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ORIGINAL ARTICLE

Short-term effectiveness and safety of photobiomodulation on low-to-moderate myopia

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Abstract

To find and assess the effectiveness and safety of short-term Photobiomodulation (PBM) treatment in children with low-to-moderate myopia. Children with low-to-moderate myopia were recruited and divided into PBM or control groups based on whether they received PBM treatment. The PBM group underwent a three-month treatment with a 650 nm low-energy semiconductor laser, while the control group did not receive any therapeutic intervention. At the end of the trial, the changes in spherical equivalent refractive (SER) and axial length (AL) before and after treatment were compared between the PBM group and the control group to evaluate the effectiveness of PBM in preventing myopia. The best corrected visual acuity (BCVA), nerve fiber layer thickness (RNFLT), ganglion cell layer thickness (GCLT), central point retinal thickness (CPRT), 3-mm subfield central retinal thickness (3 mm-CRT), superficial retinal vascular density (SCP), and central choroid thickness (CCT) were self-compared to assess the safety of PBM. A total of 57 subjects were prospectively followed from October 2020 to September 2021, comprising 28 participants (56 eyes) in the PBM group and 29 participants (58 eyes) in the control group. After three months of treatment, the AL decreased by 0.07 ± 0.11 mm, and the SER decreased by -0.12 ± 0.39 D in the PBM group. However, both SER and AL increased in the control group. Furthermore, there were statistically significant differences between the PBM and control groups ($p < 0.01$). The BCVA, RNFLT, GCLT, CPRT, and 3 mm-CRT remained almost unchanged in the PBM group; The SCP decreased from 0.37 ± 0.03 to 0.35 ± 0.02 in the PBM group with a statistically significant difference before and after treatment ($p = 0.045$). The CCT increased from 255 ± 41 μm to 274 ± 29 μm in the PBM group without any significant difference before and after treatment. The administration of PBM significantly suppresses the elevation of AL and SER following a three-month duration. No significant adverse effects were observed on visual function and retinal morphology.

Trial Registration: This study is registered at https://clinicaltrials.gov/ (registration number: NCT04604405).

Keywords Photobiomodulation · Low-level laser therapy · Myopia prevention · Macular microcirculation

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Introduction

Photobiomodulation (PBM) refers to the direct exposure of near-infrared (NIR) emitted by low-power lasers or light-emitting diodes (LEDs) to modulate biological functions or induce therapeutic effects in a non-destructive and non-thermal manner, previously known as low-level light/laser therapy (LLLT). These biological or therapeutic effects encompass the augmentation of mitochondrial cytochrome C oxidase (CCO) activity[1–4], anti-inflammation [5], alleviating oxidative stress [5, 6], enhancement of microcirculation [7], and promotion of protective factors expression[8, 9].

Although the therapeutic mechanism of PBM remains incompletely elucidated, research conducted in ophthalmology over the past two decades has substantiated its relatively significant therapeutic efficacy in various clinical conditions, including age-related macular degeneration (AMD) [10–12], diabetic retinopathy (DR) [13, 14], retinitis pigmentosa [15], amblyopia in adolescents and adults [16]. Recent research has revealed that the application of 650 nm low-energy NIR may also exert a beneficial influence on myopia control [17].

The aforementioned literature reports suggest that PBM may hold significant potential for the treatment or rehabilitation of various eye diseases. We hypothesize that the potential explanation is that PBM has two major functions of regulating mitochondrial CCO activity and improving microcirculation. The retina and choroid are rich in mitochondrial cells and blood supply, making them susceptible to ischemia and functional degradation of mitochondrial cells, which plays a crucial role in the occurrence and progression of fundus diseases. Additionally, the ocular refractive medium transparency facilitates direct light irradiation on the retina and choroid, thereby maximizing the therapeutic efficacy of PBM. In recent years, Wong et al. [18] have demonstrated a significant correlation between choroid thickness and macular degeneration in myopia. Wu et al. [19] have also identified that choroid hypoxia resulting from ischemia plays a pivotal role in the progression of myopia. The hypoxia-inducible factor-1α (HIF-1α) signal, activated by reduced oxygen levels, can promote myopia progression through inducing transdifferentiation of myofibroblasts. Ameliorating choroid-scleral hypoxia may represent an effective approach for regulating axial elongation and impeding myopia advancement.。

