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Efficacy comparison of atropine, orthokeratology and repeated low-level red-light therapy for myopia control in children: a systematic review and network meta-analysis

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ABSTRACT

Objectives This study aimed to compare the efficacy of different interventions for myopia control in children, including 0.01% atropine (AP), orthokeratology (Ortho-k), and repeated low-level red-light therapy (RLRL), and their combinations by conducting a network meta-analysis.

Methods We searched for randomised controlled trials (RCTs) in PubMed, Web of Science and Embase. The primary outcomes were the mean changes in the cycloplegic spherical equivalent (SE) and axial length (AL) at the 12-month follow-up. A Bayesian random-effects network meta-analysis was performed to estimate pooled weighted mean differences and 95% credible intervals.

Results The analysis included 41 RCTs with 6434 eyes. Compared with the control group, all interventions were found to be effective at slowing myopia progression, combining direct and indirect evidence at the 12-month follow-up: RLRL therapy (AL −0.31 (0.39, 0.24), p<0.05; SE 0.76 (0.54, 0.98), p<0.05), 0.01% atropine (AL −0.13 (−0.20, 0.07), p<0.05; SE 0.25 (0.08, 0.42), p<0.05), Ortho-k therapy (AL −0.16 (−0.26, 0.06), p<0.05; SE 0.58 (0.05, 1.13), p<0.05) and 0.01% atropine+Ortho-k therapy (AL −0.27 (−0.38, 0.16), p<0.05; SE 0.76 (0.23, 1.31), p<0.05). The cumulative probability ranking suggested that RLRL therapy was the most effective intervention in slowing AL, followed by 0.01% atropine+Ortho-k, Ortho-k and 0.01% atropine.

Conclusions This network meta-analysis provides evidence that RLRL, 0.01% atropine, Ortho-k and 0.01% atropine+Ortho-k are all effective in suppressing myopia progress. In terms of long-term treatment efficacy in slowing AL and SE procession, RLRL was the most effective intervention.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A number of interventions, including low-dose atropine and orthokeratology, have been demonstrated to slow the progression of myopia in children. Repeated low-level red light (RLRL) therapy is a comparatively recent intervention for which there is encouraging but limited comparative evidence.

WHAT THIS STUDY ADDS

⇒ This Bayesian network meta-analysis, which was based on 41 randomised controlled trials, found that RLRL was associated with the greatest reduction in axial elongation and refractive error progression compared with low-dose atropine and orthokeratology.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support the potential of RLRL as a leading non-invasive intervention for paediatric myopia control and may inform clinical decisions and future policy on early intervention strategies.

INTRODUCTION

Myopia is a refractive error characterised by images of distant objects in front of the retina, resulting in blurred vision, mainly in childhood.[1] It is estimated that by 2050, nearly half of the world's population will be myopic, and nearly 10% will have high myopia.[2] Higher myopia may result in comorbidities associated with significantly increased risks of severe and irreversible loss of vision, which in turn leads to significant productivity loss and economic burden on a global scale.[3 4]

It is particularly important to conduct myopia intervention as early as possible. At present, common interventions can be divided into the following four categories. First, optical lenses, such as orthokeratology (Ortho-k) lenses, specially designed spectacles, and red-light and violet-light therapy, are needed. Second, various concentrations of atropine (AP) are used as pharmacological agents. Third, environmental factors, such as outdoor lighting, are used.[5] Fourth, combinations of various therapies, such as low-concentration AP combined with Ortho-k, low-concentration AP combined with defocus incorporated multiple segments, repeated low-level red-light (RLRL) combined with Ortho-k.[6]

Interventions for myopia have long been widely used in East Asia. The main intervention methods include AP, Ortho-k, combination therapy and the emerging RLRL.[7 8] Therefore, this study aimed to determine the most effective interventions for preventing the progression of myopia in children and ranked them to provide more comprehensive and reliable evidence-based medical recommendations.

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METHODS

Study registration

The International Prospective Register of Systematic Reviews (PROSPERO) had prospective registration of the protocol for this systematic review (identifier: CRD42024588568). Each study complied with the Declaration of Helsinki's principles. The reporting of this NMA was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2015 NMA Checklist.[9]

Search methods and eligibility criteria

We searched for English-language randomised controlled trials (RCTs) on PubMed, EMBASE and Web of Science. Search strategy and eligibility criteria are in online supplemental additional file 1.

