Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.64, No.1(2024). p.28-35 ; DOI: https://doi.org/10.14238/pi64.1.2024.28-35

Original Article

Low-level red-light therapy as a novel modality for myopia control in children: A systematic review

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Abstract

Background Due to the COVID-19 pandemic causing a rise in digital technology use, online e-learning, and decreased outdoor time, the prevalence of myopia is expected to increase. Therefore, finding an effective strategy for myopia progression control is of high importance. Low-level red-light therapy (LLRT) has been proposed as a new modality in myopia progression control.

Objective To assess the efficacy of LLRT for myopia control in children.

Methods A comprehensive literature search of four online databases (*PubMed, Cochrane, ProQuest,* and *WorldCat*) was performed. We included original studies that assessed the efficacy of LLRT for myopia control in children and excluded animal studies, case reports, articles with no full-text available, and articles not in English. Risk of bias assessment was performed using different tools according to the study type. The main outcome measurements were changes in axial length (AL) and spherical equivalent refraction (SER).

Results Three clinical studies, two randomized controlled trials and one retrospective cohort study, were reviewed. A total of 296 children in the treatment group were evaluated. Children using single-vision spectacle only or orthokeratology lenses were evaluated for comparison. All studies had reported significantly improved outcomes, with lower mean AL changes and greater SER improvement in the LLRT group compared to the control group ($P<0.001$ in all studies).

Conclusion Although studies on LLRT are still limited, the treatment has shown promising results for myopia control in children. More studies to evaluate the efficacy of this new strategy are needed.

Paediatr Indones. 2024;64:28-35; DOI: 10.14238/pi64.1.2024.28-35].

Keywords: *myopia control; low-level red-light therapy; children*

Myopia is not just a simple refractive error. It is an ocular disease characterized by an abnormally elongated eyeball, which cannot be corrected by optical lenses or refractive surgeries.[1] There are many complications of myopia, including presenile cataracts, glaucoma, retinal detachment, myopic choroidal neovascularization, foveoschisis, staphyloma, and macular atrophy, which can lead to blindness.[1-4] One of the complications of myopia, myopia maculopathy, has become a leading cause of untreatable visual loss in East Asia.[1] A high prevalence of myopia, 80-90%, is reported in young adults in East Asia. Additionally, the myopia progression rate in East Asian children is high, at nearly -1 diopter (D) per year.[1] In 2016, Holden *et al.*[4] estimated that 50% of the global population will have myopia by 2050, a two-fold increase from the myopia prevalence in 2000. During the COVID-19 pandemic, the rise in digital technology use, online e-learning, and decreased outdoor time may have precipitated the myopia progression rate.[5-9] Considering the high prevalence of myopia and the complications that may

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Submitted November 5, 2022. Accepted February 22, 2024.

occur from it, myopia is an important problem that needs to be addressed.

With the rising burden of myopia, many studies have been carried out to find the accurate treatments or medical devices to control myopia. Atropine and orthokeratology (OK) are the most studied treatments for controlling myopia. However, treatment with atropine showed that myopia progression accelerated dramatically once the treatment was discontinued, especially on a high dose.[10-12] OK was deemed to be a promising medical device to control myopia. In May 2021, the *U.S. Food and Drug Administration* (FDA) approved an OK device, *Acuvue*® Abiliti™ by *Johnson & Johnson Vision*, as the first medical device for myopia management.[13] Unfortunately, OK is not an option for everyone. Safety and efficacy concerns, rebound effect, convenience, and treatment cost affects the usage of OK.[10,14-17] Microbial keratitis, corneal staining, lens binding, corneal thinning, and tear film stability are some OK complications.[10,16]

Outdoor activity has recently been recognized as a protective factor for myopia.[1,2,18] Even though the mechanism through which outdoor activity can help prevent the onset of myopia is still unclear, studies have shown that more time spent on outdoor activities is associated with lower odds of myopia, and brighter light might be a possible protection mechanism against myopia.[1,2] During the COVID-19 pandemic, when people engaged in less outdoor activity, an alternative to increasing bright light exposure was proposed in the form of low-level red-light therapy (LLRT).[2,3,5] The LLRT uses low levels of red and near-infrared light with wavelength ranges from 600 nm to 1100 nm.[2,3,5] This new method contributes to restricting the progression of myopia by preventing cell apoptosis, thereby minimizing inflammation and increasing cell turnover.[5] In this systematic review, we aimed to assess the available literature on the efficacy of LLRT for myopia control in children.

Methods

This review was conducted following the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) guideline.[19] The *PROSPERO* registration number for this systematic review is CRD42022326123.