Considering that myopic patients often have transparent refractive medium and a higher incidence rate, this study selected myopia as the condition to assess the efficacy and safety of PBM for treating ocular diseases. The intervention involved directing 2.5mW/cm2 red light at 650 nm onto the eyes without using any additional equipment such as contact lenses. Red light's penetrating ability allows it to simultaneously affect the retina and choroid, with its vasodilation effect on the rich vascular tissue in the choroid improving microcirculation, alleviating scleral hypoxia, and decelerating myopia progression. This forms the theoretical foundation for this experiment. Further clinical research is needed to elucidate how red light specifically impact on intraocular tissues. The intervention method employed in this experiment is consistent with the PBM intervention method mentioned above for treating other ocular diseases, albeit utilizing significantly lower energy levels than those used in the aforementioned clinical trials. Based on the results of said trials, no complications were observed during treatment, thus theoretically confirming the safety of this experiment. In order to further ensure safety, a pilot experiment involving adults was conducted over a period of three months prior to commencing this trial, which revealed no adverse reactions or complications.

Methods and participants

Study design

The present study was conducted in Chongqing, China as a prospective, non-randomized, non-blinded, parallel controlled, single-center clinical trial to assess the efficacy and safety of PBM for myopia prevention in children with low-to-moderate myopia over a three-month period. Ethical approval was obtained from the human ethics committee of Chongqing Aier Eye Hospital. This research adhered to the principles outlined in the World Medical Association Declaration of Helsinki [20]. The study protocol was registered on the ClinicalTrials.gov website (https://www.clinicaltrials.gov/, registration number: NCT04604405).

Participants

Children aged seven to seventeen with low-to-moderate myopia (with SER ranging from –0.50 D to –6.00 D in both eyes, astigmatism < 1.5 D, AL < 26.00 mm) were recruited. Exclusion criteria included ocular pathologies such as amblyopia, strabismus, uveitis, retinopathy, media opacity, optic neuropathy or congenital ocular lesions; abnormal visual function; previous use of atropine or Orthokeratology; any treatment for controlling myopia other than wearing spectacles; photophobia; previous ocular surgeries (e.g., refractive surgery, lens surgery or vitrectomy); systemic illnesses (including cardiac or respiratory diseases); and pregnancy or expecting a child. Written informed consent was obtained from the participants and their guardians prior to

enrollment into the study. The subjects were non-randomly divided into two groups: PBM group and control group. The projected sample size was set at 30 individuals per group.

Intervention

In their daily lives, all subjects wear spectacles. The PBM group received twice-daily administration of PBM. This involved the use of a continuous wave semiconductor laser diode (RS-200–2A, EYERISING, Su Zhou, China) with a wavelength of 650 nm and an average power output of 2.0 ± 0.5 mW/cm^2. Each treatment delivered approximately 0.36 J/cm^2 of total energy to patients who were instructed to gaze at the light for a duration of 180 s. To ensure adherence to the treatment regimen and monitor compliance, investigators reviewed the subjects' treatment records on a weekly basis and contacted them via phone if any treatments were missed. Subjects failing to complete ten treatments per week would be excluded from further participation in the clinical research.

Study procedures

The participants underwent a baseline examination within one to three days prior to enrollment, followed by a first follow-up examination after one month, and a second follow-up examination after three months. Including:

