知情同意后，符合条件的儿童被随机分配到 RLRL 治疗组作为干预组，或 SVS 矫正组作为对照组。现场工作人员登录中山眼科中心的集中网络随机化服务（中国广州视觉科技医疗技术所罗门电子数据采集系统）获取受试者的随机号。系统中的随机列表是由一位没有接触任何研究人员的统计专家使用一个简单的随机抽样包（Seedrandom.js,3.0.5 版本；JavaScript node 包管理器）预先生成的。随机分配序列可在附录文件中查到。被分配的研究 ID、受试者姓名和分组情况在系统中被锁定，无法进一步更改。

因为干预的性质，除受试儿童外，所有结果评估人员包括技术人员、验光师和统计人员都不知道研究分配。

干预

作为近视光学矫正的标准方法，所有儿童在整个研究过程中都配戴 SVS，并在需要时更换眼镜。在配戴 SVS 的基础上，干预组儿童增加进行 RLRL 治疗。这种治疗是由一种台式红光治疗设备提供（中国江苏省，艾尔兴，苏州宣嘉光电科技有限公司；附图 1，可在 www.aaojournal.org 查阅）。该设备在中国已经上市，并且已通过中国国家药品监督管理局（注册号 170808-01039）二类甲等医疗器械认证，十多年来广泛应用于弱视治疗。该设备由半导体激光二极管光源构成，发出的红光波长为 650 ± 10 nm、照度约 1600lux。根据独立实验室的测算，通过 4 mm 瞳孔的光功率为 0.29 mW。根据国际电子技术委员会 IEC 60825-1:2014 标准，其分类为一类水平，该水平下对眼部的直接照射是安全的，不会对视网膜造成热损害。[14]RLRL 组的儿童需要将设备带回家，在父母的监督下完成治疗，治疗频率为每周 5 天，每天两次，两次间隔至少 4 小时，每次治疗持续 3 分钟。重复这种治疗，直到最后一次即第 12 月的随访。

干预依从性监测

该设备已联网，有自动记录功能，可记录治疗日期和时间，并根据预定义的治疗计划（每次 3 分钟，每个工作日 2 次，2 次间隔至少 4 小时）来控制红光的照射。儿童或其父母/法定监护人使用指定的账户登录系统，开始并完成治疗过程。对每次登录的日期和时间的数据，建立一个在线自动记录，从而可以对治疗依从性进行精确监测。如果一名儿童每周完成少于 8 次治疗，制造商系统会通知试验经理，并自动向父母/合法监护人发送手机短信提醒，以提高治疗依从性。根据设备系统自动记录的数据计算治疗的依从性。治疗依从性计算方式为整个治疗期间完成治疗的次数除以指定治疗的总次数（每天 2 次，每周 5 天）的百分比。

研究结局

关注的结局指标包括近视控制的有效性和红光治疗的安全性。主要结局指标是相较于基线第 1，3，6 及 12 月的眼轴变化。睫状肌麻痹前，使用部分相干测量光学生物测量仪 IOLMaster（Carl Zeiss 500, Meditec）对每只眼分别测量 5 次眼轴长度，去除信噪比小于 10 的测量值，

对 5 次达到要求精度（即≤0.05mm）的眼轴长度测量值取平均值。

本次试验的次要结局指标包括睫状肌麻痹 SER 变化（近视进展）。其他眼部生物学参数包括前房深度（ACD）、角膜曲率（CC）和白对白（WTW）角膜直径，以及 1 个月、3 个月、6 个月和 12 个月随访中的视力与基线的差别。

使用自动验光仪（KR-8800；Topcon）对每只眼睛屈光数据进行三次测量，取平均值，直到达到所要求的精度（即球镜和柱镜≤0.25 D；轴向≤5 度），否则将全部重新测量。每只眼滴 1 滴 0.5%的盐酸丙美卡因滴眼液（爱尔康），然后分别在 0、5、20 分钟时每只眼各滴 1 滴 1%的环喷托酯（爱尔康），共 3 滴进行睫状肌麻痹。15 分钟后检查瞳孔对光反射和瞳孔直径以确认睫状肌是否完全麻痹。记录瞳孔散大和对光反射情况。如果瞳孔扩大至 6mm 或以上且没有对光反射，则证明睫状肌已完全麻痹。SER 值为球镜度数和 1/2 柱镜度数的和。在用光学生物测量仪 IOLMaster 测量睫状肌麻痹前每只眼的 AL 时，也同时获得了其他眼部生物学参数（ACD、CC 和 WTW 角膜直径）（达到要求精度时取平均值）。

裸眼视力（UCVA）和 BCVA 由经验丰富的验光师使用早期治疗糖尿病视网膜病变研究视力表（Precision Vision）在 4 米距离进行测量。本研究检查方案与儿童屈光不正研究（一项由世界卫生组织发起的多国的儿童人群研究）中使用的方案相同。