We included studies that met the following criteria: (1) the study population included children with myopia, and (2) the study used LLRT. Our exclusion criteria were: (1) studies performed on animals, (2) unavailable full text publication, (3) case reports or reviews, and (4) articles not written in English. A comprehensive search was performed on four databases: *PubMed, ProQuest, Cochrane*, and a grey-literature database, *WorldCat* on April 6, 2022. Searches were performed by 3 independent reviewers, using the following terms: "low red-light therapy," "children," and "myopia." We also included their synonyms and *MeSH* terms when available. No filters based on year of publication or language was applied. We adapted the search terms to fit the requirements of each database. We also hand-searched bibliographies of relevant studies. After removing duplicates, the three reviewers independently screened the results based on title and abstract, using Rayyan, an online-based tool.[20] Reviewers' decisions were blinded from each other until the screening process was finished. Disagreements between reviewers were resolved through discussion. Data were compiled into two tables: study characteristics and study results.

The risk of bias assessment was performed for randomized controlled trials (RCT) included in this review using *RoB 2.0*.[21] The quality assessment for the cohort study was performed using N*ewcastle-Ottawa Scale*.[22] Assessments and data extraction were performed independently by the three reviewers. The following data were extracted from each study: authors, year of publication, study design, country, sample size, intervention given, comparison, and outcomes. The main outcomes extracted for this review were axial length (AL) and spherical equivalent refraction (SER) at three, six, and nine months following LLRT.

Myopia was defined as a spherical equivalent of -0.50 D or less, and high myopia was defined as -5.00 D or less.[1,3] The spherical equivalent refraction (SER) was obtained using the following formula: SER=spherical + (astigmatism/2).[3] Axial length has a very strong correlation with refractive status. The eyeball grows rapidly in early childhood, increasing from 18 mm of axial length at birth to 23 mm at 3 years of age.[1] A 1-mm increase in axial length is correlated with a 2- to 3-D myopic shift.[1]

Results

Our search strategy identified 575 articles. We excluded three articles written in Russian. After duplicate removal and screening, three studies were included: two RCTs and one retrospective case series. A total of 636 subjects aged 3 to 16 years were included in this review, with 296 in the LLRT group, 259 in the single vision spectacle (SVS) group, and 81 in the OK group. All studies were conducted in China. The inclusion criteria of SER for each study differed, ranging from ≤-0.50 D to -5.00 D. The characteristics of each study are presented in **Table 1**. Light therapy in these studies was similar, despite different terms used in each study. All studies used LLRT with a wavelength of 635-660 nm and power ranging from 0.29 to 2.5 mW. Therapy was provided twice daily, in 3-minute sessions. All studies used this treatment protocol alongside single-vision spectacle (SVS) use. **Tables 2** and **3** list the critical appraisal results for each study, using tools based on the study design.

The primary outcome (AL changes) and secondary outcome (SER changes) from each study are presented in **Table 4**. The three reviewed studies showed that LLRT is an effective tool to control myopia progression, based on its ability to slow axial elongation and minimize SER changes. In addition, Zhou et al. observed the trend of AL changes and SER increase before and after the treatment was started. Before treatment onset, there was a steady increase in AL. After LLRT, the opposite trend was observed. There was also a steady increase in SER pre-treatment, while the opposite trend was observed after LLRT was started.[5]

Risk of bias assessment for RCTs are presented in **Table 2**. Both RCTs had one 'high risk' domain and another domain which had 'some concerns.' The quality assessment of the cohort study is presented in **Table 3**. The study had good results with a total score of 7 (good quality).

Discussion

To the best of our knowledge, this is the first systematic review on the use of LLRT as myopia control therapy in children. All 3 clinical studies included in this

Table 1. Study characteristics

Author	Study design	Country	Sample size (included in analysis)	SER	Intervention	Comparison
Jiang *et al.*[2] (2021)	RCT	China	246 children (8 to 13-year-olds) 117 LLRT 129 SVS	-1.00 to -5.00 D	LLRT + SVS Wavelength 650 ± 10 nm power 0.29 mW 3 minutes/ session Twice daily with 4 hours interval 5 days/ week (weekdays) Repeated every week/12 month	SVS
Zhou *et al.*[5] (2022)	Retrospective case series	China	161 children (3 to14-year-olds) 105 LLRT 56 SVS	< -1.00 D	LLRT + SVS Wavelength 635 nm Power 0.4 mW 3 minutes/session Twice daily with 4 hours interval	SVS
Xiong *et al.*[3] (2021)	RCT	China	229 children (6 to 16-year- olds) 74 LLRT 74 SVS 81 OK lens	≤ -0.50 D	LLRT + SVS Wavelength 650nm Power 2 ± 0.5 mW 3 minutes/ session Twice daily with 4 hours interval	SVS OK: Children were fitted with OK lenses (RGP material) every night for 7 consecutive hours

