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Original Article

Efficacy of repeated low-level red-light therapy combined with optical lenses for myopia control in children and adolescents

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Abstract: Purpose: To evaluate the efficacy of repeated low-level red-light (RLRL) therapy combined with optical lenses in children and adolescents with myopia. Methods: This retrospective study included 108 children and adolescents. Based on the difference in the combination intervention scheme participants were divided into four groups based on the intervention they received: the RLRL+orthokeratology (OK) lens intervention group (RLRL+OK group), the RLRL+defocus distributed multi-point (DDM) lens intervention group (RLRL+DDM group), the RLRL+single-vision spectacles (SVS) intervention group (RLRL+SVS group), and a control group. Visual acuity, spherical equivalent refraction (SER), and axial length (AL) were measured before and after the intervention. Binary logistic regression was used to identify factors influencing vision recovery. Results: The SER and AL at baseline were statistically different ($P<0.01$). After the intervention, the AL increase in the RLRL+OK, RLRL+DDM, and RLRL+SVS groups was significantly better than the control group across time points ($P<0.001$). Changes in SER were also statistically significant in the RLRL+DDM and RLRL+SVS groups compared to the control group across time points ($P<0.001$). The intervention method was identified as a significant factor influencing vision recovery ($P<0.001$). Conclusion: RLRL therapy combined with optical lenses is effective in controlling myopia progression in children and adolescents.

Keywords: Myopia, children and adolescents, repeated low-level red-light therapy, orthokeratology lens, defocus distributed multi-point lens

Introduction

Myopia has emerged as a major public health concern worldwide, with its prevalence increasing substantially over the past few decades, especially in East Asia. By 2050, it is estimated that approximately 54% of the global population will be affected by myopia, and 10% will develop high myopia [1]. Among them, East and Southeast Asia exhibit the highest prevalence, with myopia affecting 80% to 90% of young individuals and high myopia affecting 10% to 20%. This trend conveys an increased risk of low vision and blindness caused by pathologic myopia [2].

Current research has generally confirmed that increasing outdoor activities can reduce the risk of myopia in school-aged children and slow its progression, lowering the incidence by 20% to 50% compared to control groups. The beneficial effect of outdoor activities on myopia is thought to be related to the intensity of outdoor light exposure [3-6]. However, implementing effective outdoor activity interventions in school and family environments remains challenging, especially in extending the duration of outdoor light exposure. Based on the principle of preventing and controlling myopia in children through appropriate lighting, some studies in China have explored the use of repeated low-level red-light (RLRL) therapy as a means to control myopia in school-aged children. Data from studies spanning one to two years indicate that RLRL therapy has a significant effect in assisting myopia treatment, with no reported eye damage and acceptable compliance among subjects [7, 8]. To further observe the effectiveness and safety of RLRL therapy combined to optical interventions in controlling myopia in school-aged children, and to explore its underlying mechanisms, we conducted a review of two-

