STUDY PROTOCOL

Study Title:

The Rebound Effect on Repeated Low-Level Red Light Therapy for Myopia: A Randomized Controlled Clinical Trial

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1. Research Background

Myopia is a globally recognized public health concern, with its prevalence and severity increasing annually among children and adolescents[1]. Existing projection models estimate that by 2050, the global prevalence of myopia will reach 49.8%, among which the proportion of high myopia will account for 9.8%[2]. With the increasing prevalence of myopia, the risk of its related complications including cataract, glaucoma, myopic maculopathy and retinal detachment also increases[3–5]. Without effective intervention, these conditions may lead to significant visual impairment and impose a substantial societal burden[6]. Consequently, the implementation of effective prophylactic and interventional strategies to mitigate the onset and progression of myopia has become a paramount priority in contemporary ophthalmic public health.

Among emerging therapeutic modalities, repeated low-level red light (RLRL) therapy has garnered considerable attention as a novel non-invasive intervention for myopia control. In a landmark 12-month multicenter randomized controlled trial, RLRL therapy demonstrated a 69.4% and 76.6% reduction in axial elongation and myopic refractive progression, respectively, relative to the single-vision spectacle (SVS) control group[7]. Moreover, compelling evidence indicates that RLRL therapy exerts pronounced efficacy in cohorts with high myopia, with 53.3%–59% of treated individuals exhibiting axial shortening exceeding 0.05 mm[8,9]. Comparative effectiveness research has further established that RLRL therapy significantly outperforms 0.01% atropine in constraining axial elongation over a 12-month treatment horizon[10]. In addition, adjunctive RLRL application has been shown to effectively suppress axial progression in patients exhibiting

suboptimal responses to orthokeratology monotherapy[11].

Given the inherently progressive nature of juvenile myopia, the sustained durability of therapeutic efficacy remains a critical consideration. In this context, Xiong and colleagues investigated the extended efficacy and safety profile of RLRL therapy over a 2-year continuum, reporting favorable tolerability and a 75% overall effectiveness rate in terms of axial length and refractive control at the 2-year milestone. Notably, however, a decrement in therapeutic potency was observed during the second year relative to the first[12]. Furthermore, paralleling observations documented for other myopia interventions, a pronounced rebound phenomenon was identified upon treatment cessation after one year; the subsequent myopic progression rate during the second year approximated that of the SVS group during the initial year of follow-up[12].

Against this backdrop, the present investigation is designed to further elucidate the long-term efficacy trajectory and the post-cessation rebound dynamics associated with RLRL therapy. Moreover, we seek to interrogate potential strategies to attenuate this rebound phenomenon by directly comparing the longitudinal changes in axial length (AL) and cycloplegic spherical equivalent refraction (SER) among participants who either maintain, discontinue, or undergo a graduated tapering of RLRL treatment following one year of continuous therapy.

2. Research Objectives

Investigate the rebound effect of myopia progression after discontinuing RLRL continuous treatment, and explore strategies to mitigate this effect by comparing changes in AL and SER between participants who interrupted treatment and those who gradually reduced treatment intensity.

3. Research Design

This study was a three-arm, randomized controlled, prospective trial conducted at the Ophthalmology Center of the First Affiliated Hospital of Anhui Medical University, enrolling pediatric participants who had received continuous RLRL treatment for one year. The participants were randomly assigned to three groups: the continued RLRL treatment group (RLRL-C), the discontinued RLRL treatment group (RLRL-I), and the gradually reduced RLRL treatment group (RLRL-T). The gradual reduction protocol for RLRL treatment was as follows:

1. First month: twice daily, for 5 days per week.
2. Second month: Once daily, for 5 days per week.
3. Third month: once daily, for 3 days per week.

Data including AL, SER, uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), and choroidal thickness (CnT, optional) were collected from subjects at baseline and at months 6 and 12. Additionally, adverse events were assessed using questionnaires at baseline and during follow-up.

Expected Sample Size

A one-way ANOVA was conducted to test for differences in axial length increases among the three groups. With an alpha level of 0.05 and a power of 80%, the expected axial length increase in Group RLRL-I at 12 months was 0.40 mm (standard deviation: 0.30 mm), while the anticipated intervention effects for Groups RLRL-T and RLRL-C were reductions of 25% and 50% in axial length increase (0.30 mm and 0.20 mm, respectively). Consequently, each group required 45 participants. Accounting for a 15% loss-to-follow-up rate, the final sample size was adjusted to 159 participants.

Inclusion and exclusion criteria for participants:

Inclusion Criteria:

a. Children and adolescents aged 8 to 16 years
b. The patient has received continuous RLRL treatment for 1 year (±1 month) without interruption.
c. Diagnosed with myopia (ciliary muscle paralysis SER ≥ -0.50 D), astigmatism ≤ 2.50 D, anisometropia ≤ 1.50 D, and bilateral best corrected visual acuity (BCVA) ≥ Snellen 20/20 before receiving RLRL treatment.
d. The consent of the guardian and the consent of the participant.

Exclusion Criteria:

a. History of any ophthalmic surgery or ocular diseases (e.g., glaucoma, retinal disorders).

b. Systemic diseases that affect vision or eye health (e.g., diabetes).

c. After discontinuing RLRL treatment, other myopia control interventions other than monocular glasses should be employed (including atropine, orthokeratology lenses, defocused/DOT lenses, etc.).

Main and secondary measurement results:

Main measurement results:

AL change at 12 months (ΔAL)

Secondary measurement results:

Changes in SER (ΔSER), BCVA, ocular biometric parameters (corneal curvature, anterior chamber depth), and CnT at 12 months

Ophthalmic examination methods:

1. Vision: Assess UCVA and BCVA at 4 m using the ETDRS visual acuity chart (Precision Vision).
2. Ocular biometric parameters: Before ciliary muscle paralysis, measure the ocular biometric parameters using an IOLMaster (Carl Zeiss 500), including axial length (AL), corneal curvature (CC), and anterior chamber depth (ACD). Perform five measurements and calculate the average value.
3. Ciliary muscle paralysis and refraction: One drop of 0.5% topical anesthetic eye drops (Alcon, Pours, Belgium) and one drop of 1% cyclopentolactone eye drops were administered to each eye respectively; subsequently, two drops of cyclopentolactone eye drops were instilled after 5 minutes and 20 minutes. Complete ciliary muscle paralysis was defined as the absence of pupillary light reflex with pupil size reaching or exceeding 6 mm. Refraction data were obtained using an automated refractometer, with measurements averaged over three trials; the minimum deviation for spherical and cylindrical powers should not exceed 0.25 D, and the minimum axial deviation should not exceed 5°. The SER (Spherical-Elastic-Rational) value is defined as half of the sum of spherical and cylindrical powers.
4. OCT examination (optional): Following ciliary muscle paralysis, perform a scan of the region

centered on the optic disc using a swept-source optical coherence tomography (SS-OCT) to measure choroidal thickness (ChT).

adverse event ：

Through questionnaire surveys, ocular and systemic discomforts recorded at baseline and during follow-up were documented, including but not limited to sudden vision loss in more than two lines, scotomas, glare, transient glare, flash blindness, and residual images.

time axis ：

Subject recruitment: October 2025

Data Collection: November 2025

Data Analysis: December 2025

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