脉络膜厚度是一个可选的结局指标，备有 OCT 扫描设备的研究中心可以选择收集。这一结局指标的相关结果来自广州中山眼科中心的受试者（n=162；RLRL 组，n=72；SVS 组，n=90）。广州中山眼科中心运用扫频源 OCT（DRI-OCT Triton；Topcon）在散瞳和标准的暗室光照条件下，对受试者进行光学相干断层扫描。DRI-OCT 系统轴向扫描频率为 100,000Hz，激光波长为 1050nm，轴向分辨率为 8μm，横向分辨率为 20μm。采用以黄斑中央凹为中心的 12.0mm 的辐射扫描模式（分辨率：1024×12）对受试儿童进行扫描。自动显示模式会显示扫描质量，并借助 SS-OCT 软件自动获取脉络膜厚度（外层脉络膜巩膜边缘与视网膜色素上皮-Bruch 膜之间的距离）。

光学生物测量仪 IOLMaster 和自动验光仪上的数据自动提取到电子数据采集系统中，而其他次要结局指标的数据最初记录在纸质病例报告表中并在检查当天输入电子数据采集系统。研究协调员每周监督数据的完整性和真实性并向独立的 DSMC 报告。

不良事件

对至少接受一次治疗的患者进行安全性分析。在每次随访和必要的任何计划外随访时，在儿童、父母或法定监护人那里进行不良事件调查问卷的填报收集。不良事件包括但不限于眩目、短期眩光，闪光盲和后像残留。这些均记录在病例报告表中，并发给 DSMC。根据研究方案，如果儿童出现非预期性的严重不良反应事件，如在几秒钟或几分钟到几天内突然视力下降超过两行，或者出现视野中心暗点，则治疗将被终止。在这项研究结束后，研究人员联系了所有停止使用 RLRL 治疗的受试者，以弄清可能存在的副作用。

样本量

样本量估算基于α水平为 0.05、检验效能为 80%、12 个月年眼轴增长为 0.30 mm 的假设（标准偏差[SD]：0.40 mm），50%的治疗效果（眼轴增长 0.15 mm）。所需样本量为每组 112 名受试者，即总共 224 名受试者。以 15%的失访率进行调整后，得到了总共 264 名受试者的样本量。

中期分析

为确保治疗的安全性，计划在 3 个月时进行中期分析。根据收集的数据，独立的 DSMC 得出结论，该研究可以继续进行到 12 个月。鉴于这项中期分析，我们对主要结果进行 O'Brien-Fleming α-消耗调整，将显著性阈值调整为 P 值 0.048。[15]

统计分析

所有的统计分析都严格遵循预先设定的分析计划，由独立的 DSMC 批准。采用意向性分析方法（ITT）对完成随机分配的所有儿童的所有结果进行分析。无论治疗依从性或随访依从性如何，所有至少参加一次后续随访的儿童的数据均纳入分析。没有对缺失数据进行填补。转用其他近视防控方法的受试者，如角膜塑形镜或阿托品滴眼液，或停止 RLRL 的受试者，被视为删失数据。只有他们删失前最后一次随访的数据被纳入分析。如右眼符合入排标准，右眼数据纳入分析。如果右眼不符合入排标准或右眼数据缺失，则改用左眼数据代替（n=6）。

基于纵向混合模型对多个随访时间点的有效性进行分析，包括主要结局指标（AL）和次要结局指标（SER、ACD、CC 和 WTW 角膜直径）的变化。治疗效果通过将组间差值除以对照组相应值来计算。使用非结构化协方差矩阵和限制最大似然法，将组别、随访和组别与随访交互作用作为固定效应，以及基线年龄、性别和基线 AL 作为协变量纳入模型。受试者作为随机效应被纳入。计算估计的平均治疗差异以及相应的 95%置信区间（CI）和双侧 p 值。只有完全睫状肌麻痹 SER 数据纳入分析，以确保屈光测量的准确性。干预组治疗效果和治疗依从性之间的相关性，我们进行了进一步的纵向混合模型，其中干预组的治疗依从性估计为治疗次数占规定治疗的总次数的百分比。

UCVA（有序变量）的变化分为三组：2 行或更多行的降低、无变化（1 行内）和 2 行或更多行的提高。12 个月时的最佳矫正视力分为达到 20/20 阈值和未达到阈值。

所有不良事件均单独详细报告。两名眼科医生（Y.J.和 Z.Z.）独立审阅了所有 OCT 扫描，以确定可能的结构性损伤。

我们采用符合方案数据分析方法进行敏感性分析，以分析 RLRL 治疗对主要结局（眼轴增长）和次要结局（SER 进展）的有效性。符合方案数据分析方法仅纳入按照最初分组完成干预组（SVS 和 RLRL 治疗计划为每次 3 分钟，每天两次，最小间隔为 4 小时，每周五天）和对照组（SVS）治疗，且未发生任何重大违反方案行为的受试者儿童。按 SER 和年龄分组进行亚组分析，以评估 RLRL 治疗不同组中控制近视进展的效果（眼轴增长和 SER 进展）。

