Clinical science

Repeated low-level red-light therapy combined with orthokeratology for myopia control in Spain: a randomised controlled study

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ABSTRACT

Aim To evaluate the 12-month efficacy and safety of repeated low-level red-light (RLRL) therapy combined with orthokeratology (ortho-k) (RCO) for controlling myopia in Spanish children.

Methods In this single-site, randomised, parallel-group, non-blinded clinical trial (NCT06899139), eligible myopic children aged 10–13 years were recruited and assigned randomly either to the RCO group or the ortho-k group. Follow-up assessments were conducted at 6, 9 and 12 months after baseline. The primary outcome and secondary outcome were the axial length (AL) and macular thickness (MT) changes at 12 months estimated by longitudinal mixed model.

Results All participants (n=26; 11 in the RCO group and 15 in the ortho-k group) were included in the analysis. After 12 months, the adjusted mean AL change was −0.124 mm (95% CI −0.164 to −0.084) in the RCO group, whereas the ortho-k group continued to exhibit a modest axial elongation of 0.102 mm (95% CI 0.068 to 0.136). The adjusted mean difference in AL change was −0.226 mm (95% CI −0.279 to −0.174) between the groups (p<0.001). Additionally, the adjusted mean change in MT showed no significant difference between groups at 12 months. In the RCO group, 80% of children achieved AL shortening >−0.05 mm, whereas no children in the ortho-k group showed AL shortening. No severe adverse events were reported during the study.

Conclusions Combining RLRL therapy with ortho-k is an effective and safe myopia control strategy in Caucasian Spanish children, supporting the potential generalisability of the synergistic effect across diverse ethnic groups.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Orthokeratology (ortho-k) and repeated low-level red-light (RLRL) therapy are both effective interventions for myopia control, but evidence on their combined use is limited, particularly in non-Asian populations.

WHAT THIS STUDY ADDS

⇒ This randomised trial in Spanish children showed that combining RLRL with ortho-k (RCO) reduced axial elongation by 0.215 mm per year compared with ortho-k alone, with sustained axial shortening and no serious adverse events.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results confirmed that RCO was an effective and safe myopia control strategy in Caucasian Spanish children, supporting its potential generalisability across diverse ethnic groups. Further studies are needed to understand its long-term efficacy, safety and the underlying mechanisms.

INTRODUCTION

Myopia is the most common refractive error and a public health concern around the world, resulting in a high socioeconomic burden.[1 2] As the degree of myopia increases, the risks of complications such as macular degeneration, retinal detachment and glaucoma also rise significantly.[3] Given its high prevalence and associated vision-threatening complications, it is crucial and urgent to find an efficient intervention for myopic children to slow the progression.

Orthokeratology (ortho-k) is a non-surgical treatment that reshapes the cornea with overnight gas-permeable contact lenses for vision improvement and myopia management. Previous studies have shown a positive impact of ortho-k on delaying axial elongation by approximately 0.25 mm over 2 years.[4 5] However, the efficacy varies among studies, ranging from 43% to 63% compared with control participants, and a subset of children shows suboptimal response, with rapid elongation exceeding 0.36 mm per year.[6 7] There is an urgent need to explore adjunctive therapies and further enhance treatment outcomes.

Repeated low-level red-light (RLRL) therapy has emerged as a promising intervention for myopia control.[8–11] A multicentre study led by Jiang *et al* demonstrated that RLRL effectively reduced axial elongation and spherical equivalent refraction progression by 69.4% and 76.6% over 12 months, respectively.[11] Its ease of administration, high efficacy and favourable safety underscore the potential of RLRL therapy as an adjunct to existing myopia interventions. Combining these therapies may enhance their efficacy,[12] yet current evidence is limited, particularly outside Asian populations.

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To address these gaps, we conducted a randomised controlled trial (RCT) to evaluate the combined effects of RLRL therapy with ortho-k in Spanish children.

METHODS

Study design and setting

The study was a single-site, parallel-group, non-blinded RCT conducted in Spain from October 2023 to December 2024. Participants were recruited from Centro Fernandez-Velazquez, Spain between 3 October 2023 and 30 November 2023. The study was approved by the Institutional Review Board of Centro Fernandez-Velazquez (number (01/2023)) and was performed in accordance with the declaration of Helsinki. Study registration was completed on ClinicalTrials.gov (identifier, NCT06899139). Written informed consents were obtained from all children and their guardians prior to participation. All participants were covered by a 12-month research insurance indemnity scheme.