Study selection and data collection

Two investigators (Z-TZ and XJ) independently assessed the titles, abstracts and full-text documents for inclusion with Zotero7. They engaged in a targeted dialogue to address any disputes. We obtained the following information from each trial: (1) first author, (2) publication year, (3) period of follow-up, (4) intervention method, (5) sample size, (6) baseline parameters (axial length (AL), age and spherical equivalent (SE)) and (7) end points (average change in AL and SE).

Outcomes

We analysed two follow-up times that had complete data and sufficient intervention types, and the rest were discussed only. The primary outcome was outcomes with a longer follow-up period. As primary outcomes, we used SE (in dioptres) and AL (in millimetres) at the 12-month follow-up, and the 6-month follow-up data as secondary outcomes. Further information is provided in the online supplemental additional file 1.

Quality assessment

The Confidence in Network Meta-Analysis (CINeMA) was used to assess the quality of the studies. Further information is provided in the online supplemental additional file 1.

Statistical analysis

We first estimated weighted mean differences and 95% credible interval (Crl) via direct comparisons via a random effects model.

We also computed probabilities for each therapy at each conceivable rank, as well as cumulative ranking probabilities, via the surface under the cumulative ranking curve. All the rankings used the 'placebo/single-vision spectacle lenses/no treatment' reference group.

R software was used to examine the heterogeneity of the included studies prior to calculating the effect size. I^2 was used to assess the variability between studies.

The node-splitting approach was used to conduct local inconsistency testing for both direct and indirect comparisons.

Sensitivity analysis was used to assess the impact of the studies on the random effects model.

Publication bias was assessed via funnel plots and Egger's regression test.

For the funnel plot, we used a comparison-adjusted funnel plot instead of the traditional funnel plot. We performed a subgroup analysis and meta-regression of the sample size, year of publication, risk of bias, myopia progression (AL, SE at baseline) and non-myopic status.

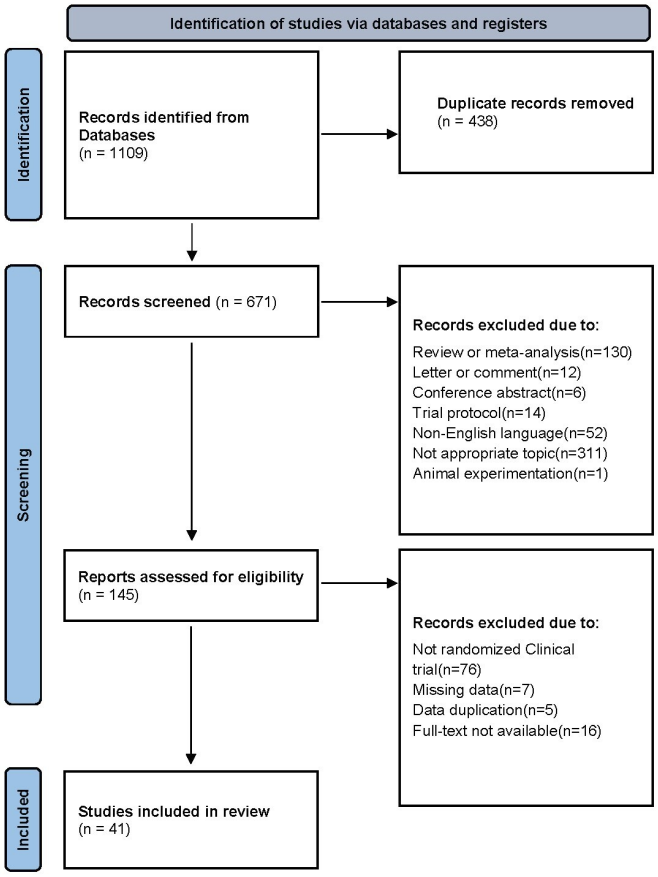

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

All the details of the Methods are shown in online supplemental additional file 1.