a. The subject's eyes underwent slit lamp examination and fundus examination using a 90 D indirect ophthalmoscope to assess for the presence of any abnormalities in both the anterior and posterior segments.
b. The measurement of best corrected visual acuity (BCVA) was conducted through non-cycloplegic subjective optometry, and the results were recorded using the logMAR scale.
c. Non-cycloplegic computerized optometry utilizing the NIDEK ARK5–1 (NIDEK Inc. Ltd., Tokyo, Japan) was employed to accurately measure and convert refractive error into spherical equivalent refraction (SER).
d. The AL was measured using the IOL-master 700 (Carl Zeiss Meditec, Inc., California, USA). The AL measurement was precisely aligned with the macular center, and the retinal anatomy chart accurately displayed the location of the macular fovea.
e. The retinal morphology and macular microcirculation were evaluated using the CIRRUS HD-OCT 5000 (Carl Zeiss Meditec, Inc., California, USA) for optical coherence tomography (OCT) assessment. Retinal morphology parameters included measurements of retinal nerve fiber layer thickness (RNFLT), ganglion cell layer thickness (GCLT), central retinal thickness within a 3-mm subfield (3 mm-CRT), and central point retinal thickness (CPRT). Macular microcirculation parameters consisted of analysis of the superficial capillary plexus within a 3-mm subfield (SCP) and measurement of central choroid thickness (CCT). SCP images were acquired using the "macular angio 3×3" mode and automatically analyzed by dedicated software. The inner retina was defined as extending from the inner limiting membrane (ILM) to a depth of 9 μm below the boundary of the inner plexiform layer. Further details have been described elsewhere [21]. In this investigation, the parameters encompassed the entire circular area centered at the fovea with a radius of 3 mm. CCT was manually calculated by measuring the distance between Bruch's membrane interface and the sclerochoroidal interface due to the absence of automatic choroid segmentation provided by OCT. Additionally, suboptimal scans were accepted but repeated until achieving good quality, with a minimum signal strength cutoff of $\geq 9/10$.

Statistical analyses

The statistical analyses were conducted using SPSS software version 21.0 (SPSS Inc., Chicago, IL). Repeated measures ANOVA was employed to investigate the measurement data, while the count data were examined using Fisher's chi-square test with a confidence interval (CI) of 95% and a significance level (α) of 0.05.

Results

1. Participant assignment and baseline measures

A total of 65 subjects were deemed eligible for the study (Fig. 1). At the conclusion of the three-month period, a total of 57 participants successfully completed the trial, comprising 28 individuals (56 eyes) in the PBM group and 29 individuals (58 eyes) in the control group. Five subjects were lost to follow-up, with three withdrawing due to receiving alternative methods for myopia prevention.

The baseline characteristics, including sex, age, SER, and AL, are presented in Table 1. There were no significant differences observed between the PBM group and the control group.

2. Effectiveness of PBM in the prevention and management of myopia

After three months of treatment, the PBM group exhibited a significant decrease in AL by 0.07 ± 0.11 mm and SER by -0.12 ± 0.39D, while the control group showed an increase in both SER and AL. The differences in the changes

