Article

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Low-Power Red Laser Treatment for Anisometropic Myopia Control in Children: A Contralateral Comparison Study

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Background: There are some uncertainties about the effect of low-power red laser treatment on myopia control for anisometropic myopia in children. To evaluate the effect and safety of low-power red laser treatment on refractive development for anisometropic myopia in children, a contralateral comparison study was conducted.

Methods: The more myopic eye of child with anisometropic myopia was treated with low-power red laser treatment (LRL group), the other eye received no treatment other than the wearing of single-focus spectacles (SFS) (SFS Group). The LRL treatment was given at home under parental guidance for 3 minutes each time, twice daily with a minimal interval of 4 hours, 7 days per week, using an equipment that produces red laser of 650 nm wavelength at an illuminance range of roughly 1200–1800 lux and an energy of 0.60 mw for a 4-mm pupil (class I classification).

Results: Among 51 included children, 44 (86.27%) completed the 3-months study, consisting of 15 girls (34.1%) and 29 boys (65.9%). After 3-months axial length (AL) and spherical equivalent refraction (SER) progression were –0.08 mm [95% CI (confidence interval), 0.11 to 0.06 mm] and +0.23 diopter (D) (95% CI, 0.13–0.33 D) for LRL group and +0.08 mm (95% CI, 0.05–0.11 mm) and –0.07 D (95% CI, –0.16–0.03 D) for SFS group. AL and SER progression between the groups varied by 0.17 mm (95% CI, 0.13–0.20 mm) and –0.30 D (95% CI, –0.42 to –0.18 D). There was no visible structural damage on optical coherence tomography (OCT) scans.

Conclusions: AL growth, myopia progression, and anisometropia of the binoculars can all be slowed down by LRL treatment. Compared to SER progression, axial elongation is more accurate and simpler to monitor. LRL treatment unrecorded functional and structural damage of binoculus.

Keywords: contralateral comparison; low-power red laser treatment; anisometropic; myopia; axial length

Background

Myopia is currently the primary factor causing preventable blindness in developing countries. Globally, and by 2050, myopia prevalence is projected to be about 84% among children and adolescents (3 to 19 years) [1]. East Asia had the highest prevalence of myopia [2]. This may be connected to habits like learning using computers, and using smartphones. Environmental factors like spending time outdoors also play a significant role [3–6]. High myopia can cause very serious problems, including macular lesions, retinal detachment, and changes in the optic disc [7]. Myopia commonly occurs in children [8,9]. Its prevalence increases throughout primary school and continues through the adolescence [10]. The probability of developing high myopia increases with early onset of myopia [11]. Outdoor lighting and activities are generally agreed to be important in myopia prevention and management [12–14].

It was found in an animal study that long-wavelength red light at 630 nm promotes hyperopia and delays the onset of myopia in young rhesus monkeys [15]. In another animal study short-term red laser maintained young tree shrews with hyperopic [16]. Low-Power red laser (LRL) treatment is a new method that has shown excellent effectiveness in controlling the progression of myopia [17–19]. LRL can increase mitochondrial activity and play an aggressive role in the treatment of retinal diseases [20,21]. Children with anisometropia were frequently excluded from earlier myopia research studies. Children's health and refractive development are negatively impacted by anisometropia. Moreover, anisometropia is a risk factor for the development of exotropia [22]. Binocular anisometropia may gradu-

ally worsen as myopia progresses [23]. We adopted a contralateral comparison study to examine the efficacy of LRL treatment on refractive development in children with anisometropic myopia.

Methods

Study Design and Setting

The study used a test method of binocular self-control and contralateral control to ensure a single variable of binocular. Eligible participants were children of 6 to 12 years with cycloplegic spherical equivalent refraction (SER) and at least one eye diagnosed with myopia (SER of 2.5×10^{-1} or less). Children presented no ocular and systemic organic lesions, astigmatism of 2.50 D or less, anisometropia of 1.00 D or more, and BCVA (best corrected visual acuity) of 0.0 Log MAR (logarithm of the minimum angle of resolution) or more in binoculus. All children voluntarily participated in the study and accepted all the requirements of the trial. Children with systemic diseases, such as hyperactivity disorder, or ocular abnormalities in either eye were excluded. Children who had previously received orthokeratology or low-concentration atropine therapy to control their myopia were further excluded. Additionally, if researchers felt that a child's condition rendered them unfit for participation, the researcher did not allow them to participate. All subjects were enrolled at the Tianjin Medical University Eye Hospital Strabismus and Pediatric Ophthalmology from September 2021 to August 2022. This study ended in August 2022. All children used single-focus spectacles (SFS) as the standard method of myopia optical correction throughout the study, and they changed their glasses as needed. Children with anisometropic myopia in the LRL group received 650 nm low-power red laser treatment in the more myopic eye. SFS group received only single-focus spectacles as treatment.