Participants

Children aged 10–13 years with the baseline non-cycloplegic spherical equivalent refractive (SER) between −0.75 and −6.75 dioptres (D), astigmatism of no more than 1.50 D, best visual acuity (BCVA) of no worse than 20/20 bilaterally were included. The age group was set to enhance homogeneity and reduce the potential age-related variability of combination therapy.[13 14] Exclusion criteria included having ophthalmic diseases or systemic diseases that affect refractive development, contraindications for ortho-k lens wear and prior use of myopia-control interventions within 3 months. Although the use of non-cycloplegic SER in eligibility may introduce measurement variability at the baseline, it would affect both groups equally, thereby maintaining group comparability.

Randomisation and blinding

Participants were randomised into either the RLRL combined with ortho-k (RCO) group or the ortho-k group alone, using a computer-generated randomisation sequence in Excel (RAND function) with a 1:1 allocation ratio. Allocation was concealed in opaque, sequentially numbered envelopes by an independent coordinator who was not involved in enrolment or outcome assessment. Although blinding of participants was not feasible, all outcome assessors were blinded to group allocation to minimise potential bias in outcome assessment.

Interventions

All participants need to wear ortho-k lenses (optic zone diameter=5.80 mm, Jessen factor=+1.5 D) manufactured by TS LAC (Milan, Italy) overnight for a minimum of 8 hours. Appropriate fitting was verified by corneal topography and fluorescein slit-lamp examination. Participants assigned to the RCO group received additional RLRL therapy delivered by a desktop device (Eyerising, China) two times per day for 3 min per session, 5 days per week. Each session should be spaced at least 4 hours apart. Detailed information and operational methods were described in the previous study.[11] In brief, the device emitted low-level red light at 650±10 nm wavelength, providing roughly 100 lux and 0.29 mW from the pupil to the fundus via semiconductor laser diodes. To ensure good compliance, guardians were reminded if participants missed two consecutive sessions.

Outcomes

Follow-up assessments were conducted at 6-month, 9-month and 12-month follow-up visits, with additional visits at 1-month and 3-month for participants in the RCO group. All the research staff underwent standardised training before study initiation, and measurements at each visit were consistently performed by the same masked examiner using the same instruments.

The primary outcome was the axial length (AL) change from baseline to 12 months, measured by Myopia Master (Oculus, Germany). Measurements were repeated and averaged until the maximum allowable variation was ≤0.02 mm. AL was selected as the primary outcome because the SER was unsuitable for assessing myopia progression in participants receiving ortho-k treatment. The secondary outcome was the macular thickness (MT) change from baseline to 12 months, measured by spectral-domain optical coherence tomography (OCT) (3D OCT-1 Maestro, Topcon, Japan) with a 6 mm-diameter volumetric scan (512 A-scans×128 B-scans) centred at the fovea. Pupil dilation was not performed, since previous findings found that pupil dilation did not affect scan repeatability in participants with transparent ocular media.[15 16] OCT images were accepted only if alignment was accurate, eye movements were minimal and structural signal quality ≥7/10; otherwise, images would be retaken. MT, defined as the average distance between the internal limiting membrane and outer segments/retinal pigment epithelium junction boundary, was automatically calculated and averaged by the built-in software.[17]

Adverse events

At all follow-up visits, participants and their guardians completed structured questionnaires to document ocular symptoms, including but not limited to eye pain, eye itching, dry eye, short-term glare, flash blindness, afterimages and general discomfort. Slit-lamp examination and fluorescein staining were conducted to detect potential complications associated with ortho-k wearing. BCVA was assessed and OCT images were reviewed for any structural changes. Serious adverse events were defined as the reduction in visual acuity of 2 or more lines, the presence of central visual field scotoma, functional visual loss or structural damage identified through OCT scans. Participants who reported serious adverse events would be withdrawn immediately from the intervention.

Sample size calculation

The sample size was calculated based on previously reported AL changes of 0.02 mm in the RCO group (95% CI 0.19 to 0.34) and 0.27 mm in the ortho-k group (95% CI −0.08 to 0.03) over 12 months.[18] Using a two-sided α of 0.05 and 80% power, the required sample size was estimated at 11 participants per group.