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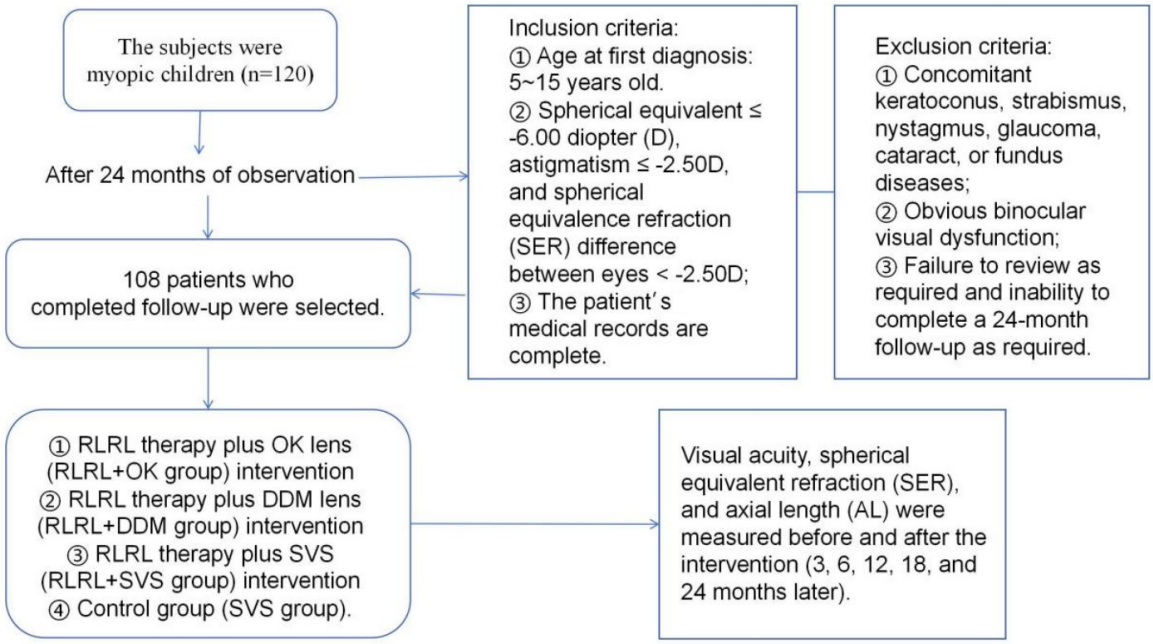

Figure 1. Flowchart of the research design. RLRL, repeated low-level red-light; DDM, defocus distributed multi-point; SVS, single-vision spectacles; OK, orthokeratology.

year clinical data on the use of RLRL therapy in combination with orthokeratology (OK) lens, defocus distributed multi-point (DDM) lens, and single-vision spectacles (SVS) for the purpose of controlling myopia progression. In addition, it is important to note that research on the efficacy of RLRL combined with the aforementioned optical methods for myopia control in children and adolescents is currently limited. Existing studies mainly focus on comparing RLRL with SVS or examining sequential effects of these interventions, or comparing RLRL with atropine eye drops. The novelty of this comparative study is that is provides more robust clinical evidence on the optimal optical combination therapy to use alongside RLRL, thereby offering more effective treatment options for myopia control in children and adolescents.

Participants and methods

Participants

This retrospective study included myopic children who visited Jinhua Eye Hospital from January 2021 to December 2021. Inclusion criteria were as follows: ① Age at initial diagnosis between 5 and 15 years; ② Spherical equivalent ≤-6.00 diopters (D), astigmatism ≤-2.50D, and spherical equivalence refraction (SER) difference between eyes <-2.50D; ③ Complete case data. Exclusion criteria were: ① Presence of concomitant keratoconus, strabismus, nystagmus, glaucoma, cataract, or fundic disease; ② Obvious binocular visual dysfunction; ③ Noncompliance with re-examination requirements and inability to complete a 24-month follow-up. The patient selection process is presented in **Figure 1**. This study was approved by the Ethics Committee of Jinhua Eye Hospital and followed the principles of the Declaration of Helsinki.

Intervention methods

A total of 120 subjects who met the inclusion criteria were initially recruited. Relevant examinations were conducted, including uncorrected visual acuity (UCVA), corrected visual acuity (CVA), dilated eye examination, anterior segment examination, intraocular pressure measurement, ocular biometrics, fundus photography, and optical coherence tomography (OCT). After a non-randomized assignment to intervention or control groups and a 24-month observation period, 108 participants completed the follow-up and were included in the final analysis. ① RLRL+OK lens group: Participants received OK lenses (Eyebright Medical Technology (Beijing) Co., Ltd.), which were made from a

fluorosilicone acrylate polymer with an oxygen permeability (DK) of 125. The lenses featured an anti-geometric four-arc design with a total diameter of 10.0-11.20 mm. Red light irradiation was performed following the protocol established for the RLRL intervention group. ② RLRL therapy plus DDM lens (RLRL+DDM group) intervention: Participants in this group wore DDM lenses provided by Shanghai Weixing Optics, featuring a central optical zone of 10 mm and 420 aspherical microlenses with diopter of +3.25-+4.75 D, arranged in hexagonal patterns around the periphery. Red light irradiation was administered as described for the RLRL intervention group. ③ RLRL therapy plus SVS (RLRL+SVS group) intervention: Participants wore SVS and received red-light irradiation (Class 1 laser, Londa optics) with a wavelength of 635 nm and power of 0.35 mw, twice daily with at least a 4-hour interval. ④ Control group (SVS group): Participants in this group wore SVS without additional treatments during the intervention period.