我们使用了 Stata（StataCorp，Stata 统计软件：版本 14）进行统计分析。除另有说明外，所有统计检验均为双侧检验，并在 5%显著性水平下进行。

资金来源的作用

资助者不涉及研究构思和设计、数据确认和统计分析以及研究开展。设备制造商不提供研究经费，仅免费提供设备。所有作者都有权访问研究中的所有数据，并参与数据解释和报告撰写。通讯作者对最终结果提交发表的决定负有最终责任。

结果

2019 年 7 月 23 日至 2019 年 8 月 23 日期间，在 5 个研究中心共招募并筛查了 291 名近视儿童。共有 264 人（90.7%）被纳入研究，通过简单随机抽样，119 名近视儿童被随机分配到 RLRL 组，145 名近视儿童被随机分配到 SVS 组（图 1）。当达到预定的样本量时，停止招募。在 5 个研究中心招募的受试者人数见附表 S1（可在 www.aaojournal.org 查阅）。图 1 总结了在每次随访中完成招募、基线检查、干预的受试者。一些受试者没有完成所有后续随访。由于新型冠状病毒肺炎（COVID-19）和相关的隔离封闭，第 6 个月的随访中，受试者的数量受到显著影响。根据咨询委员会的指示，我们决定继续试验，并努力最大限度地提高 12 个月随访率。在 264 名受试儿童中，225 名（85.2%）完成了 12 个月的研究，其中 RLRL 组 111 名（93.3%）儿童和 SVS 组 114 名（78.6%）。

RLRL 组的 117 名儿童和 SVS 组的 129 名儿童被纳入分析。该分析队列排除了 2 名 RLRL 组和 16 名未参加任何随访的 SVS 组的儿童。除 SER 外（-2.61D vs. -3.23 D；p=0.03），本研究分析中纳入和排除的 SVS 组的受试者的其他基线特征在统计学上无显著差异（附表 S2，可在 www.aaojournal.org 查阅）。

RLRL 组共有 6 名儿童停止了 RLRL 治疗。RLRL 组的 1 名儿童和 SVS 组的 8 名儿童转为角膜塑形镜治疗，SVS 组有 1 名儿童改行其他治疗。相关数据视为删失数据，删失前最后一次随访的数据纳入分析。

基线特征

RLRL 组和 SVS 组的中位年龄和性别相似（10.4 岁[四分位数间距，IQR：8.0 至 13.0 岁]与 10.5 岁[四分位数间距，IQR：8.10 至 13.0 岁]；男性：47.9%[n=57]与 50.3%[n=73]）。包括 UCVA、AL 和 SER 在内的眼部特征在两组中的平衡良好（表 1）。