RESULTS

Literature results and basic characteristics

Figure 1 shows the study analysis flow chart. After removing duplicates, reviewing titles and abstracts and detailed evaluating, 41 eligible articles were identified from the initial 1109 articles. The combined data from all 41 studies included information about 6434 eyes (online supplemental additinal file 2). Online supplemental additional file 3 lists the studies that did not meet the eligibility criteria and their exclusion reasons. Analysis included 41 trials covering 5 main intervention types: 8 combining AP+Ortho k, 10 using Ortho-k alone, 12 applying RLRL and 20 focusing on AP alone. Two studies reported only SE, 11 only AL and 28 both outcomes. 20 trials reported results from both 6-month and 12-month follow-ups, while 9 and 12 studies reported data from only the 6-month and 12-month follow-ups, respectively.

Online supplemental additional file 4 presents the risk of bias in included studies. Most trials reported sufficient methods for random sequence generation, allocation concealment and outcome assessment blinding. These factors suggest the analysis has an overall low to moderate risk of bias. The CINeMA analysis revealed all studies received a 'high' confidence rating, indicating good quality (online supplemental additional file 5).

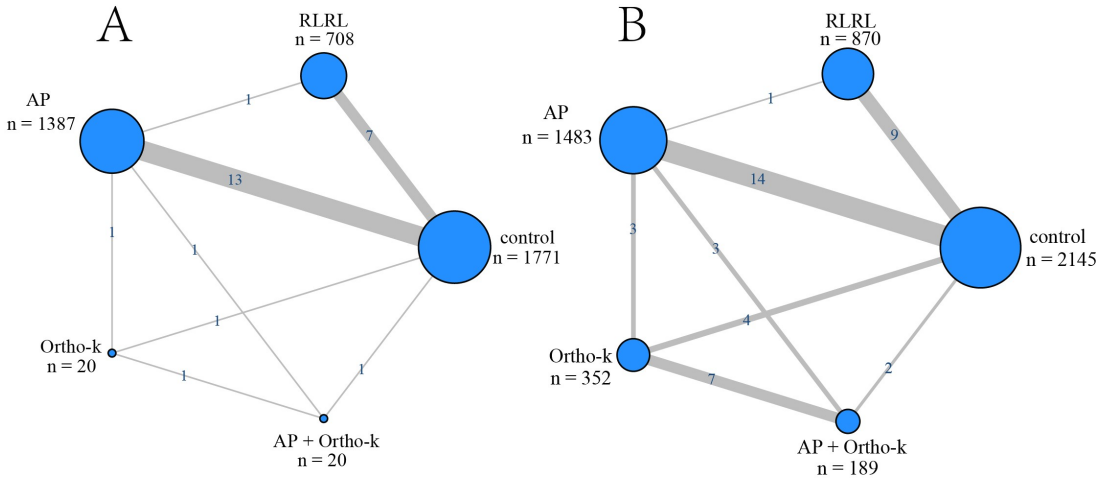

Figure 2 Network of direct comparisons for myopia interventions. Network plots for efficacy: (A) mean axial length change; (B) mean spherical refraction change. The number of eyes allocated to each therapy is reflected in the node size. A line connects treatments that have direct comparisons. The number of attempts to assess the comparison is shown in the line thickness. AP, atropine; Ortho-k, orthokeratology; RLRL, repeated low-level red-light.

NETWORK META-ANALYSIS RESULTS

Evidence network and direct comparison

All interventions were connected through direct comparison data (figure 2).

Consistency test

The AL and SE test findings in deviance information criterion were similar for consistency and inconsistency models (difference values <3), indicating negligible global inconsistency. Therefore, a consistency model could be applied. Local discrepancies of AL and SE were tested independently via the node splitting method: AL showed no significant differences between interventions except AP+Ortho k versus control ($p<0.05$), while SE outcomes remained non-significant across all comparisons ($p>0.05$) (online supplemental additional file 6).

Heterogeneity test

Most direct comparisons showed high heterogeneity ($I^2>50\%$): AP versus control and RLRL versus control at 6-month and 12-month follow-ups in AL and SE; Ortho-k versus control in AL; AP+Ortho k versus Ortho-k and RLRL versus AP in AL at 6 months; AP versus Ortho-k and AP+Ortho k versus control in AL at 12 months (online supplemental additional file 7).