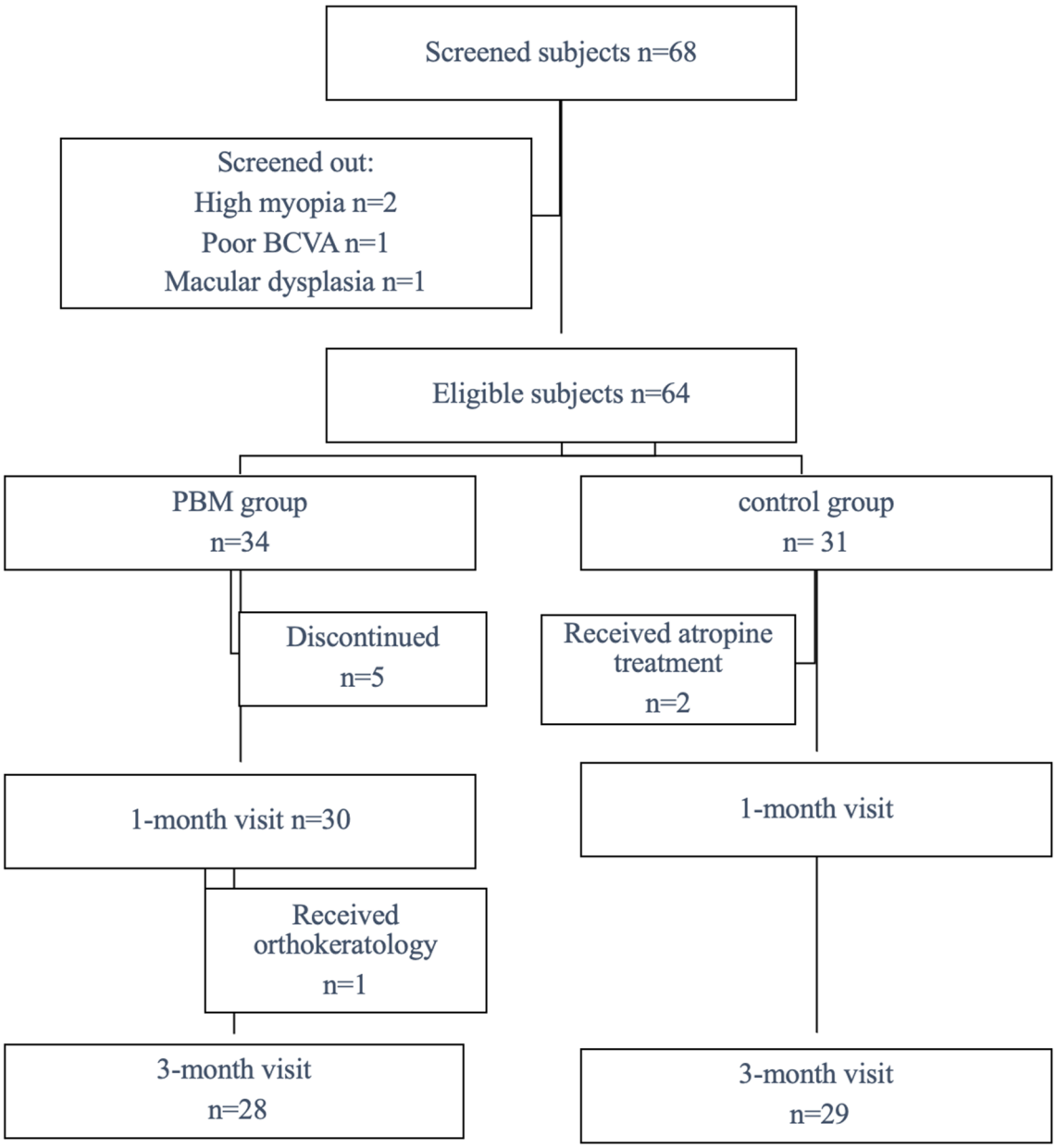

Fig. 1 Flow chart of participant assignment

Table 1 Baseline examination parameters of subjects

Characteristics	PBM	Control	*p*
Sex(F/M)	17/11	12/17	0.19[a]
Age(y)	9.86 ± 2.22	10.68 ± 2.35	0.18[b]
SER(D)	-1.78 ± 0.96	-1.91 ± 1.21	0.53b
AL (mm)	24.46 ± 0.93	24.30 ± 0.76	0.32b

a: Chi-square test, b: Independent sample T test

of AL and SER between the PBM and control groups exhibited statistical significance ($p < 0.01$), as depicted in Fig. 2. Moreover, Table 2 demonstrates that a higher proportion of eyes in the PBM group experienced reductions in both AL and SER at one month and three months compared to the control group.

3. Safety of PBM in the prevention and management of myopia

No subjects from the PBM group exhibited any damage in visual acuity (logMAR) following treatment. Analysis of retinal morphology revealed that measurements of RNFLT, GCLT, CPRT, and 3-mm CRT at one or three months

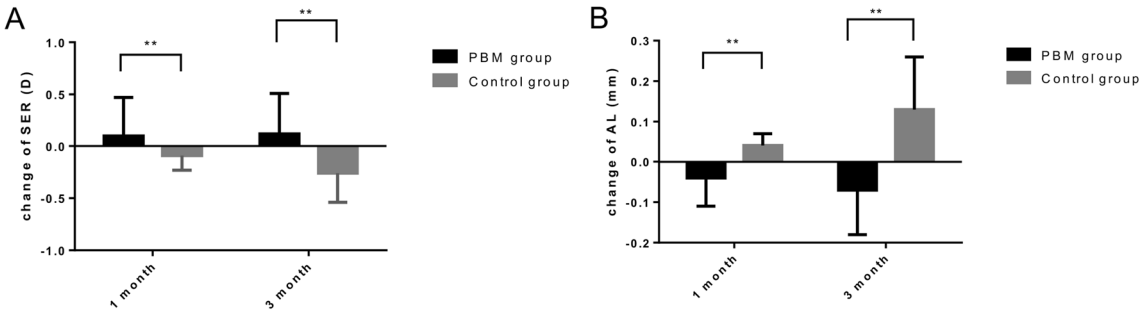

Fig. 2 Change of SER (mean ± SD) and Change of AL (mean ± SD). As can be seen from the figure, SER (**A**) and AL (**B**) in the PBM groups decreased significantly after treatment, while those in the control group increased. The differences between the PBM groups and control groups were statistically significant. SER: spherical equivalent refractive. AL: axial length. Change: Value of follow-up examination minus baseline examination. **: Statistically different, $p < 0.01$