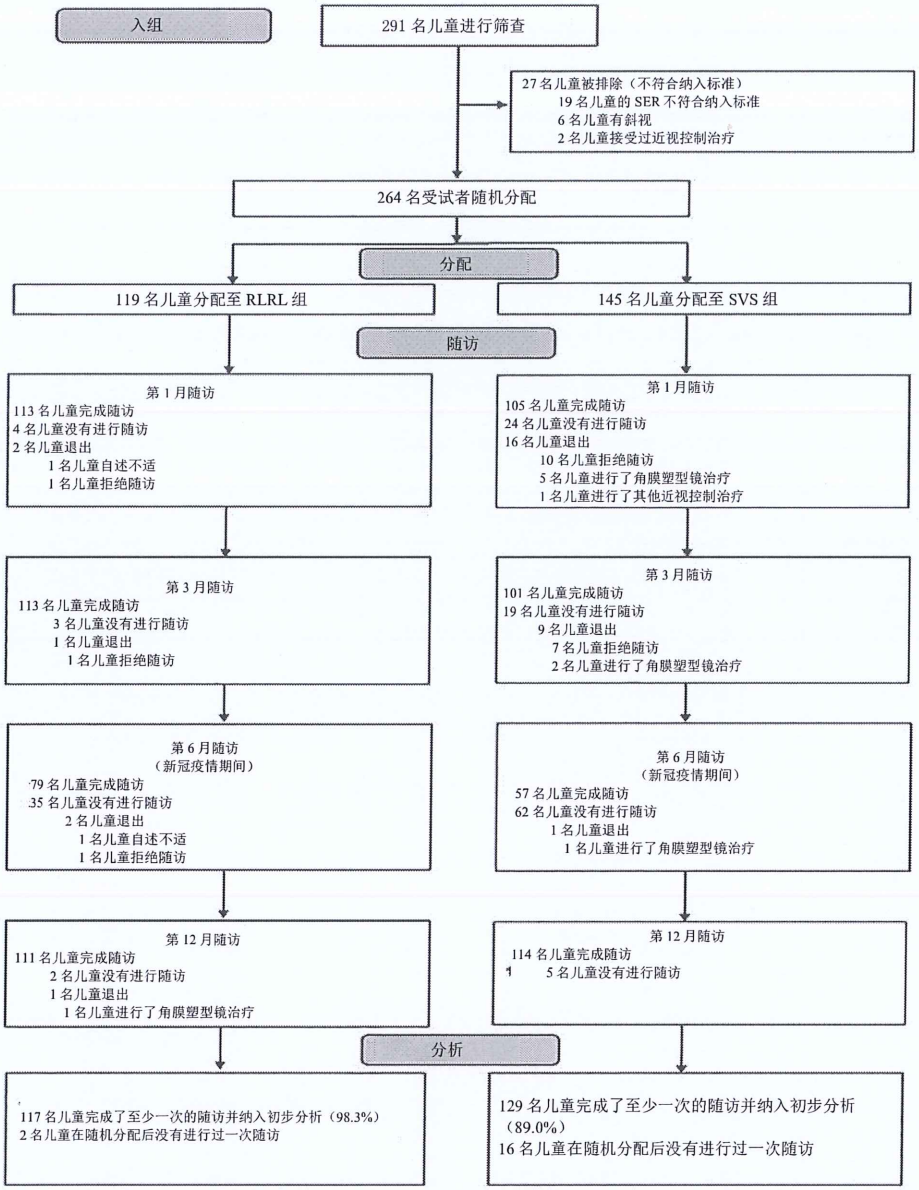

图 1. 说明试验概况的报告试验的综合标准的流程图。COVID-19=新型冠状病毒肺炎；RLRL=重复低强度红光；SER=散瞳后等效球镜；SVS=框架眼镜。

表 1.重复低强度红光组和框架眼镜组之间的人口统计学和基线眼部特征

特征	所有随机分配的患者	
	重复低强度红光组 (N=119)	*框架眼镜组 (N=145)*
年龄，岁		
8-10	49（41.2）	58（40.0）
11-13	70（58.8）	87（60.0）
中位数	10.4（8.0 至 13.0）	10.5（8.1 至 13.0）
性别		
男	57（47.9）	73（50.3）
女	62（52.1）	72（49.7）
UCVA，logMAR		
平均值	0.25±0.13	0.25±0.15
中位数	0.20（0.10 至 0.50）	0.20（0.05 至 0.63）
AL，mm		
平均值	24.54±0.67	24.62±0.86
中位数	24.52（23.41 至 25.79）	24.63（23.18 至 26.17）
SER，D		
平均值	-2.49±0.92	-2.67±1.06
中位数	-2.38（-4.38 至-1.00）	-2.63（-4.75 至-1.13）

AL=眼轴长度；D=屈光度；lpgMAR=最小分辨角的对数；SER=散瞳后等效球镜；UCVA=裸眼视力。
数据为平均值±标准偏差、数量（%）或中位数（四分位数间距）。

主要结局指标

对于 RLRL 组，12 个月校正后（根据随机化时的年龄、性别、基线 AL、治疗、随访、治疗随访的交互作用）的平均眼轴增长为 0.13mm（95% CI：0.09 至 0.17mm）。对应 SVS 组的平均眼轴增长为 0.38mm（95% CI：0.34 至 0.42mm）。在近视进展中，SVS 和 RLRL 组的眼轴增长的平均差异为 0.26mm（95% CI：0.20 至 0.31mm；p<0.001；预先规定的主要结局；图 2 和附表 S3，可在 www.aaojournal.org 查阅），表明红光治疗延缓了 69.4%的眼轴增长。图 2 和附表 S3 显示了各组 1 个月、3 个月和 6 个月的校正后眼轴增长值以及两组之间的平均差异。主要结局指标的校正后混合模型显示：年龄、组别、随访和组别与随访交互作用具有统计学意义（附表 S4，可在 www.aaojournal.org 查阅）。