Axial length

Compared with the control group, statistically significant effects were found for: RLRL (6-month follow-up, −0.20 (−0.25, 0.15), $p<0.01$; 12-month follow-up, −0.31 (0.38, –0.24), $p<0.01$); AP (6-month follow-up, −0.13 (−0.18, –0.08), $p<0.01$; 12-month follow-up, −0.14 (−0.22,–0.06), $p<0.01$); Ortho-k (6-month follow-up, −0.09 (−0.14, –0.03),

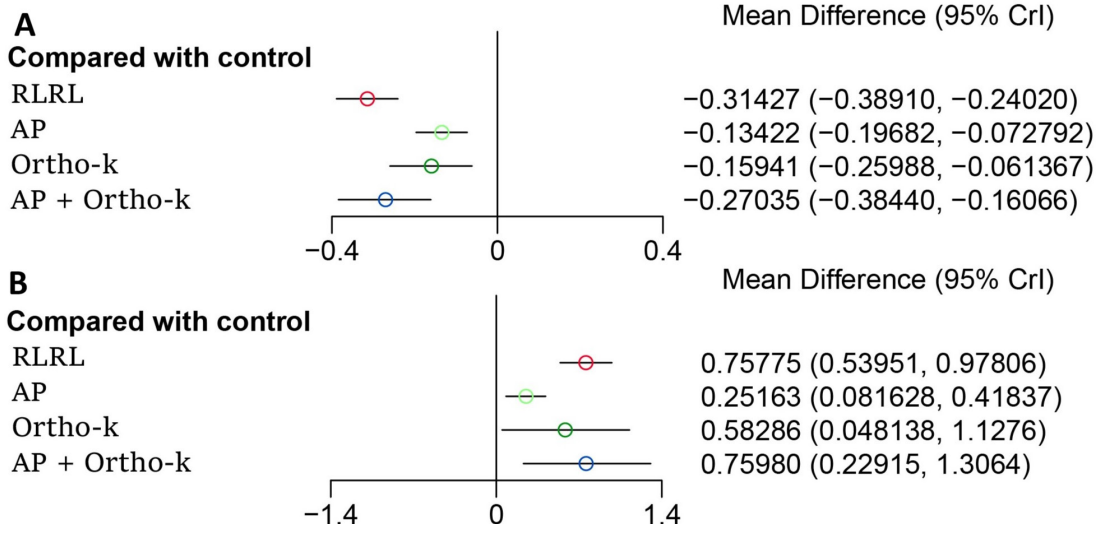

Figure 3 Forest plots of the network meta-analysis of different treatments compared with the control group at the 12-month follow-up. (A) The axial length and (B) the cycloplegic spherical equivalent. Each horizontal line on the forest plots represents the mean difference in individual interventions (compared with the control group), with the mean difference plotted as a circle and the 95% credible interval plotted as a line. AP, atropine; Ortho-k, orthokeratology; RLRL, repeated low-level red-light therapy.