SER=spherical equivalent refractive error; LLRT=low-level red-light therapy; SVS=single vision spectacle; OK=orthokeratology; D=diopter

Table 2. Risk of bias assessment using *RoB 2.0*

Author	Domain 1 (Risk of bias arising from the randomization process)	Domain 2 (Risk of bias due to deviations from the intended interventions)	Domain 3 (Missing outcome data)	Domain 4 (Risk of bias in measurement of the outcome)	Domain 5 (Risk of bias in selection of the reported result)
Jiang *et al.*[2] (2021)	Low risk	Some concern	High risk	Low risk	Low risk
Xiong *et al.*[3] (2021)	Some concern	High risk	Low risk	Low risk	Low risk

Table 3. Quality assessment using Newcastle-Ottawa Scale[5]

Selection				Comparability	Outcome			Overall quality
Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up cohorts	
★	★	★	-	★	★	★	★	7

review used the same LLRT protocol for all samples. These studies evaluated SER and AL to measure the outcome of treatment. We chose SER and AL for this review because both are commonly used to measure outcomes in most clinical trials of myopia control. All studies showed decreased SER progression and slowed AL elongation, thus, inhibiting myopia development in children better than only SVS or OK lens usage ($P<0.001$).[2,3,5]

In recent years, LLRT using red to near-infrared light energy (λ=600-1100 nm) has gained attention, with therapeutic applications in ophthalmology.[23] Different wavelengths are thought to have different capacities to penetrate tissue. Red and near-infrared light energy are assumed to have higher penetration compared to lower or higher wavelengths.[23-25] With low energy doses delivered by LLRT, heating and tissue destruction effects are low, but high enough to modulate cell functions.[24] The precise mechanisms of this treatment are still unclear. Recent studies have shown that scleral hypoxia promotes scleral remodelling and myopia development.[26,27] Jiang *et al.* [2] hypothesized that LLRT treatment might disrupt that process by increasing blood flow and metabolism of the fundus, thus, repairing scleral hypoxia and restoring scleral collagen levels. Another study found that severe myopia was correlated to a significant increase in certain levels of cytokines (IL-1 and IL-6).[28] This finding was in agreement with the hypothesis by Francisco et al. that LLRT inhibits nitric oxide synthesis and inflammatory cytokine production, thereby decreasing the severity of oxidative stress. The study by Xiong *et al.*[3] was in agreement with the study by Jiang *et al*.[2]

In the studies reviewed, LLRT was delivered using a desktop light therapy device that emitted red light. Two studies used a wavelength of 650 mW, while one study used 630 mW. The duration of LLRT treatment in these studies was 3 minutes twice daily, with a 4-hour interval, 5 days per week.[2,3,5] The device used for LLRT and the treatment protocol were considered safe and approved in China for myopia treatment. This treatment protocol was intentionally adopted from an amblyopia treatment protocol in China.[2] Therefore, an identical protocol was used in the three studies.[2,3,5] Increased treatment efficacy was directly proportional to improved treatment compliance.[2] This result suggests that longer treatment duration might result in better myopia control. However, no study has been conducted on the safety of longer treatment duration.

The SVS and OK were the most common optical devices for myopia control, despite its limitations.[10,14,16,29] SVS was considered the most conventional way to reduce myopia progression. SVS offers clear vision with low potential side effects. SVS for myopia correction uses concave lenses that focus light more posteriorly, resulting in a clear object focused on the retina.[29] Atropine is known to be another treatment strategy for controlling myopia. However, the use of atropine might accelerate myopia