Acquisition of evaluation indexes

Age was recorded as the actual age in years. Visual acuity was detected with a phoropter and standard logarithmic visual acuity chart and recorded in decimal notation. For the dilated eye exam, Compound Tropicamide Eye Drops (1 ml, Shenyang Xingqi Pharmaceutical) were used for cycloplegia, administered once every 10 minutes for 3 times, followed by a 30-minute wait before optometry, which was performed using an automatic computer optometer (AR-310A, Nidek, Japan). Measurements were repeated 3 times, and the average was taken. Axial length (AL) was measured by a Lenstar biometric instrument (Lenstar-2000, Haag-Streit, Switzerland) 5 times, and the average value was recorded. SER was calculated as the spherical equivalent plus half the cylinder. All operations were carried out by the same trained inspector. To ensure consistency, only data from the right eye were used for analysis to avoid confounding effects of binocular myopia progression.

Grouping and observation indicators

Participants were assigned to one of four groups based on their intervention: RLRL+OK, RLRL+DDM, RLRL+SVS, or SVS (control). Changes in AL and diopter were assessed before intervention (baseline) and after intervention (3, 6, 12, 18, and 24 months after treatment). SER and AL were designated as primary outcome measures, while gender and age were considered secondary measures.

Statistical methods

SPSS27 was used to analyze the data. Measured data were expressed as mean ± standard deviation and assessed for normality. An analysis of variance (ANOVA) was used for inter-group comparisons of baseline data before intervention. Repeated measures ANOVA was employed to assess changes in diopter and AL after intervention, while the least significant difference (LSD) t-test was used for pairwise comparisons. The factors influencing patients' vision recovery were analyzed through binary logistic regression. All statistical analyses adhered to a significance criterion of $P<0.01$.

Results

Follow-up

Of the 120 subjects initially enrolled, 108 completed the follow-up and were included in the final analysis. None of them developed organic eye lesions during the follow-up period. All patients in the intervention groups underwent macular OCT every six months, with no organic macular lesions detected. In the RLRL+OK group, 2 participants discontinued RLRL therapy due to self-perceived glare from the red light, and 2 switched to glasses due to difficulties with OK lens use; 26 participants (52 eyes) were successfully followed, yielding a follow-up success rate of 86.7%. In the RLRL+DDM group, 2 participants discontinued RLRL therapy due to perceived red light stimulation, and 1 could not adapt to the DDM lenses and switched to regular lenses. A total of 27 participants (54 eyes) were followed, with a success rate of 90%. In the RLRL+SVS group, 3 participants were excluded due to incomplete data, leaving 27 participants (54 eyes) followed, also with a success rate of 90%. In the control group, 28 participants (56 eyes) completed the follow-up, resulting in a follow-up success rate of 93.3% after 2 were lost to follow-up.

Baseline data before intervention

Analysis of baseline data such as sex, age, baseline SER, and baseline AL revealed no sig-

Table 1. Comparison of baseline data among groups before intervention

Indicator	RLRL+OK group	RLRL+DDM group	RLRL+SVS group	Control group	*F*	*P*
Sex					3.672	0.299
Male/n (%)	24 (46.2%)	18 (33.3%)	26 (48.1%)	20 (35.7%)		
Female/n (%)	28 (53.8%)	36 (66.7%)	28 (51.9%)	36 (64.3%)		
Age/years old	8.81±1.59	7.96±1.66	8.59±1.51	8.14±2.10	2.736	0.045
Baseline SER/D	-3.12±1.78	-3.00±1.59	-1.51±0.97	-1.96±0.88	18.207	<0.001
Baseline AL/mm	24.96±0.99	24.45±0.90	24.22±0.85	24.34±0.60	7.847	<0.001

Note: RLRL, repeated low-level red-light; OK, orthokeratology; DDM, defocus distributed multi-point; SVS, single-vision spectacles; SER, spherical equivalent refraction; AL, axial length.