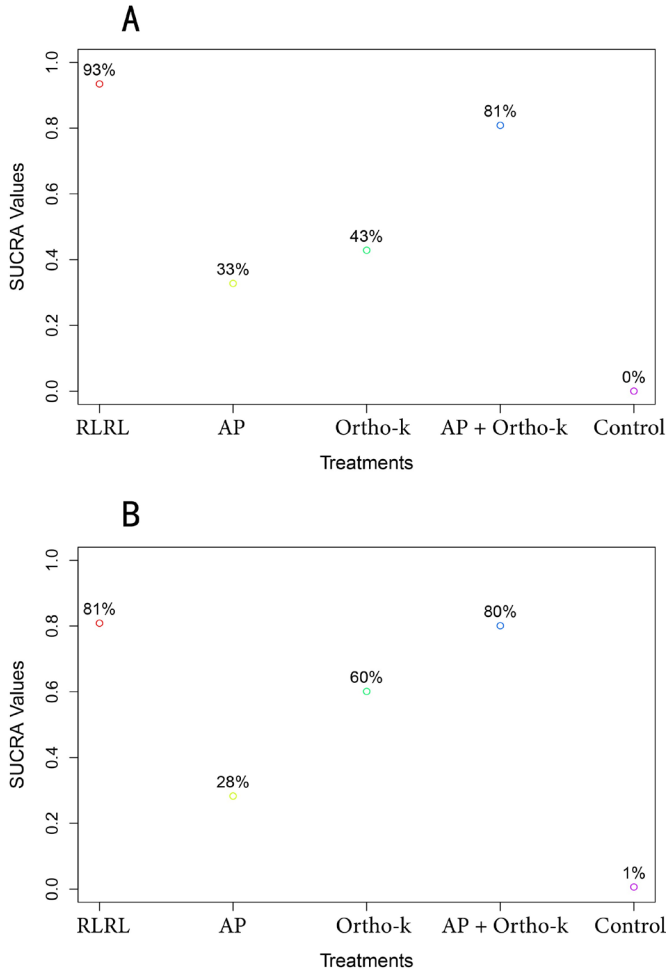

Figure 4 Surface under the cumulative ranking curve (SUCRA) rankings for treatment efficacy. (A) The axial length and (B) the spherical equivalent. The plot presents the SUCRA values for each treatment, which reflect the relative probability of each treatment being ranked highest among the alternatives. A higher SUCRA value indicates a greater likelihood of the treatment achieving the best outcome across all comparisons. AP, 0.01% atropine; RLRL, repeated low-level red-light therapy; Ortho-k, orthokeratology.

p=0.02; 12-month follow-up, −0.24 (−0.39, –0.09), p<0.01) and AP+Ortho k (12-month follow-up, −0.45 (−0.71, –0.20), p<0.01) (online supplemental additional file 7).

Compared with the control group (combining direct and indirect evidence at 12-month follow-up), RLRL (−0.31 (−0.39, –0.24)), AP (−0.13 (−0.20, –0.07)), Ortho-k (−0.16 (−0.26, –0.06)) and AP+Ortho k (−0.27 (−0.38, –0.16)) all showed significant effects (p<0.05) (figure 3A). For axial progression slowing, cumulative probability rankings were: RLRL (93.4%)>AP+Ortho-k (80.9%)>Ortho k (42.8%)>AP (32.8%) at 12-month follow-up (figure 4A) and RLRL (94.8%)>AP+Ortho-k (78.5%)>AP (48.6%)>Ortho k (27.9%) at 6-month follow-up. These results indicate RLRL therapy may be the most effective axial growth delay intervention (online supplemental additional file 8A).

Spherical equivalent

For SE, RLRL (6-month follow-up, 0.27 (0.17, 0.38), p<0.01; 12-month follow-up, 0.75 (0.55, 0.95), p<0.01) and AP (6-month follow-up, 0.28 (0.17, 0.40), p<0.01; 12-month follow-up, 0.26 (0.09, 0.42), p<0.01) showed statistically significant effects compared with single-vision spectacle (SVS) lenses/placebo. The p values for Ortho-k and AP+Ortho k could not be calculated due to small sample sizes (online supplemental additional file 7).

Compared with the control group (with both direct and indirect evidence at 12-month follow-up), RLRL (0.76 (0.54, 0.98), p<0.05), AP (0.25 (0.08, 0.42), p<0.05), Ortho-k (0.58 (0.05, 1.13), p<0.05) and AP+Ortho k (0.76 (0.23, 1.31), p<0.05) all showed effects (figure 3B). Due to the temporary SE-reducing effect of Ortho-k, separate comparisons were required: Ortho-k and AP+Ortho k were compared separately, and RLRL and AP were compared separately. For SE progression slowing, cumulative probability rankings were: RLRL (80.8%)>AP (28.3%) and AP+Ortho k (80.0%)>Ortho k (60.4%) at 12-month follow-up (figure 4B), and AP+Ortho k (89.9%)>Ortho k (59.8%) and RLRL (52.9%)>AP (46.8%) at 6-month follow-up (online supplemental additional file 8B).

Sensitivity analyses

When each study was excluded sequentially, RLRL, AP and Ortho-k subgroups showed no qualitative changes in combined effects. In subgroups using other myopia interventions as references, heterogeneity sharply decreased after excluding three studies. Due to few included studies, we could not analyse heterogeneity changes postexclusion. We explored possible heterogeneity sources from these three studies in the discussion section. Overall, results remained stable (online supplemental additional file 9).

Subgroup analysis and meta-regression

Regression analysis included sample size, publication year, risk of bias and baseline myopia progression (AL, SE) as covariates. These variables did not correlate with dependent outcomes (95% CrI all through 0). Thus, the heterogeneity source could not be explained and requires further discussion (online supplemental additional file 10).