Table 4. Study results

Author	Period	AL changes				SER changes			
		LLRT	Control	OK	Comparison	LLRT	Control	OK	Comparison
Jiang *et al.*[2] (2021)	1 month	Mean axial elongation: -0.04 mm (95%CI -0.05 to -0.03)	Mean axial elongation: 0.02 mm (95% CI 0.01 to 0.03)	N/A	Mean difference: 0.06 mm (0.04 to 0.07)	0.08 (0.04 to 0.13)	-0.01 (-0.06 to 0.03)	N/A	-0.10 (-0.16 to -0.04)
	3 months	-0.01 (-0.03 to 0.00)	0.10 (0.09 to 0.12)		0.12 (0.10 to 0.14)	0.07 (0.02 to 0.12)	-0.18 (-0.27 to -0.13)		-0.25 (-0.33 to -0.18)
	6 months	0.04 (0.02 to 0.07)	0.23 (0.20 to 0.26)		0.19 (0.15 to 0.23)	-0.03 (-0.11 to 0.05)	-0.38 (-0.47 to -0.30)		-0.35 (-0.47 to -0.24)
	12 months	0.13 (0.09-0.17)	0.38 (0.34-0.42)		0.26 (95%CI 0.20 to 0.31; P< 0.001), representing 69.4% reduction in myopia progression	-0.20 (-0.29 to -0.11)	-0.79 (-0.88 to -0.69)		0.59 (95%CI 0.72 to 0.46; P< 0.001), representing a 76.6% reduction in myopia progression
Zhou *et al.*[5] (2022)	Baseline	0.21 ± 0.15	0.21 ± 0.16	N/A	Changes in AL were significantly lower in LLRT group (P<0.001)	-0.27 ± 0.11	-0.28 ± 0.10	N/A	In the treatment group, changes in SER showed significant improvement at the 3-month, 6-month, and 9-month follow up (P<0.001). While in the control group, myopia continued to progress significantly (P<0.001).
	3 months	-0.07 ± 0.19	0.35 ± 0.14			0.07 ± 0.14	-0.47 ± 0.09		
	6 months	-0.09 ± 0.11	0.54 ± 0.19			0.19 ± 0.25	-0.65 ± 0.16		
	9 months	-0.06 ± 0.19	0.65 ± 0.15			0.22 ± 0.17	-0.94 ± 0.13		
Xiong *et al.*[3] (2021)	1 month	-0.05 ± 0.07	0.02 ± 0.02	0.01±0.08	P<0.001	0.11 ± 0.17	-0.07 ± 0.11	N/A	P<0.001
	3 months	-0.07 ± 0.12	0.10 ± 0.04	0.02 ± 0.17	P<0.001	0.22 ± 0.32	-0.24 ± 0.16		P<0.001
	6 months	-0.06 ± 0.15	0.23 ± 0.06	0.06 ± 0.15	P<0.001	0.21 ± 0.34	-0.50 ± 0.24		P<0.001

AL=axial length; SER=spherical equivalent refractive error; LLRT=low-level red-light therapy; SVS=single vision spectacle; OK=orthokeratology; D=diopter

progression dramatically once discontinued.[10-12] In this review, all studies compared two groups of children using SVS only, with children using SVS and undergoing LLRT simultaneously. All children in the LLRT groups showed significant improvements in inhibiting axial length progression ($P<0.001$) and significant decreases in SER ($P<0.001$) compared to the SVS only group.[2,3,5] OK uses a flat-fitting rigid contact lenses that is worn overnight to flatten the cornea. This method is used to correct myopia temporarily; children or adults do not need to wear spectacles during the day to achieve good vision. However, OK must be worn routinely to continue the effect.[3,10] Xiong *et al*.[3] did not measure a SER result after OK lens intervention. They stated that slightly better myopia control was observed with LLRT treatment than with overnight OK lens-wearing. The LLRT group showed a decreased AL of -0.06 ± 0.15mm, while OK lens-wearing children had an AL increase of 0.06 ± 0.15mm.[3]

Several myopia prevention light therapy studies have been conducted in animals. Previous studies with monkeys and tree shrews suggest a potential role in preventing myopia progression.[30,31] However, a study in guinea pigs showed contrasting results.[32] Improvement in myopia progression was also found in mice, chicks, and humans who were exposed to violet light.[33-35] These promising findings provide the motivation to investigate the efficacy of LLRT compared to other light therapy in humans.

The three studies in this review used different age ranges, resulting in a diverse pool of samples, regarding age and baseline SER. A study compared the efficacy of LLRT for different age groups and found that the decrease in both SER and AL in the older age group were greater compared to those in the younger group.[5] This finding might suggest that LLRT can work more effectively in certain age groups. Studies to determine which age group would benefit the most from LLRT treatment are needed. Furthermore, studies to determine if LLRT is effective for different groups based on SER or AL are also needed.

This review has some limitations. Firstly, studies on the effectiveness of LLRT for myopia control are still very limited, hence limiting the pool of studies our review could draw from. Secondly, this review did not include some studies that were written in languages other than English, which may have offered significant additions to the results. Finally, each of the two RCT studies included in this review had a high risk of bias in one of the domains. Therefore, further research on this topic is necessary to evaluate long-term efficacy and safety, rebound effects, optimal treatment strategies (wavelength, duration, frequency of treatment), and potential underlying mechanisms, especially studies with a longer follow-up period, double blinding, and placebo control. Additionally, the terms used to describe this method of treatment varied among the studies, which may cause confusion. Using standardized terms will facilitate further studies and discussions about this treatment.

In conclusion, LLRT treatment has high potential for myopia control in children. More studies to evaluate the efficacy of this new therapeutic modality, as well as the best protocol for this treatment, are of high importance.

Conflicts of interest

None declared.

Funding acknowledgment

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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