Statistical analysis

Statistical analyses were performed using R V.4.4.1. A two-sided $p<0.05$ indicated statistical significance. Data from the right eye were used for analysis. Continuous variables were presented as mean±SD, and categorical variables as counts (percentages). Treatment compliance was calculated as the percentage of completed sessions out of the total assigned. Longitudinal mixed models using unstructured covariance matrices and restricted maximum likelihood method were used to evaluate changes in primary (AL) and secondary (MT) outcomes. Group, visit and group-by-visit interactions were modelled as fixed effects, and baseline age, sex and baseline outcome measures were included as covariates. Subjects were included as a random factor. Estimated mean differences with 95% CIs were reported. Additionally, AL change was classified at three cut-offs: <−0.1 mm, <−0.05 mm and <0.1 mm, based on previous studies.[18–21] Proportions of

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children showing clinically significant axial shortening (AL change ≤−0.05 mm, a change exceeding typical measurement error) and efficient myopia control (AL changes <0.10 mm at the 12-month follow-up visit) were calculated for each group.

Primary analysis followed a modified intention-to-treat principle, including all randomised participants who received the intervention and completed at least one follow-up. Those who discontinued or switched treatments were classified as withdrawals. Missing data were not imputed. The per-protocol sensitivity analysis included only participants who adhered to the assigned treatment with complete follow-up. Post hoc analysis was conducted to compare the proportions of children with AL shortening of >0.05 mm between groups.

RESULT

Baseline characteristics

A total of 33 children were initially screened for eligibility. Of these, 7 were excluded and finally 26 eligible children were enrolled and randomised into either the RCO group (n=11) or the ortho-k group (n=15). Of these children, 25 children (96.2%) completed the trial, and one child (3.8%) withdrew due to family relocation after finishing the 6-month follow-up. The participant flow through the trial is detailed in figure 1. The mean age was 12.00±1.13 years for the ortho-k group and 11.9±1.14 years for the RCO group. The ortho-k group contained 10 female (66.7%), and the RCO group contained eight female (72.7%). The mean SER, AL, MT and logMAR were −2.93±1.25 D, 24.74±0.67 mm, 278.70±13.53 µm, −0.14±0.08 for the ortho-k group and −2.77±1.89 D, 24.68±0.65 mm, 277.12±12.25 µm, −0.15±0.08 for the RCO group, respectively (online supplemental table S1). The median RLRL treatment compliance rate in the intervention group was 71% (IQR, 55%–85%).

Primary outcome

The RCO group exhibited sustained negative AL changes, with an annual mean AL change of −0.124 mm (95% CI −0.164 to −0.084). AL has the largest shortening within the first month, remained relatively stable from months 3 to