Subgroup analyses were conducted based on whether included studies enrolled only myopic children (covariate=0) or also included non-myopic children (covariate=1). Intervention effects demonstrated higher consistency and significance in myopic-only child studies. Conversely, intervention effects exhibited greater variability and were partially non-significant in studies encompassing non-myopic children. This pattern indicates that non-myopic children's inclusion may have compromised intervention effect uniformity and intensified heterogeneity (online supplemental additional file 11).

Publication bias

The comparison-adjusted funnel plot of AL and SE revealed that each point was symmetrical and the Egger's regression test confirmed the funnel plot symmetry (p>0.05), suggesting that the publication bias was not significant (online supplemental additional file 12).

DISCUSSION

In this study, we conducted a network meta-analysis (NMA) to evaluate the effectiveness of various therapies in slowing the progression of myopia in children.

The main findings of our analysis are as follows: First, compared with the control group, all interventions (RLRL, AP, Ortho-k, AP+Ortho k) demonstrated statistically significant effectiveness (p<0.05). Second, in general, efficacy of interventions in

slowing myopia progression ranked as follows at the 12-month follow-up for AL: RLRL>AP+Ortho-k>Ortho k>AP; for SE: RLRL>AP and AP+Ortho k>Ortho k (RLRL in first place).

With the emergence of new interventions for myopia and the increasing number of RCTs, several meta-analyses have investigated various interventions for myopia control. A 2016 NMA[10] comparing various non-pharmacological and pharmacological interventions revealed that low-dose AP (0.01%) was more effective than Ortho-k for long-term treatment. But our study revealed different results at the 12-month follow-up. Similar to our study, a 2023 Bayesian NMA by Zhang *et al*[11] revealed that Ortho-k, RLRL, 0.01% AP and 0.01% AP+Ortho k were significantly different from control in AL or SE, but RLRL had only moderate efficacy, which is different from our study. However, Zhang's study included only one trial on RLRL, suggesting that further evidence is needed to update these conclusions. In a more recent 2024 Bayesian NMA by Zaabaar *et al*,[12] RLRL was the only intervention associated with significantly decreased AL elongation and SE growth across different wavelengths of light.

As RLRL studies emerged mainly between 2022 and 2024, it is important to conduct updated evidence-based analyses. In addition, we focused on interventions commonly used in East Asia, ensuring that each intervention had a sufficient number of RCTs. The data were analysed across different follow-up durations, providing a clearer picture of intervention efficacy over time. Zaabaar's 2024 study, which included more RLRL trials, found reduced myopia progression in terms of AL and SE, though network analysis was not performed.[13] RLRL has generated great interest in myopia control. Initial studies on outdoor activities suggested a possible role for light exposure in slowing myopia progression,[14] leading to the hypothesis that RLRL, with its similar optical properties, might exert a comparable effect. Current research suggests three potential mechanisms for RLRL. First, RLRL may relieve scleral hypoxia by enhancing choroidal blood flow, thereby reducing oxidative stress and inflammation while increasing scleral collagen levels.[15] Second, it may inhibit axial elongation via choroidal thickness, reducing vitreous cavity growth.[16] Third, thickened choroid pushes the retina forward, reducing the distance from the cornea to the retina and slowing axial elongation.

In our study, RLRL was significantly effective in controlling myopia, outperforming all other interventions, including AP+Ortho k, which ranked first in previous meta-analyses.[11] A 2024 single-masked RCT reported that RLRL unexpectedly reversed increased dioptre and AL, achieved AL regression and decreased dioptre during 1 year of treatment.[17] Other studies have shown similar results but only in early follow-up periods, with RLRL inhibiting AL growth and SE dioptre increasing.[18]

Choroid thickening may explain the reduction in AL with RLRL. RLRL significantly thickens the choroid,[19] and with prolonged treatment, the thickening range decreases continuously, consistent with the trend that AL initially decreases, then elongates.[20] As a result of choroid thickening, RLRL delays axial elongation and possibly causes regression. Despite this, AL shortening is not solely caused by choroidal thickening. According to research in adults,[15] RLRL improves local blood flow, which is similar to that in children, as indicated by the choroidal vascularity index, which mitigates scleral hypoxia and inflammation.[21] Furthermore, studies have shown no change in anterior segment morphology after RLRL, suggesting AL may be caused by posterior segment morphology.[19]

The RLRL has been shown to cause ocular injuries when it exceeds the maximum permissible exposure limit, leading to vision loss in some cases.[22] Further studies are needed to clarify its long-term safety, rebound effects and underlying mechanisms.