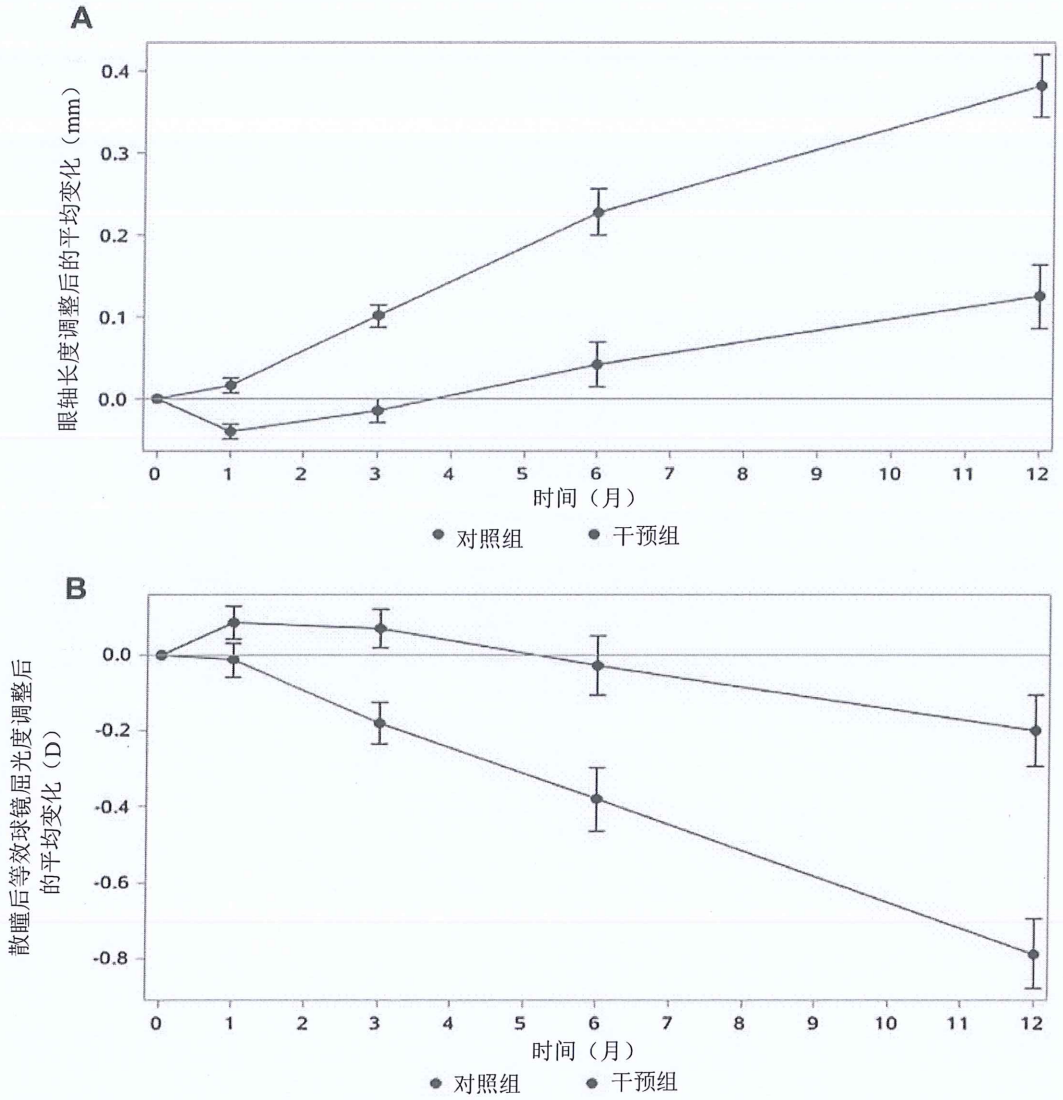

图 2. 折线图显示在重复低强度红光组和框架眼镜组之间的每个时间点从基线到随访 12 个月的（A）眼轴长度和（B）睫状肌麻痹散瞳后等效球镜屈光度（SER）的调整后平均变化。 D＝屈光度。

值得注意的是，在 1 个月的随访中，重复低强度红光组 39.8%的近视儿童出现了超过 0.05mm 的眼轴回退，超过了光学生物测量仪测量所产生的测量误差。[16] 在 3 个月、6 个月和 12 个月的随访中，有临床意义的眼轴回退分别为 29.2%, 32.9%和 21.6%。

次要结局指标

对于重复低强度红光组，12 个月校正后的平均散瞳后等效球镜进展为-0.20 D（95%置信区间：-0.29 至-0.11 D）。对于框架眼镜组，12 个月校正后的平均散瞳后等效球镜进展为-0.79 D（95%置信区间-0.88 至-0.69 D）。框架眼镜组和重复低强度红光组之间散瞳后等效球镜进展的平均差异为-0.59 D（95%置信区间，-0.72 至-0.46 D；p<0.001；图 2 和附表 3），表明红光治疗可延缓 76.6%的近视进展。各组的 1 个月、3 个月和 6 个月校正散瞳后等效球镜进展值，两组之间的平均差异如图 2 和附表 3 所示。基线散瞳后等效球镜、组别、随访和组别与随访交互作用在校正后的混合模型中有统计学显著性（附表 4）。重复低强度红光组出现散瞳后等效球镜回退的近视儿童（近视回退>0.25D，这一数值提示屈光测量误差）的百分比在 1 个月、3 个月、6 个月和 12 个月的随访中分别为 15.1%、17.9%、15.8%和 18.9%。

在其他眼部生物学参数（前房深度、角膜曲率和白对白角膜直径）的平均变化方面，重复低强度红光治疗与框架眼镜相似。1 个月、3 个月、6 个月和 12 个月内各组的眼部生物学参数的校正后平均变化以及低强度重复红光组和框架眼镜组之间的差异见附表 5。（可在 www.aaojournal.org 查阅）

在 12 个月的随访中，重复低强度红光组近视儿童裸眼视力提高至少 2 行的比例明显大于框架眼镜组（21.8%和 7.9%；p<0.001）。重复低强度红光组和框架眼镜组儿童最佳矫正视力至少达到 20/20 的比例相似（97.3%和 92.9%；p>0.05；表 2）。重复低强度红光组和框架眼镜组未达到 20/20 的儿童的（BCVA）均为 20/25，这可能是测量误差导致的。17