Randomization and Masking

Children were aware of the trial allocation and the equipment information. Results evaluators, including optometrists, medico-technicians and data-managers, were blinded during the trial.

Intervention

The LRL group received 650 LRL treatment throughout the trial. The light power was certified as class 1 under the International Electrotechnical Commission 60825-1:2014 standards [24]. The equipment (Seconee, Sky-n1201a, Beijing Mingren Shikang Technology Co., Ltd., Beijing, China) consisted of semiconductor laser diodes that produced 650nm low-power red laser applied on the pupil at an illuminance range of about 1200–1800 lux, which is the safe range for direct eye exposure and wouldn't pose a thermal risk to the retina. Participants took the equipment to home, and they performed the treatment under the supervision of their parents as required. Treatment consisted of eye exposure to the laser for three minutes once in the morning and once in the night, seven days a week for three months. After 1 month of treatment, the subjects underwent related ophthalmic examinations and received follow-up notices.

Intervention Compliance Monitoring

Intervention compliance was calculated based on the frequency of use of the equipment system's records. Treatment compliance was determined by dividing the percentage of sessions completed by the total number of sessions planned (180 times) for a complete treatment.

Study Endpoints

Endpoints of the study included the effectiveness of LRL therapy for myopia control in children with anisometropic and the safety of phototherapy equipment.

The primary endpoint was the change in axial length (AL) measured at the 1-month and 3-month after treatment. Five AL measurements were taken for each eye using partial coherence interferometry with the Lenstar LS 900 (Haag-Streit AG, Koeniz, Switzerland) and averaged until the expected precision was obtained (i.e., $\leq$0.05 mm). Measurements were deleted if the signal-to-noise ratios were $<$10. The secondary endpoints included changes in cycloplegic SER and choroidal thickness, measured at 3-months after treatment, and fundus safety. Refractive data for each eye was tested 3 times with a semi-automatic optometry (KR-8800, Topcon, Tokyo, Japan) and averaged until the required accuracy (i.e., spherical and cylindrical power, 0.25 D; axis, 5) was achieved. Cycloplegia was applied using 4 drops of 0.5 % of tropicamide (H20055546, Shenyang Xingqi Pharmaceutical Co., Ltd., Shenyang, China) to each eye at intervals of five minutes. Then SER was performed after confirming full cycloplegia. We stipulated that SER = SPH (spherical power) + ½ CYL (cylindrical power). Subfoveal choroidal thickness (SFCT) was measured by SS-OCT (swept-source optical coherence tomography) (DRI-OCT Triton; Topcon, Tokyo, Japan) with full cycloplegia and under standardized mesopic light examination room. The SS-OCT (swept-source optical coherence tomography) produces an axial resolution of 8 μm and a lateral resolution of 20 μm using a 100,000 Hz axial scan rate and a 1050 nm laser wavelength. For 12.0 mm radial scanning, the central fovea served as the circle's focal point (resolution, 1024 $\times$ 12). Scanning quality was set at automatic display mode. The choroidal thickness was obtained by automatic segmentation of the scanning source OCT software (DRI-OCT Triton; Topcon, Tokyo, Japan). Trial assistants monitored the integrity and authenticity of the database on a weekly basis.

Adverse Events

Adverse events were analyzed on children who received at least 2 treatments. A questionnaire on adverse events was collected from legal guardians and participants, such as, flash blindness, short-term glare, and long-term dazzling, at each follow-up and at any time if they needed. BCVA and the structure of anterior segment and fundus were recorded at each follow-up time point. If children experienced serious adverse events, the LRL trial was stopped, and treatment associated to the adverse event were administered. The serious adverse events included loss of vision >2 lines whether sudden or persistent or a scotoma perceived to develop in the visual field.

Sample Size

Previous studies revealed that the rate of AL change was approximately 0.15 mm/year, which was slower in subjects treated with low-dose atropine or orthokeratology compared to controls [25]. The required sample size for this clinical trial was calculated for 80% power and an alpha level of 0.05, assuming that AL would change at a rate of 0.20 mm (standard deviation, SD, 0.20 mm) each year, and that the dropout rate was going to be approximately 10%. For self-parallel pairing, according to the paired study $n = [(Z_{\alpha/2} + Z_{\beta})^2 \times \sigma^2]/\delta^2$, the minimum sample size of participants in our experiment was 28 people. In the experiment, 51 children were recruited.