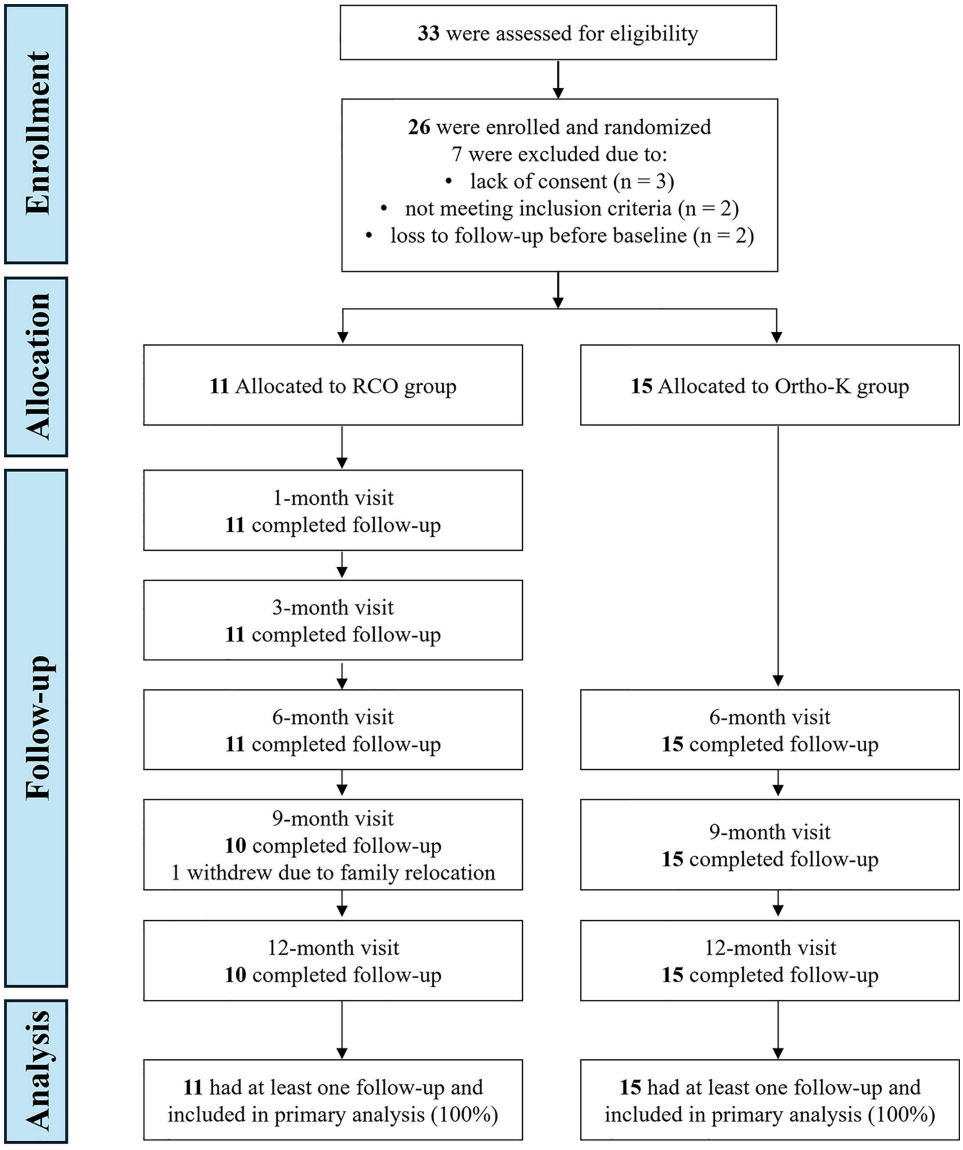

Figure 1 Consolidated standards of reporting trials flow diagram. Ortho-K, orthokeratology; RCO, repeated low-level red-light therapy combined OK.

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Table 1 Cumulative adjusted mean changes in axial length from baseline to 12 months at each time point in the RCO group and the ortho-k group

Visit	Cumulative adjusted mean (95% CI)		Mean difference (95% CI)*	P value
	RCO (n=11)	Ortho-k (n=15)		
AL changes				
1 month	−0.044 (−0.084 to 0.005)	/	/	/
3 months	−0.058 (−0.097 to 0.019)	/	/	/
6 months	−0.058 (−0.097 to 0.019)	0.043 (0.01 to 0.077)	−0.101 (−0.153 to 0.050)	<0.001
9 months	−0.110 (−0.150 to 0.070)	0.077 (0.043 to 0.11)	−0.187 (−0.239 to 0.134)	<0.001
12 months	−0.124 (−0.164 to 0.084)	0.102 (0.068 to 0.136)	−0.226 (−0.279 to 0.174)	<0.001
MT changes				
1 month	0.597 (0.183 to 1.01)	/	/	/
3 months	0.866 (0.452 to 1.279)	/	/	/
6 months	0.687 (0.273 to 1.100)	0.047 (−0.308 to 0.401)	0.640 (0.094 to 1.186)	0.022
9 months	0.914 (0.488 to 1.340)	0.106 (−0.249 to 0.460)	0.808 (0.253 to 1.363)	0.004
12 months	0.730 (0.304 to 1.156)	0.210 (−0.145 to 0.564)	0.520 (−0.035 to 1.075)	0.066

A longitudinal mixed model that adjusted for baseline age, sex, baseline outcome parameter, group, visit and the interaction between group and visit was used to calculate the cumulative adjusted mean changes at each time point to demonstrate treatment efficacy. The random slope of the change in each parameter over visit was included as a random factor.

*AL and MT changes in the repeated low-level red-light therapy combined with orthokeratology group minus those in the orthokeratology group.

AL, axial length; MT, macular thickness; Ortho-k, orthokeratology; RCO, repeated low-level red-light therapy combined OK.