表 2.重复低强度红光组和框架眼镜组从基线至 12 个月的裸眼视力和最佳矫正视力的变化

	N（%）	
视力	**重复低强度红光组**	**框架眼镜组**
裸眼视力的变化	110	114
≥2 行的下降	21（19.1）	36（31.6）
±1 行	65（59.1）	69（60.5）
≥2 行的提高	24（21.8）	9（7.9）
最佳矫正视力		
20/25	3（2.7）	8（7.1）
≥20/20	108（97.3）	104（92.9）

在 12 个月的随访中，重复低强度红光组有 1 名受试者缺失裸眼视力数据，框架眼镜组有 2 名受试者缺失最佳矫正视力数据；BCVA，最佳矫正视力；UCVA，裸眼视力。

对于重复低强度红光组，12 个月校正后的脉络膜厚度（ChT）平均变化为 12.1μm（95%置信区间：6.1 至 18.1μm）。对于框架眼镜组，12 个月校正后的脉络膜厚度（ChT）平均变化为-9.5μm（95%置信区间：-15.6 至-3.5μm，附表 6，可在 www.aaojournal.org 查阅）。

治疗依从性和疗效

重复低强度红光组的中位治疗依从性为 75%（IQR：14.1%至 112.1%；附图 2A，可在 www.aaojournal.org 查阅）。接受治疗依从率>100%的受试者平均每周进行 5 天以上的治疗。重复低强度红光治疗依从性与控制近视进展和延缓眼轴增长的疗效之间的剂量-反应关系见表 3 和附图 2B。随着治疗依从性从 50%提高到 75%，延缓眼轴增长的疗效从 44.6%提高到 76.8%，控制散瞳后等效球镜进展的疗效从 41.7%提高到 87.7%（表 3）。在校正后的线性混合模型中，治疗依从性与近视进展（眼轴增长和散瞳后等效球镜进展）之间的相关性具有统计学意义（均 $p<0.001$，附表 7，可在 www.aaojournal.org 查阅），表明治疗依从性的改善增强了重复低强度红光治疗的效果。

表 3. 不同治疗依从性组中，重复低强度红光疗法控制眼轴长度和睫状肌麻痹散瞳后等效球镜的疗效

治疗依从性分组（重复低强度红光组）	重复低强度红光组		疗效（%）
	N	平均值±标准偏差（SD）	
主要结局指标			
眼轴长度改变量，mm			
总计	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%
次要结局指标			
散瞳后等效球镜改变量，D			
总计	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，眼轴长度；D，屈光度；SER，散瞳后等效球镜；

本研究根据设备系统自动记录功能的数据计算治疗依从性。治疗依从性计算为整个治疗期间完成治疗的次数除以指定治疗总次数的百分比（每天 2 次，每周 5 天）。

对于眼轴长度的变化，框架眼镜组中 114 名平均值（SD）为 0.379±0.192 mm 的受试者作为疗效基准。对于散瞳后等效球镜的变化，在框架眼镜组中，110 名平均值（SD）为-0.787±0.460 D 的受试者被用作疗效基准。

治疗效果的计算方法是将两组间的差值除以对照组的值。

不良事件

无严重不良事件，包括在几秒钟或几分钟到几天内突然视力下降 2 行或在试验期间出现视野中心暗点。在停止重复低强度红光治疗的 6 名受试者中，原因是“感觉光线太亮”（n=2），治疗配合度缺乏（n=3），及转为角膜塑形镜治疗（n=1）。共有 3 名受试者（2.7%）在 12 个月的随访期间未达到 20/20 最佳矫正视力，但其最佳矫正视力均为 20/25。在对照组中，这一比例为 8/112（7.1%）。没有报告治疗后出现眩光、闪光盲或后像残留。对于有 OCT 数据的受试者（重复低强度红光组，n=72），光感受器层未见结构性损伤。

敏感性和亚组分析

采用符合方案数据分析方法进行敏感性分析，用以验证主要结果的可靠性。敏感性分析得到了相似的结果（附表 8）。亚组分析比较了不同基线散瞳后等效球镜组和年龄组的近视控制效果（眼轴长度和散瞳后等效球镜进展）。基线近视散瞳后等效球镜越大（-3.00 至-5.00D 和-1.00 至-2.99D）或年龄越大（11 至 13 岁）的儿童，近视控制效果越好（附表 9 和 10，可在 www.aaojournal.org 查阅）。

讨论

在这项为期 12 个月的多中心随机临床试验中，与框架眼镜相比，重复低强度红光治疗分别减缓了 0.26mm 眼轴增长、0.59D 散瞳后等效球镜进展，表明眼轴增长和近视屈光进展分别减缓 69.4%和 76.6%。