Data Analysis and Definitions

IBM SPSS 10.0 (IBM Co, Armonk, NY, USA) and GraphPad Prism version 3.0.0 (GraphPad Software, San Diego, CA, USA) were used to analyze the data. The Shapiro-Wilke test was used to assess whether continuous variables had a normal distribution. Data are reported as mean $\pm$ SD if it followed a normal distribution. Two-sample paired T test was used to assess differences between groups. To compare the mean value of the difference between the baseline and the end of the study between age groups, repeated measures analysis of variance (ANOVA) was used. Nonparametric tests were performed if data did not follow a normal distribution. Median (interquartile range) or median (95% CI) are reported if the data does not follow a normal distribution. A p-value of 0.05 showed significant differences between groups. The data of all children with at least two visits were included in the analysis. All statistical analyses were performed strictly in accordance with the pre-specified analysis plan. The analysis excluded people who stopped using the 650 nm red laser or chose other methods to control myopia like orthokeratology or low-dose atropine therapy.

Results

Between September 2021 and August 2022, 51 children with anisometropic myopia were assessed foreligibility. A total of 49 children (96.1%) received LRL study. Fig. 1 summarizes the number of the children who completed testing at baseline and at a minimum 2 times during the follow-up visits. Five children did not finish the whole trial. Due to COVID-19 (coronavirus disease 2019) measures in Tianjin during 2022, the number of children completing all follow-up visits was significantly affected. Among the 49 included children, 44 (89.8%) finished the 3-month study, consisting of 15 girls (34.1%) and 29 boys (65.9%) and were included in the statistical analysis.

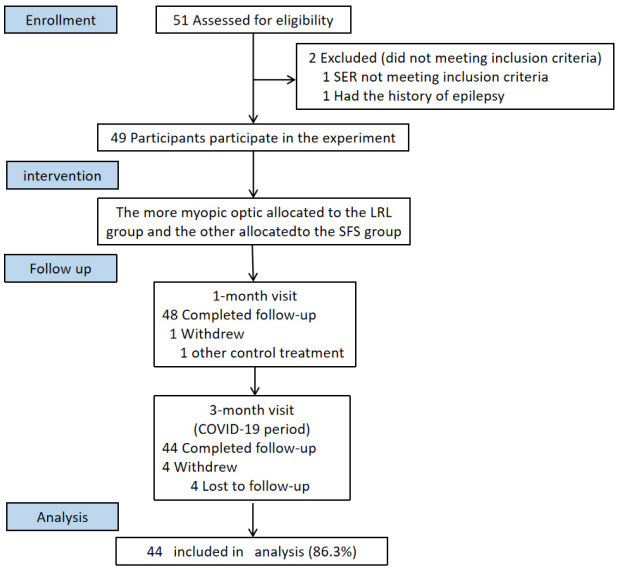

Fig. 1. Flow chart of trial progress. LRL, low-power red laser; SFS, single-focus spectacles; COVID-19, coronavirus disease 2019.

Baseline Characteristics

Table 1 summarised the demographics and baseline ocular characteristics of the 44 children included in the data analysis.

Primary Endpoint

Three months after treatment, in the LRL group, AL was shorter at 1-month and 3-months than at baseline ($p < 0.01$). In contrast SFS group showed an AL progression linear increasing trend at 1 month and 3 months after treatment compared to baseline ($p < 0.01$) (Fig. 2a; **Supplementary Table 1**). The 3-month mean AL shortening was –0.08 mm (95% CI, –0.11 to –0.06 mm) in the LRL group, AL mean elongation was 0.08 mm (95% CI, 0.05–0.11 mm) in the SFS group (Fig. 2b). After 1-month of follow-up (Fig. 2b) (**Supplementary Table 2**), the fastest AL shortening in the LRL group was –0.10 mm (95 % CI, –0.18 to –0.03 mm) ($p < 0.005$). And during the 3-month follow-ups, the AL growth rate in the LRL group was lower than that in the SFS group ($p < 0.001$). The average difference in AL progres-

Table 1. Demographics and baseline ocular characteristics between the low-power red laser group and single-focus spectacles group.