6, and then continued to decrease thereafter. The ortho-k group showed consistent axial elongation over 12 months, although at a slower pace, with a total annual increase of 0.102 mm (95% CI 0.068 to 0.136) (table 1, figure 2).

When comparing the RCO with the ortho-k group, the adjusted mean differences in AL changes progressively increased over time: −0.101 mm (95% CI −0.153 to −0.050 mm) at 6 months, −0.187 mm (95% CI −0.239 to −0.134 mm) at 9 months and −0.226 mm (95% CI, −0.279 to −0.174 mm) at 12 months (all p<0.001). The mixed model indicated that visit (p<0.001) and group-by-visit interaction (p<0.001) were significantly associated with AL changes (online supplemental table S2). After adjusting for confounders, the monthly axial elongation averaged 0.010 mm (95% CI, 0.005 to 0.014) in the ortho-k group. The significant group-by-visit interaction suggested that the efficacy of RCO therapy in slowing axial elongation became increasingly apparent over time compared with the ortho-k alone, with 0.017 mm (95% CI, −0.023 to −0.012) per month slower than that of ortho-k alone.

Secondary outcome

As shown in figure 2, the ortho-k group exhibited a slight adjusted MT increase of 0.210 µm (95% CI −0.145 to 0.564) at the 12-month. While the RCO group showed greater thickening (0.730 µm), the between-group difference was not significant at 12 months, despite being statistically significant at both the 6-month and 9-month assessments. In the RCO group, the macular retina thickened from 0 to 3 months after treatment, and there were a fluctuation and overall trend of thinning in MT from 3 months to 12 months. Older age (p=0.029) and assignment to the RCO group (p=0.023) were significantly associated with greater macular thickening (online supplemental table S3).

Adverse event

No severe adverse events were reported. All participants maintained a BCVA logMAR ≤0.0 at 12 months, with no sudden vision loss, structural retinal abnormalities or corneal complications detected. Moreover, none of the participants required additional spectacle correction during the day for distance tasks.

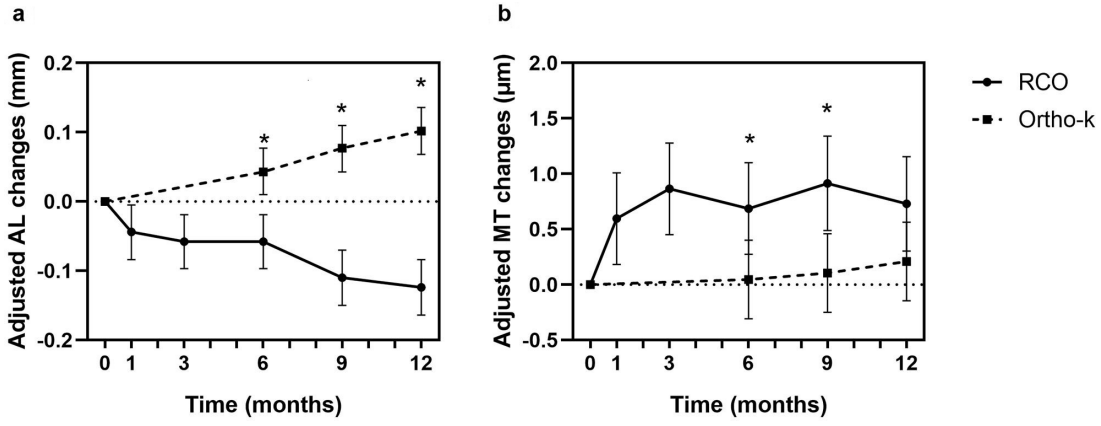

Figure 2 Adjusted changes in AL (a) and MT (b) from baseline to 12-month follow-up at each time point. Data were presented as the adjusted value (with 95% CI) estimated by the mixed model. AL, axial length; MT, macular thickness; Ortho-k, orthokeratology; RCO, repeated low-level red-light therapy combined OK.