Table 2 The proportion of the eyes with AL and SER reduced

Sampling points	Parameters	PBM	Control	*P*
1-month	Proportion of eyes with SER reduced	44.6%(25/56)	1.7%(1/58)	< 0.01
	Proportion of eyes with AL reduced	71.4%(40/56)	1.7%(1/58)	< 0.01
3-month	Proportion of eyes with SER reduced	41.0%(23/56)	3.4%(2/58)	< 0.01
	Proportion of eyes with SER reduced	71.4%(40/56)	7.9%(4/58)	< 0.01

post-treatment remained consistent with baseline values (Table 3). There were no statistically significant differences between the baseline measurements at one month and three months."

4. Changes in retinal and choroidal microcirculation

The results demonstrated a significant increase in CCT from 255.06 ± 41.03 μm to 274.00 ± 29.22 μm, while the SCP exhibited a slight decrease from 0.367 ± 0.026 to 0.354 ± 0.022 in the PBM group. However, only SCP showed a statistically significant difference between baseline and three months (P = 0.045). The statistical analysis findings are presented in Table 4.

Furthermore, no untoward reactions or complications were observed throughout the course of the trial.

Discussion

Myopia is the leading cause of visual impairment worldwide, characterized by a decrease in scleral strength and thickness due to inappropriate elongation of the AL and extracellular matrix (ECM) remodeling. However, the precise initiating factors and signaling pathways responsible for myopic scleral ECM remodeling remain unknown. Recently, Wu et al. [22] and Zhao et al. [23] have demonstrated that scleral hypoxia plays a crucial role in the pathogenesis of myopia development. In human subjects, close working conditions (a risk factor for myopia) significantly reduce choroid blood perfusion, potentially leading to scleral hypoxia. Scleral ischemia and hypoxia trigger activation of the HIF-1α signaling pathway, promoting myofibroblast transdifferentiation through stimulation of the actin cytoskeleton pathway and collagen remodeling via regulation of ECM receptor interaction pathway. Notably, pharmacological improvement of ischemia of choroid can effectively delay myopia progression. Besides ischemia and hypoxia theory, inflammation also plays a pivotal role in high myopia occurrence and development [24]. The theoretical mechanism outlined above suggests that PBM can enhance vasodilation, improve blood circulation, reduce inflammation while facilitating collagen fiber formation. Recently conducted randomized controlled clinical studies on the slowing progression of myopia using Orthokeratology and PBM have demonstrated that PBM not only reduces the AL but also significantly enhances choroid thickness, indicating its potential to improve fundus microcirculation. If PBM can effectively manage myopia progression by enhancing retinal choroid microcirculation, it may also offer therapeutic benefits for various chronic eye conditions characterized by compromised microcirculation or mitochondrial dysfunction, such as diabetic retinopathy and age-related macular degeneration. Therefore, PBM represents a valuable adjunctive treatment modality for ocular diseases.

The present study revealed a significant reduction in SER and AL, and an mild increase in CCT following

Table 3 Parameters of BCVA and retina morphology of PBM groups at different sampling points (mean ± SD)

PBM group parameters	Baseline	1-month	3-month	F	p
BCVA(LogMAR)	0	-0.007 ± 0.027	-0.006 ± 0.021	1.980	0.14
RNFLT(μm)	99.48 ± 9.73	99.64 ± 8.20	100.43 ± 9.02	0.524	0.59
GCLT(μm)	81.79 ± 4.80	82.12 ± 4.75	82.17 ± 0.67	0.093	0.91
CPRT(μm)	238.07 ± 17.86	239.30 ± 20.43	238.24 ± 18.78	0.057	0.95
3 mm-CRT(μm)	278.22 ± 13.31	278.04 ± 12.14	278.13 ± 12.88	0.158	0.85

BCVA: Best corrected visual acuity; RNFLT: Retinal nerve fiber layer thickness; GCLT: Ganglion cell layer thickness; CPRT: Central point retinal thickness, 3 mm-CRT: 3-mm subfield central retinal thickness