Characteristic	Participants binocular contralateral controlled		*p*
	Low-Power red laser group	Single-Focus spectacles group	
	Participant' more myopic eye	Participant' the other eye	
Age (years)			-
6–8	13 (29.55%)	13 (29.55%)	
9–10	15 (34.09%)	15 (34.09%)	
11–12	16 (36.36%)	16 (36.36%)	
Median	10 (6–12)	10 (6–12)	
Sex			-
Male	29 (65.91%)	29 (65.91%)	
Female	15 (34.09%)	15 (34.09%)	
AL (mm)			<0.001
Mean	24.61 (1.04)	23.98 (1.08)	
Median	24.58 (22.81–27.18)	23.94 (21.85–26.89)	
SER (D)			<0.001
Mean	–2.86 (1.77)	–1.35 (1.92)	
Median	–2.38 (–6.75 to –0.50)	–0.50 (–6.50 to –1.50)	
SFCT (μm)			0.003
Mean	218.47 (51.53)	240.47 (62.86)	
Median	219 (183–263)	236 (195–281)	

AL, axial length; D, diopter; SER, spherical equivalent refraction; SFCT, sub-foveal choroidal thickness. Data are presented as mean (standard deviation), number (%), or median (interquartile range).

sion was 0.17 mm (95% CI, 0.13–0.20 mm) between groups (**Supplementary Table 2**). Overall, 54.76% of participants in the LRL group achieved AL shortening >0.05 mm at 1-month what exceeded the error of the results of AL measurements with the Lenstar LS900. We defined clinically significant of AL shortening as >0.05 mm. The proportion of clinically significant of AL shortening was 28.57 % at 3-month.

Secondary Endpoints

At three months after treatment the mean SER progression in the LRL group was 0.23 D (95% CI, 0.13–0.33 D) ($p < 0.01$), while in the SFS group was –0.07 D (95% CI, –0.16–0.03 D) ($p = 0.11$) (Fig. 2c, **Supplementary Table 1**). Between the SFS and the LRL groups, there was a mean difference in SER progression of 0.30 D (95% CI, –0.42 to –0.18 D) (**Supplementary Table 2**). While AL increased, SER did not change in the SFS group. At 3 months, the mean changes of SFCT in the LRL group and the SFS group were 24.21 μm (95% CI, 14.86–33.56 μm) and –4.28 μm (95% CI, –15.91–7.35 μm). The difference in SFCT progression between the LRL group and the SFS group was –27.84 μm (95% CI, –40.02–15.67 μm).

Therapy Adherence and Efficacy

Adherence related to mean AL changes over the 3 months are reported in **Supplementary Table 3** and **Supplementary Fig. 1**. Median therapy adherence in the LRL group was 75% (interquartile range, 88.89%–94.44%). Children with a therapy adherence rate of >100% received an average of >2 times daily which from the equipment's counting system. Dose-response relationships between LRL treatment adherence and effectiveness for AL and SFCT reduction are shown in Table 2. As therapy compliance increased (from <50% to >75%) efficacy in delaying AL growth (from 37.5% to 188%), and increasing SFCT (from 91.9% to 117%). There was a significant correlation between therapy adherence and myopia progression (AL growth rate and SFCT) ($p < 0.001$), indicating that the improvement of therapy compliance enhanced the efficacy of controlling myopia progression.

Myopia at Different Ages

Previous study found that at 6–8 years old is the period when children suffer refractive development [26], and at 8–9 years old is the critical period for myopia prediction [27,28]. Therefore, age may affect the efficacy of myopia progression (AL elongation). There was no difference in treatment compliance among different age groups ($p = 0.13$). In the study, sensitivity analysis was performed on the efficacy of myopia control (AL) in children of different age groups in the LRL group. Older children (11–12 years) showed a better effect in controlling myopia progression (Fig. 2d).