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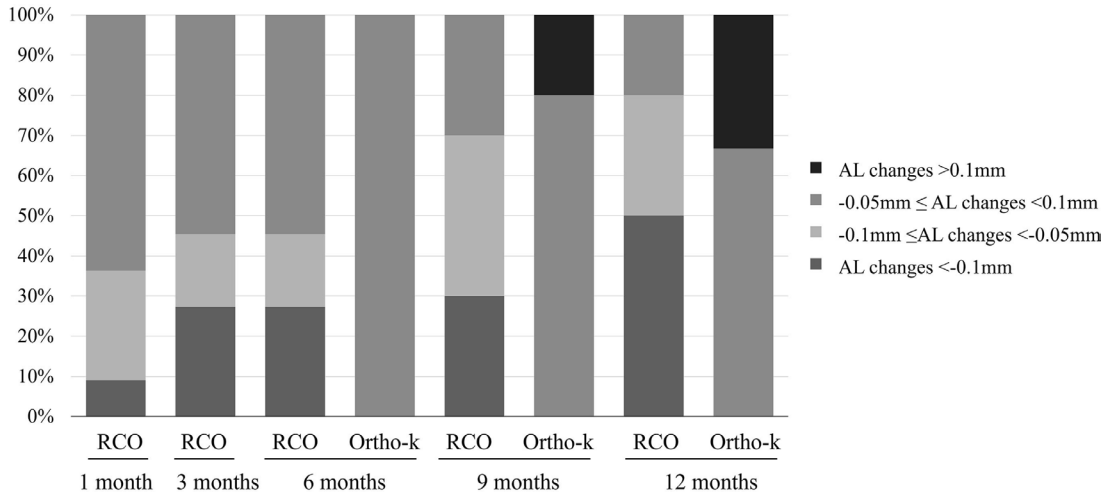

Figure 3 Distribution of changes in AL at each visit for the RCO and ortho-k groups. AL, axial length; Ortho-k, orthokeratology; RCO, repeated low-level red-light therapy combined OK.

Sensitivity analysis

A total of 25 children were included in the sensitivity analysis based on the per-protocol principle. Results were consistent with those of the primary analysis. The annual mean adjusted AL changes in the RCO group minus AL changes in the ortho-k group were −0.214 mm (95% CI −0.259 to −0.169) (online supplemental table S4).

Post hoc analysis

Over 12 months, all the participants in the RCO group showed <0.10 mm in AL changes, whereas only 66.7% (10/15) of those in the ortho-k group achieved similar control. None of the participants in the ortho-k group experienced AL shortening during follow-up. In contrast, the RCO group showed significantly higher proportions with AL shortening at 6, 9 and 12 months (45.5% (5/11), 70.0% (7/10), 80.0% (8/10); all $p<0.05$), with rates of 36.4% (4/11) at 1 month and 45.5% (5/11) at 3 months. Furthermore, 27.3% (3/11), 40.0% (4/10) and 50.0% (5/10) of them exhibited AL shortening exceeding −0.1 mm, respectively (figure 3).

DISCUSSION

In this RCT of Caucasian Spanish children, we found that RCO significantly slowed the axial elongation over 12 months compared with ortho-k alone. Additionally, we observed significant AL shortening but no significant MT thickening during the combination therapy. This study demonstrated the synergistic effect of RLRL on ortho-k in a European population, for which data had been limited.

After 12 months, the adjusted mean AL change was −0.111 mm in the RCO group, whereas the ortho-k group continued to exhibit a modest axial elongation of 0.104 mm. Despite the satisfactory efficacy of ortho-k in this cohort, adding RLRL therapy to ortho-k provided a significantly greater myopia control effect and slowed the axial elongation by 0.215 mm annually more than ortho-k monotherapy, potentially lowering the long-term risk of vision-threatening complications such as myopic maculopathy.[22] Compared with Xiong *et al*,[18] who reported a −0.29 mm adjusted AL difference between RCO and ortho-k groups in Chinese children aged 8–13, our European cohort showed a smaller effect (−0.215 mm). The former study specifically enrolled poor ortho-k responders with rapid myopia progression, which may magnify the incremental benefit of the combination therapy. In contrast, our study included a wider baseline SER distribution without stratifying prior progression rates, likely incorporating individuals with a broader range of natural progression rates. Moreover, limiting the age group to 10–13 may also affect the generalisability of our findings to younger myopic children, among whom ortho-k monotherapy is already highly effective. Ethnic differences may also contribute, as European children generally experience slower myopia progression and variable treatment responses.[23 24] Interestingly, both their study and ours demonstrated 30%–40% AL shortening within the first month, similarly indicating an early and sustained effect in the RCO group. The proportion of children in the RCO group who exhibited AL shortening was 44.8% after 12 months, compared with 80% in our study. Given the small sample size and different inclusion criteria across studies, it remained unclear how much ethnicity independently influences treatment response and required further investigation through multi-ethnic studies. Notwithstanding these considerations, our results align with those findings observed in East Asia[12 18 25] and further support the efficacy and safety of RCO as a broadly applicable myopia control approach across populations with different racial backgrounds.