与其他治疗比较的疗效

角膜塑形镜、一种特别设计的眼镜和阿托品滴眼液是控制近视最常见的光学和药物干预。OK 镜是在夜间佩戴以压平角膜，主要用于暂时矫正近视，使儿童白天无需佩戴眼镜即可达到良好的视力。来自随机对照试验的证据表明，这种治疗能够在控制儿童近视进展方面达到 30-59%的疗效，这可能是由于周边视网膜上的远视离焦的减少。[18-21] 然而，这种治疗与危及视力的角膜感染的风险相关，而且每晚配戴压迫性接触镜对保持良好的依从性是有困难的。22 同样，阿托品也是用于近视控制最广泛的滴眼液。使用浓度为 0.01%至 0.05%的阿托品，以实现疗效、反弹效应和副作用（如瞳孔扩张、畏光和近视模糊）23,24 的最佳平衡。在近视控制方面其疗效约为 50%。12, 25 在阿托品控制近视研究（ATOM）和低浓度阿托品控制近视进展研究（LAMP）中都发现，虽然 0.01%的阿托品显示散瞳后等效球镜变化减少，但与安慰剂相比，眼轴长度没有统计学差异，表明这种低浓度的阿托品不能完全控制近视。12, 26 除了角膜塑形镜和阿托品滴眼液外，最近两种创新设计的眼镜镜片，对视网膜产生近视离焦，即多区正向光学离焦眼镜片（DIMS）和高非球面微透镜镜片（HALT），显示了 52%的近视控制效果。与框架眼镜相比，2 年以上的眼轴增长率降低了 62%。一份报告进一步显示，这种近视控制效果在第三年仍在持续。13, 27 虽然研究设计的差异使得直接比较变得困难，但与这些治疗方式相比，本文报告的重复低强度红光的疗效至少有一定的竞争力。

眼轴回退和散瞳后等效球镜逆转

通常近视被认为是一种进行性和不可逆转的眼病。在我们的研究中证明，重复低强度红光治疗能够在 1 个月时使 39.8%的受试者和在 12 个月时使 21.6%的受试者实现超过 0.05mm 的眼轴回退。光学生物测量仪测量的眼轴长度测量结果普遍被认为是精准的，测量误差在 0.05mm 以内。因此仅用测量误差无法完全解释所观察到

的眼轴回退。16 在我们的研究中，我们在 2 个研究中心测量了脉络膜厚度变化。在 1 个月访视时，脉络膜厚度平均增加了 16.1 μm（95%置信区间：12.0 至 20.2μm）（附表 6），而此次访视眼轴回退测量为-0.04 mm（95%置信区间：-0.05 至-0.03 mm）；因此，眼轴回退也不能完全用脉络膜增厚来解释。由于最近的证据证实巩膜缺氧是巩膜重塑和近视发展的促进因子，28, 29 我们设想重复低强度红光治疗可能会增加眼底的血流量和代谢，从而改善巩膜缺氧和巩膜胶原蛋白水平的恢复。

治疗方法和治疗依从性

本研究中，重复低强度红光干预要求每天重复治疗 2 次，每次 3 分钟，每周 5 天。这种治疗方案与弱视治疗完全相同。为了实现这一日常治疗计划，我们向患者家属提供了设备，这样他们就可以在家里实施治疗。该设备连接到互联网，要求用户使用指定的用户名和密码登录系统，以开始治疗。这样的步骤使研究协调员可以观察、记录和监控设备使用中的治疗依从性。我们的研究进一步证明，随着治疗依从性的提高，治疗效果显著提高。这种显著的剂量-反应效应可能进一步支持重复低强度红光在近视控制方面的疗效，更重要的是强调了建立适当激励系统以鼓励儿童使用该设备，并最大限度地提高治疗效果的必要性。这种显著的剂量-反应效应也可能意味着将治疗持续时间从每次治疗 3 分钟延长到更长的治疗时间可能会提高疗效。值得注意的是，根据伦理委员会的指示，选择与弱视治疗一致的每次 3 分钟照射的方案。该方案是该设备的最初治疗指征。没有证据表明进一步延长治疗持续时间是不可行或不安全的。

关注的结局指标

散瞳后等效球镜和眼轴长度通常被选为几乎所有近视控制临床试验的关注结局。虽然在大多数近视控制试验中散瞳后等效球镜被选为主要结局，但看到治疗对散瞳后等效球镜有统计学显著影响而对眼轴增长没有影响的情况并不少见。例如，在 LAMP 研究中，0.01%阿托品组与安慰剂组的眼轴增长差异无统计学意义（0.36 vs 0.41 mm，p=0.180），[30] 在 ATOM 研究中也观察到类似的效果。[26] 根据美国食品药品监督管理局和国际眼科协会（IMI）联合主办的研讨会建议，鉴于屈光测量高度依赖于睫状肌麻痹的完全性，并且受自动验光仪或检查者的测量误差和变化的影响，我们选择使用由同一光学生物测量仪测量的眼轴长度作为 [31] 当前研究的主要结局。[32] 有趣的是，正如预期的那样，我们观察到散瞳后等效球镜的近视控制效果优于眼轴长度。与许多其他临床试验的结果类似，我们没有观察到两组在光学生物测量仪测量的眼前段生物学参数变化方面的差异，如前房深度、角膜曲率和角膜直径，因为近视进展的大部分生物特征变化发生在眼后段。[27]