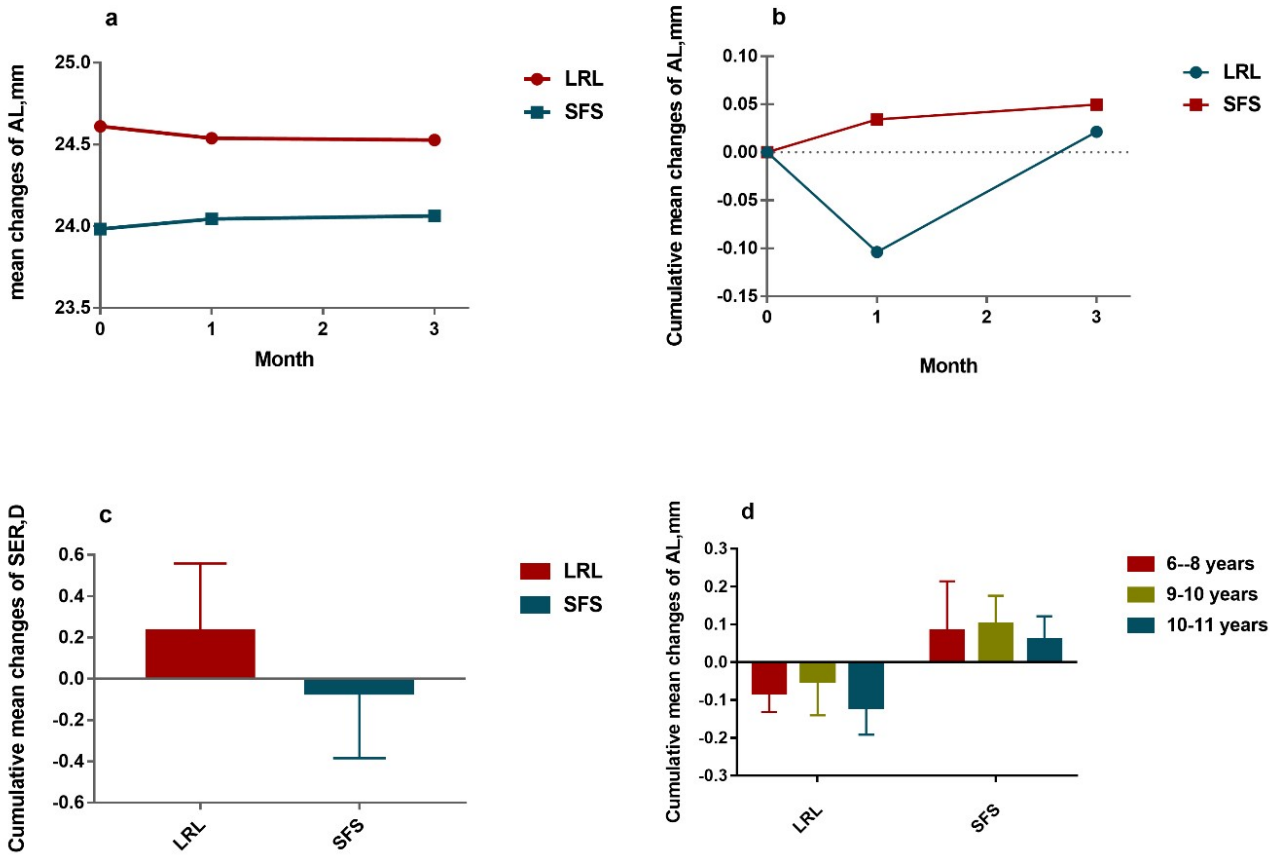

Fig. 2. AL distribution (a), AL cumulative change (b), SER cumulative change of SER (c), and AL Cumulative change of AL (d) at different ages between the LRL group and the SFS group for 3 months. Data from 44 children were included in the statistical analysis of the 4 figures. SER, spherical equivalent refraction; AL, axial length; LRL, low-power red laser; SFS, single-focus spectacles; D, dioptre.

Adverse Events

No severe adverse events were observed.

Discussion

In this 3-month, contralateral comparison study, LRL treatment slowed AL elongation by 0.16 mm, SER progression by 0.30 D, and SFCT by 28.49 μm compared with SFS.

Reversal of Myopic Progression: AL Shortening and SER Hyperopia

Generally, myopia is perceived as a progressive, permanent ocular condition. In this study, we demonstrated that LRL therapy might provide >0.05 mm AL shortening in 54.76% of children at 1 month and in 68.18% of children at 3 months. However, the Lenstar LS 900r's measurement of AL is accurate, with a measurement error of less than 0.05 mm, so we speculated that LRL induced shortening of AL. This study found that the choroid becomes thinner with AL elongation [29]. But there was no association between the average values of AL elongation and choroidal progression. It is uncertain if AL elongation and choroidal advancement are interconnected.