Another finding is the time-dependent synergistic effect of the combined therapy. AL shortening in the RCO group became increasingly apparent over 12 months, with a significantly slower axial elongation rate (−0.017 mm/month) than ortho-k alone. A significant treatment effect was already observed within the first month, indicating the early efficacy of the combined approach over a relatively short period. Given that many myopia control interventions, including RLRL, show maximal effects in the first year followed by a plateau phase,[26] the maintenance of AL shortening of RCO in the long term still needs further investigation.

Regarding secondary outcomes, the adjusted MT increase at 12 months was greater in the RCO group than in the ortho-k group, but the difference was not statistically significant. Previous studies evaluating MT changes after RLRL therapy have reported inconsistent results.[27–31] Zhao *et al* found no significant changes within the first month,[27] whereas Liu *et al* observed transient retinal thickening followed by gradual thinning after 3 months,[28] which is similar in our RCO group. Another study found sustained MT thickening after 1 month of RLRL treatment in school-age children.[31] While previous studies hypothesised that increased retinal thickness after RLRL may reflect altered

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metabolic activity, microvascular perfusion or a neurotrophic effect,[28] in our study, it remains uncertain, as angiographic or retinal-layer-specific data were unavailable.[32 33] Although we observed statistically significant MT increase at several time points, the subtle MT changes fall within the reported repeatability limits of spectral-domain OCT in children.[34 35] It may reflect test-retest variability rather than structural alteration. Importantly, no participant demonstrated signs of retinal toxicity, abnormal reflectivity or morphological disruption. These observations reinforce the retinal safety of RCO and support the use of MT as a safety parameter.[30] Moreover, since the sample size was calculated based on the primary outcome, comparisons of other parameters might be underpowered, potentially leading to false-negative results. Further studies are warranted to determine the significance of the retinal alterations and whether they represent a beneficial effect.

No severe adverse events were reported during the study. All participants maintained BCVA of logMAR 0.0 or better at the 12-month visit. No corneal abnormalities were detected, and none of the participants receiving RLRL therapy showed structural damage on OCT. Overall, the combination of RLRL and ortho-k did not increase the risk of adverse events over 12 months.

This study has several limitations. First, although post hoc power analysis via G-power software indicated sufficient power (>95%) to detect AL changes, the small sample size limited the possibility of further association analysis and the generalisability. Second, the single-centre open-label design may introduce biases. Third, the 12-month follow-up period is relatively short, making it challenging to fully evaluate the long-term sustainability of RCO intervention effects and its impact on retinal structure over time. Recently, choroidal thickness has been used as an important early indicator of treatment response in ortho-k and RLRL. Although our study demonstrated significant AL reduction in the RCO group, choroidal thickness was not assessed due to the limitations of the OCT device. Whether the differential AL changes between groups were related to choroidal response should be further investigated using EDI-OCT or SS-OCT. Future studies should include long-term multicentre RCTs with larger sample sizes to validate the findings and explore the durability and safety of RLRL combination therapy in different populations.

CONCLUSION

Our study confirmed that RCO was an effective and safe myopia control strategy in Caucasian Spanish children, supporting its potential generalisability across diverse ethnic groups. The combination therapy significantly reduced AL elongation compared with using ortho-k alone, without significant MT difference at 12 months. No serious adverse event was observed during the study. Moreover, AL shortening is sustained over 12 months. Moving forward, ortho-k lenses may provide clear daytime vision, while adding RLRL could further enhance myopia control. Further studies are needed to understand its long-term efficacy, safety and the potential underlying mechanisms.

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Competing interests Y-MA and ZZ are employees of Eyerising International. ZZ reported having a patent for CN110237432A. No other conflicting relationship exists.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Institutional Review Board of Centro Fernandez-Velazquez (approval number (01/2023), approval date 2023/09/01). Participants gave informed consent to participate in the study before taking part.

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