Table 2. Comparison of AL growth among groups after 24 months of intervention (mm) ($\bar{x}$±s, mm)

Group	Number of eyes	3 months after intervention	6 months after intervention	12 months after intervention	18 months after intervention	24 months after intervention	*F*	*P*
RLRL+OK group	52	-0.12±0.11[a]	-0.10±0.15[a]	-0.03±0.17[a]	0.02±0.21[a]	0.09±0.24[a]	11.757	<0.001
RLRL+DDM group	54	-0.07±0.13[a]	-0.04±0.15[a]	0.01±0.20[a]	0.06±0.22[a]	0.14±0.24[a]	10.121	<0.001
RLRL+SVS group	54	-0.05±0.10[a]	-0.01±0.15[a]	0.05±0.18[a]	0.11±0.22[a]	0.22±0.25[a]	17.324	<0.001
Control group	56	0.11±0.09	0.23±0.19	0.47±0.21	0.67±0.26	0.86±0.31	105.356	<0.001
F		46.200	44.303	81.549	98.418	103.290		
P		<0.001	<0.001	<0.001	<0.001	<0.001		

Note: Basic AL is uses as a covariant. RLRL, repeated low-level red-light; OK, orthokeratology; DDM, defocus distributed multi-point; SVS, single-vision spectacles; AL, axial length. [a]P<0.001 versus control group.

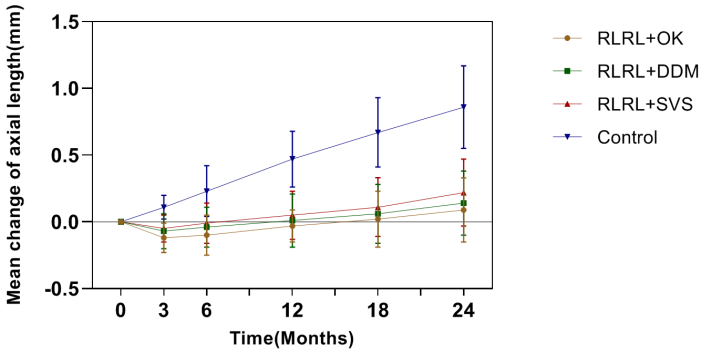

Figure 2. Changes in AL in each group after 24 months of intervention. RLRL, repeated low-level red-light; OK, orthokeratology; DDM, defocus distributed multi-point; SVS, single-vision spectacles.

nificant differences in gender or age among the groups (*P*>0.01), but significant differences were present in baseline SER and AL (*P*<0.01) (**Table 1**).

Changes in AL at 24 months after intervention

The AL growth demonstrated statistically significant differences across time points and among groups (F_{time}=3.01, P_{time}=0.020, $F_{between\text{-}group}$=18.89, $P_{between\text{-}group}$<0.001, $F_{interaction}$=12.64, $P_{interaction}$<0.001). Pairwise comparisons among the RLRL+OK, RLRL+DDM, and RLRL+SVS groups indicated significant variation in AL growth across time points and between groups (*P*<0.001). In the first 6 months, all three groups exhibited a reduction in AL; however, subsequent pairwise comparison among the three groups did not reveal any significant differences (*P*>0.001). Detailed results are shown in **Table 2** and **Figure 2**.

Changes in SER after intervention

Due to the inability to measure diopters accurately resulting from corneal morphology changes after OK lens use, the RLRL+OK group was excluded from this analysis. The remaining three groups showed staa significant difference in SER changes across time points and between groups after intervention (F_{time}=20.12, P_{time}<0.001, $F_{between\text{-}group}$=16.32, $P_{between\text{-}group}$<0.001, $F_{interaction}$=17.68, $P_{interaction}$<0.001). Compared to the control group, changes in SER in the RLRL+DDM and RLRL+SVS groups were significant (*P*<0.001). In the first 6 months, both the RLRL+DDM and RLRL+SVS groups experienced a decrease in diopter, but without significant inter-group differences (*P*>0.001) (**Table 3**; **Figure 3**).