Low-Power Red Laser Induced Choroidal Thickening

The choroid plays an essential function in the supply of nutrients to the retina and the structural and functional integrity of the choroid is critical to retinal function [30]. In myopic children, the choroid becomes thinner as myopia progresses [31]. In our study, we observed that LRL induced choroidal thickening of 24.21 (14.86–33.56) μm during three months. In response to this finding, we speculate on several possibilities to explain this process. First, LRL increases choroidal thickness by increasing choroidal perfusion, meanwhile controlling the progression of myopia [32]. Second, red laser as long wavelength light is focused on the retina after, as red light is focused on the retina images made up of other wavelengths of light produce myopic defocusing in front of the retina, inducing choroidal thickening.

Results of Endpoints

Previous studies on myopia control therapy commonly selected SER and AL as primary outcomes, and SER was chosen as the primary endpoint [33–35]. However, the change of AL was more sensitive to the short-term pro-

Table 2. The effectiveness of low-power red laser therapy in controlling AL and sub-foveal choroidal thickness in different treatment adherence groups.

Therapy adherence group (low-power red laser group)	Low-power red laser group		Efficacy (%)
	No	Mean (SD)	
Primary endpoint			
Change of AL (mm)			
Total	44	–0.08 (0.08)	100
<50%	21	–0.03 (0.06)	37.5
50%–75%	14	–0.12 (0.07)	150
>75%	9	–0.15 (0.05)	188
Secondary endpoint			
Change of SFCT (μm)			
Total	43	24.21 (30.38)	100
<50%	20	22.25 (29.20)	91.9
50%–75%	14	31.43 (25.14)	130
>75%	9	28.44 (19.18)	117

AL, axial length; SFCT, sub-foveal choroidal thickness. Therapy adherence was determined by dividing the percentage of sessions completed by the total number of sessions planned for the whole trial period (2 times a day, 7 days a week). For changes in AL, 44 patients with a mean (SD) of –0.08 (0.08) mm in the repeated low-power red laser group were used as the benchmark for efficacy. For changes in SFCT, 43 patients with a mean (SD) of 24.21 (30.38) μm in the repeated low-power red laser group were used as the benchmark for efficacy. Treatment efficacy was calculated by dividing between arm difference in values by trial group arm value.

gression of myopia in children, according to our clinical research. It has been reported that AL can grow 1 mm and SER can progress to 3.00 D [36]. In this study, we found that the mean changes of AL and SER in the SFS group were +0.07 mm (95% CI, 0.05–0.11 mm) and –0.07 D (95% CI, –0.16–0.03 D), respectively. When myopia developed, AL changed quicker than SER. Furthermore, AL elongation preceded SER progression.

Study Limitations

We acknowledged that there were some shortcomings in the study. First, the trial length was 3 months, which only evaluated the changes in myopia progression after short-term LRL treatment. Second, the participants were children between the ages 6 to 12 with rapid myopia progression, the efficacy on middle school pupils who utilized eyes at close range for a prolonged period is unknown. Third, due to the pandemic of COVID-19, although we tried all efforts to improve the response rate at follow-up, 5 (10.20%) out of 49 people lost follow-up and did not complete the entire trial.

Conclusions

In conclusion, LRL treatment can reduce the speed of the progression of myopia and reduce anisometropia in binoculus, with no adverse effects during the follow-up period. However, due to the short follow-up time, further research is required to determine whether LRL treatment is also effective in middle school pupils with slow myopia progression and high intensity eye use.

Trial Registration

Chinese Clinical Trial Registry: ChiCTR2200066960. Registered 22 December 2022; Retrospectively registered (http://www.chictr.org.cn/edit.aspx?pid=183921&htm=4).

Consent for Publication

Not applicable.

Abbreviations

AL, axial length; LRL, low-power red laser; SER, spherical equivalent refraction; SFS, single-focus spectacles; D, diopter; OCT, optical coherence tomography; Log MAR, logarithm of the minimum angle of resolution; BCVA, best corrected visual acuity; CI, confidence interval; SFCT, sub-foveal choroidal thickness; COVID-19, coronavirus disease 2019.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

XHQ, YZW, XL, GD—review and editing (equal); YZW, XL—conceptualization (lead), writing-original draft (lead), formal analysis (lead); JL, XL, KA, WZD, YXN, XLQ, NH, NW, LLS, YZ—conceptualization (supporting), writing-original draft (supporting); XHQ, YZW, XL—writing-review and editing (equal). All authors have read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study and protocol followed the tenets of the Declaration of Helsinki and were approved by the Ethics Committee of the Tianjin Medical University Eye Hospital (Identifier, 2021KY-14). Written, informed-consent of the parents was obtained.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202335174.2.

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