安全性

所使用的治疗设备已获得中国国家药品监督管理局（相当于美国食品药品监督管理局）批准作为一种长期多次重复治疗的弱视治疗方式。在治疗开始阶段，极少数（共 2 名）患者觉得发出的光“太强”，因此停止治疗。在接下来的 12 个月治疗中，没有其他受试者因不耐受或不适而退出研究。在 12 个月的随访期间，没有自述不适、功能丧失（最佳矫正视力）或解剖结构改变（光学相干断层扫描）等方面的副作用记录。

研究局限

本研究有几点局限性。首先，由于可行性的问题，我们没有实施盲法，例如使用低照度的“光治疗模拟器”作为安慰剂。其次，疗效随不同依从性水平而提高的结果中，不同的依从性水平并不是随机分配的。第三，由于新型冠状病毒肺炎（COVID-19）的爆发，尽管我们尽一切努力最大限度地提高 12 个月随访的随访复查率（干预组的复查率为 93.3%，对照组的复查率为 78.6%），但仍有大约 50%的儿童在 6 个月时失访。使用符合方案数据分析方法的敏感性分析与在主要分析中使用 ITT 策略的结果相似。第四，观察到的控制近视进展的治疗效果仅适用于本研究中使用的设备。其他波长、功率强度、每次照射持续时间或治疗频率是否有类似甚至更好的疗效，还有待证实。第五，试验期限设计为 1 年。这可能不足以完全观察近视控制效果。然而，我们的数据表明，累积治疗效果非常明显，而且这种治疗效果实际上会随着时间的推移而增加。例如，两组之间散瞳后等效球镜的平均差异分别从 1 个月时的-0.10D、3 个月时的-0.25D、6 个月时的-0.35D 增加至 12 个月时的-0.59D。随着时间的推移，观察到类似的眼轴长度疗效增加，这表明如果延长随访时间，我们可能会观察到更好的疗效。分组和随访之间具有统计学意义的交互作用进一步支持了这一点。第六，在目前的研究中，我们无法描述终止治疗后可能的停止和反弹效应或持续效应。最后，我们还有待证明疗效在除华裔儿童以外的其他族裔群体中是否一致。所有这些都需要进一步研究以进一步探索。

结论

在中国 8 至 13 岁的近视儿童中，重复低强度红光治疗是一种有效的的新近视控制替代疗法，用户接受度良好，且无功能和结构损伤的记录。然而，需要进一步的双盲和安慰剂对照研究，以了解其长期有效性和安全性、反弹效应、最佳治疗策略（波长、功率、持续时间和治疗频率）以及可能的潜在机制。

致谢

我们感谢参与本次试验的受试者，没有他们本次试验就不可能进行。我们还要感谢数据安全监查委员会的成员，他们在整个研究过程中提供了宝贵的意见：Leon B. Ellwein、Robert Chang 和 Lei Zhang。

脚注和披露

收稿日期：2021 年 7 月 28 日
修改日期：2021 年 11 月 23 日
接受日期：2021 年 11 月 24 日
可在线查阅：2021 年 12 月 1 日。 稿件号：D-21-01511。

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所有作者均已填写并提交 ICMJE 披露表。
作者已作出以下披露。Z.Z.：“专利 - 一种增加视网膜血流量和新陈代谢的方法”（CN201910490186.6）
M.H.：专利：“一种增加视网膜血流量和新陈代谢的方法”（CN201910490186.6）
这项研究得到了国家自然科学基金委员会眼科学国家重点实验室基础研究基金的部分资助（批准号：81420108008 和 81271037）。
人类受试者：本研究包含人类受试者。该方案经中国广州中山大学中山眼科中心医学伦理委员会批准（2019KYPJ093），随后得到所有研究点的批准，包括深圳市儿童医院、佛山市第二人民医院和中南大学湘雅医院。该试验是按照《良好临床实践指南》、《赫尔辛基宣言》和所有适用法规进行的。父母或法定监护人在孩子参与之前提供书面知情同意书。
本研究不包含动物受试者。

作者贡献：
研究理念与设计：江、朱、谭、孔、钟、张、曾、Morgan、何
数据分析或解释：江、朱、谭、孔、钟、张、Morgan、何
数据采集：江、朱、谭、孔、钟、熊、袁、曾
获得资金：无
全面负责人：江、朱、谭、孔、钟、何

缩写和缩略词：
ACD=前房深度； AL=眼轴长度；BCVA=最佳矫正视力；CC=角膜曲率；CI=置信区间；D=屈光度；DSMC=数据安全监查委员会；RLRL=重复低强度红光；SER=散瞳后等效球镜； SVS=框架眼镜；UCVA=裸眼视力； WTW=白对白角膜直径。

关键词：
眼轴长度、近视控制、随机临床试验、重复低强度红光治疗、散瞳后等效球镜。

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