Table 3. Comparison of SER changes among groups after 24 months of intervention (D) ($\bar{x}\pm s$, D)

Group	Number of eyes	3 months after intervention	6 months after intervention	12 months after intervention	18 months after intervention	24 months after intervention	*F*	*P*
RLRL+DDM group	54	0.07±0.32[a]	0.06±0.48[a]	-0.03±0.44[a]	-0.11±0.43[a]	-0.20±0.35[a]	4.265	0.002
RLRL+SVS group	54	0.09±0.27[a]	0.08±0.42[a]	-0.01±0.49[a]	-0.03±0.54[a]	-0.15±0.55[a]	2.362	0.054
Control group	56	-0.26±0.36	-0.39±0.74	-0.92±0.58	-1.31±0.80	-1.80±0.74	52.208	<0.001
F		20.955	12.172	57.981	75.736	149.015		
P		<0.001	<0.001	<0.001	<0.001	<0.001		

Note: The baseline SER is uses as a covariant. RLRL, repeated low-level red-light; SER, spherical equivalent refraction; DDM, defocus distributed multi-point; SVS, single-vision spectacles. [a]P<0.001 versus control group.

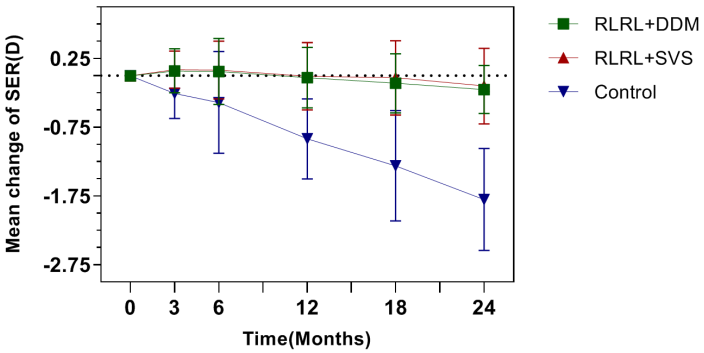

Figure 3. Comparison of SER changes among groups after 24 months of intervention. SER, spherical equivalent refraction; RLRL, repeated low-level red-light; DDM, defocus distributed multi-point; SVS, single-vision spectacles.

Table 4. Variable assignment

Variable	Assignment
Sex	Male (n=44) = 0, female (n=64) = 1
Age/years old	<9 (n=64) = 0, ≥9 (n=44) = 1
Baseline SER/D	<-2 (n=55) = 0, ≥-2 (n=53) = 1
Baseline AL/mm	<24 (n=35) = 0, ≥24 (n=73) = 1
Treatment modality	RLRL (n=80) = 0, SVS alone (n=28) = 1

Note: SER, spherical equivalent refraction; AL, axial length.

Multivariate regression analysis

According to UCVA recovery before and after treatment, patients were divided into a vision improvement group (n=61) and a low vision group (n=47). A binary logistic regression analysis was conducted using vision recovery as the dependent variable and sex, age, AL, SER, and treatment method as independent variables. The results indicated that sex, age, baseline SE, and baseline AL were not significant factors influencing vision recovery. However, the treatment modality emerged as a significant influencing factor; patients who received SVS treatment alone were less likely to experience vision recovery (**Tables 4** and **5**).

Discussion

As myopia becomes more prevalent and technology advances, management strategies are constantly being updated. Customizing myopia management plans for children and adolescents is essential. However, current strategies in the management of children's myopia primarily involve optical correction and pharmacologic interventions.