Table 4 Changes in retinal and choroidal microcirculation in the PBM group

Characteristics	baseline	1-month	3-month	*p*
SCP	0.367 ± 0.026	0.359 ± 0.029	0.354 ± 0.022*	0.05[c]
CCT (μm)	255.06 ± 41.03	281.34 ± 26.25	274.00 ± 29.22	0.131[c]

PBM: Photobiomodulation. SCP: Superficial capillary plexus. CCT: central choroid thickness. *: Statistically different, $p < 0.05$.c: one-way ANOVA

PBM treatment, which is consistent with the results reported by XIONG F et al. [17].The thickening of CCT may be related to choroidal vasodilation. Several studies have suggested that PBM may enhance vasodilation by facilitating the dissociation of nitric oxide (a key signaling molecule involved in vascular dilation) from Cyclooxygenase [25] or s-nitrosothiol and dinitroferric complexes [7, 26, 27]. In contrast, the PBM group exhibited a statistically decrease in SCP. We guess that both the retina and choroid receive their blood supply from the ophthalmic artery, with a constant total blood volume. Under low-energy near-infrared radiation exposure, it is plausible that the higher density of blood vessels within the choroid may result in an increased blood volume surpassing that of the retina, leading to a corresponding reduction in SCP. This conjecture finds support from studies demonstrating diminished retinal microcirculation and augmented choroidal microcirculation under artificially elevated intraocular pressure [28–30].

In our typical understanding, the human AL is generally considered to be irreversible, making it difficult to accept that the AL of myopia patients can be shortened through treatment. However, this experiment has provided evidence of such a phenomenon. The thickening of the choroid appears to offer a plausible explanation for the observed shortening of the subjects' AL. However, in this study, we observed that the thickness of choroid thickening accounted for approximately one-third to half of the length of AL shortening, suggesting that other factors beyond choroidal changes may contribute to AL shortening. By excluding retinal thickness alterations as a potential confounding factor, our findings suggest that variations in scleral morphology or tension might be implicated in the mechanism underlying AL shortening according to the above theoretical basis. However, it should be noted that this study does not provide direct evidence for alterations in scleral morphology, necessitating further investigations for validation.

The PBM therapy, similar to drug therapy, exhibits a biphasic effect resulting from the cumulative impact of light irradiation intensity and duration. When low-intensity light is applied for a short period, no biological effects are observed. However, high-intensity light exposure in the short term or medium–low intensity light exposure over an extended period may lead to visual function impairment or damage to intraocular tissues, particularly the retina. Based on this study, we investigated whether prolonged exposure to low-energy red light had any impact on visual function or caused ocular tissue damage over time. we found that direct intraocular irradiation of 650 nm NIR at an intensity of 2.5mW/cm^2 for 3 min twice daily over a period of 3 months did not result in significant harm to ocular tissues or visual function. Similarly, other researchers extended the duration of their experiments up to one year using the same intervention approach without encountering any complications or adverse reactions [31, 32]. Therefore, overall, this treatment method can be considered safe. However, it is worth noting that our observations suggest a possible reduction in retinal microcirculation following this intervention; although mild reductions seem to have minimal impact on individuals with normal retinal microcirculation, there may be potential risks for those with poor retinal microcirculation which necessitate further investigation.

Limitations of this study include the absence of observation on additional indicators of visual function and intraocular tissue morphology, as well as the inability of OCT used in this study to automatically measure choroidal microcirculation. Moreover, manual measurement of choroidal central point thickness is prone to measurement errors and does not accurately reflect the overall status of choroidal microcirculation.

Conclusions

Short-term clinical results suggest that PBM helps control AL and diopter development in myopic eyes of children, with no adverse effects on visual acuity and retina morphology. However, it is difficult to accurately describe the effect of PBM on retinal and choroidal microcirculation in this study. Better detection equipment and more extensive clinical trials are needed to investigate its effects on fundus microcirculation, thereby exploring the wider potential application value of PBM.

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Declarations Presentation at a meeting: N/A.

Ethical approval Ethical approval was acquired from the human ethics committee of the Chongqing Aier Eye Hospital.

Conflicting interest The authors claim no competing interests.

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