The main optical interventions for the correction and control of myopia in children include eyeglasses and contact lenses. Among eyeglass options, various lens designs have been shown to be effective in mitigating myopia progression. For instance, defocus-incorporated multiple segments (DIMS) lenses have been associated with a 52% delay in myopia progression and a 62% delay in AL growth [9]. Similarly, highly aspherical lenslets have demonstrated a 67% delay in myopia progression and a 60% delay in AL growth [10]. Additionally, diffusion optics technology (DOT) spectacle lenses have shown a 74% delay in myopia progression and a 50% delay in AL growth [11]. The effectiveness of these interventions may vary based on patient compliance (e.g., length of treatment with optical glasses). Contact lenses that include OK lenses, defocus soft contact lenses, and defocus rigid gas permeable (RGP) contact lenses, with OK lenses showing the best efficacy in controlling myopia. Many studies have substantiated the effectiveness of OK lenses in reducing myopia, significantly improving UCVA, and delaying AL growth in school-aged children, with an effectiveness rate of 30% to 59% [12, 13].

Table 5. Multivariate analysis of factors influencing patients' vision recovery

Factor	β	SE	Wald	P	OR	95% CI
Sex	-0.280	0.464	0.364	0.546	0.756	0.304-1.878
Age/years old	0.067	0.463	0.021	0.885	1.069	0.432-2.648
Baseline SER/D	-0.204	0.475	0.185	0.667	0.815	0.321-2.068
Baseline AL/mm	-0.482	0.538	0.802	0.371	0.618	0.215-1.773
Treatment modality	2.449	0.674	13.203	<0.001	11.572	3.089-43.354

Note: SER, spherical equivalent refraction; AL, axial length.

In terms of medication, atropine eye drops have been shown to effectively slow myopia progression, with efficacy being concentration-dependent. Higher concentrations of atropine are more effective, but are associated with greater side effects. The long-term efficacy, safety and appropriate discontinuation time of atropine use remains under investigation [14-16]. Combining 0.01% atropine eye drops with OK lenses has been shown to be more effective than either intervention alone in controlling myopia [17, 18].

RLRL therapy has emerged as a promising intervention for myopia control in children and adolescents. A one-year, randomized, multicenter study by He Mingguang's team showed that RLRL therapy significantly slowed AL growth and myopia progression, with control rates of 69.4% and 76.6%, respectively [7]. However, a subsequent 24-month study found that the effective control rates for AL were 89.5% in the first year and 57.1% in the second year, while the rates for diopter (SER) were 84% and 63%, respectively. This indicates a decline in myopia control in the second year [8]. We also observed differences in the effects of RLRL alone on AL growth and myopia progression between the first and second years. The AL control rate was 89.36% in the first year (RLRL+SVS group: 0.05±0.18 mm; control group: 0.47±0.21 mm) and decreased to 74.42% in the second year (RLRL+SVS group: 0.22±0.25 mm; control group: 0.86±0.31 mm). The myopia progression control rate was 98.91% in the first year (RLRL+SVS group: -0.01±0.49 D, control group: -0.92±0.58 D) and fell to 91.67% in the second year (RLRL+SVS group: -0.15±0.55 D; control group: -1.80±0.74 D). The overall myopia control effect weakened in the second year, paralleling findings from previous studies. In a randomized double-blind study of 56 children aged 7 to 12, He Mingguang's group administered RLRL therapy at 100% power to control myopia, while the control group received therapy at 10% power. After a six-month observation period, the results indicated that the application of RLRL therapy at 100% power for myopia control had significantly better effects than the control group, with no treatment-related ocular adverse effects observed [19]. The overall myopia control efficacy observed in our research surpasses that reported in previous studies; however, the potential influence of instrument selection or sample selection bias warrants further investigation. Additionally, it has been found that RLRL therapy administered to premyopic children (D range: -0.50-0.50) significantly slowed AL growth and mitigated the progression towards myopia, resulting in a 54.1% reduction in the incidence of myopia over the course of one year [20].

A study has shown that the AL growth in myopic children using RLRL irradiation, OK lenses, and conventional glasses is measured at -0.06± 0.15 mm, 0.06±0.15 mm, and 0.23±0.06 mm, respectively, indicating RLRL's superior efficacy over OK lenses and ordinary glasses. In addition, it has been observed that the choroid thickness is increased in children using RLRL and OK lenses, especially in the RLRL group [20]. In another one-year randomized study, RLRL therapy was compared to 0.01% atropine eye drops for the purpose of controlling myopia progression in children. The results indicated that low-intensity red light was significantly more effective than 0.01% atropine eye drops [21]. Additionally, the combination of 0.01% atropine eye drops with OK lenses proved to be more effective than the use of OK lenses alone in managing myopia in children [17, 18]. However, the question arises regarding the potential effects of combining RLRL with OK lenses or DDM aspherical lenslets. Our findings indicated that there was no significant difference in the efficacy of myopia control when

RLRL was used in conjunction with OK lenses, DDM lenses, and SVS over a two-year period. The AL control effect was 89.53% (0.09±0.24 mm) in the RLRL+OK group, 83.72% (0.14± 0.24 mm) in the RLRL+DDM group, and 74.42% (0.22±0.25 mm) in the RLRL+SVS group. The myopia control effect was 88.89% (-0.20±0.35 D) in the RLRL+DDM group and 91.67% (-0.15±0.55 D) in the RLRL+SVS group. The AL in the RLRL+OK, RLRL+DDM, and RLRL+SVS groups exhibited reductions over a six-month period by -0.10±0.15 mm, -0.04±0.15 mm, and -0.01±0.15 mm respectively. The diopter values for the LRL+DDM and RLRL+SVS groups was decreased, yielding values of 0.06±0.48 D and 0.08±0.42 D, respectively, which is consistent with findings from previous studies [7, 8, 22]. The possible mechanism underlying the shortening of AL is related to choroidal thickening. AL shortening after RLRL therapy has been shown to correlate with factors such as older age, female gender, longer AL, and higher diopter values [23]. Additionally, we also found that treatment modality wa a risk factor for vision recovery in myopic patients, and the exclusive use of SVS identified as a risk factor that may hinder vision recovery. Conversely, the implementation of the RLRL treatment protocol is beneficial in promoting vision recovery to some extent.

The mechanisms underlying the efficacy of RLRL therapy for controlling myopia in children are related to increased choroidal blood flow [24] and choroidal thickening [25]. Similarly, OK lenses and DDM aspherical lenslets also influence myopia control through enhanced choroidal blood flow and choroidal thickening [26-28]. Given these shared mechanisms, it is pertinent to investigate whether the combined use of RLRL with OK lenses or DDM aspherical lenslets exhibits similar effects in myopia control. Another study has reported that discontinuing RLRL therapy may lead to short-term myopia rebound, such as choroid thinning and significant increases in diopter and AL [29]. It has also been shown that RLRL irradiation for 3 minutes twice daily may cause photochemical and thermal damage to the retina when using certain devices that exceed the maximum thermal and photochemical thresholds [30]. A meta-analysis suggests that RLRL therapy can moderate myopia progression by inhibiting increases in refractive power and slowing the rapid growth of AL through the promotion of choroidal thickening, but evidence regarding its long-term efficacy and safety remains insufficient [31]. The *Expert Consensus of Repeated Low-Level Red-Light Therapy for Adjuvant Treatment of Myopia in Children and Adolescents (2022)* [32] elaborates on the basic principles, suitable candidates, application methods, dosages, examination items and frequencies, equipment selection and power, adverse reactions, discontinuation guidelines, and joint application with other RLRL methods for the control of myopia progression. The consensus points out that RLRL therapy may offer some myopia control within a one-year cycle, possibly becoming a new auxiliary treatment method for myopia prevention and control in children and adolescents. However, further research is needed to evaluate its medium- and long-term effectiveness and safety. Current research and clinical practice must exercise considerable caution in controlling the indications for RLRL irradiation, ensuring diligent follow-up and monitoring of various eye indicators, while prioritizing the health and safety of children and adolescents.

Considering the above aspects, the limitations of this study are as follows: First, it is a single-center study; multi-center trials would be needed to investigate the efficacy of various treatment regimens across different regions. Second, as a retrospective study, it lacks randomization, which may introduce selection bias. Third, the study did not analyze the efficacy of different sequential treatment combinations of RLRL with the three optical treatment methods. Further research should address this gap to explore potential improvements in efficacy. Subsequent studies will aim to address these limitations.

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Disclosure of conflict of interest

None.

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