Ortho-k uses contact lenses to flatten the cornea and reduce peripheral hyperopic defocus to control myopia. Studies have shown Ortho-k effectively slows axial elongation, including large RCTs. 102 children in a large RCT had significantly slower axial growth in the Ortho-k group than in the control group ($p<0.01$).[23] In another multiarm study,[24] Ortho-k reduced AL elongation by 26.8% compared with SVS group. In evidence-based medicine, Ortho-k has also been shown to affect myopia progression and axial elongation. In contrast, Ortho-K temporarily reshapes the cornea, making SE inaccurate. The effectiveness of myopia slowing may be overstated because most studies did not measure SE after discontinuing use.

Ortho-k provides long-term effects by redistributing the corneal epithelium and thinning the central corneal epithelium. This reshaping reduces peripheral hyperopic defocus, potentially limiting eye elongation.[25] Animal studies have confirmed that this process slows myopia progression. The exact mechanism behind Ortho-k's shorter AL is unknown, but corneal thinning and choroidal thickening are likely to be involved.[15] Our network analysis revealed that Ortho-k was second in efficacy for SE change at 6-month follow-up, which is consistent with its role in reshaping the cornea. Ortho-k has a good safety profile based on systematic reviews, with no reported adverse events.[26] Long-term effectiveness depends on correct lens fitting, strict adherence to lens care regimens, routine follow-up and prompt management of complications. The primary causes of patient withdrawal from research and treatment discontinuation are intolerance and corneal infection risk.[27]

In contrast, APs are widely used in myopia management and have been shown to significantly inhibit AL elongation and SE changes. Consistent with prior studies, AP significantly slowed AL and SE progression but was less effective than other interventions.[28]However, recent studies, including the phase 2 LAMP study, suggest that the efficacy of AP improves with long-term use, indicating the need for extended follow-up in future trials.[29]

AP's effects depend on concentration; higher concentrations cause stronger effects, but also more pronounced side effects. Numerous trials have shown that low-dose AP does not significantly impair near-distance vision or accommodation and has minimal side effects,[30] with a weaker rebound effect compared with high doses of AP.[31] The mechanism of action of AP likely involves the modulation of acetylcholine receptors, which regulate growth signals in the retina and sclera. This mechanism may resemble that of RLRL, which also influences scleral remodelling[32, 33].

Similarly to a recent NMA,[11] our study found that combination therapy is often more effective than single interventions. Specifically, the AP+Ortho k showed strong efficacy in controlling both AL and SE. It is interesting to note that one recent study reported combining RLRL with Ortho-k reduced myopia progression for up to 1 year.[34] It appears that combining two or more interventions can increase efficacy. In our analysis, we revealed that RLRL therapy had weaker efficacy than AP+Ortho k therapy at the 6-month follow-up, though the effect of Ortho-k in temporarily reducing SE may influence this conclusion. However, at the 12-month follow-up, RLRL therapy outperformed both methods. This delayed effect may be attributed to the time required for RLRL to induce scleral remodelling.

Despite a high degree of heterogeneity in treatments, and the inclusion of non-myopic children as a partial source of heterogeneity, a full explanation is still unavailable. It is important to recognise that non-myopic children were not included in the development of eligibility criteria, which may have adversely

affected the interpretation. We performed a subgroup analysis of this. Fortunately, the issue did not change the final conclusion, and sensitivity analyses confirmed the robustness of our results. During the sensitivity analysis, some subgroups with fewer studies experienced a significant reversal when a certain article was excluded; however, due to the small number of studies, we were not able to reanalyse the subgroup. Reviewing the literature revealed that these cases involved primarily multiarm studies with fewer than 50 participants in each arm, reducing the reliability and highlighting the need for adequate sample sizes in multiarm studies. In terms of search methodology, we based our search on the MeSH database. An ancestry search was not performed, and several subject terms that were more popular but not included in the MeSH database were not used, which may have resulted in missing articles. In summary, these conclusions need to be interpreted with caution.

CONCLUSIONS

This study demonstrated that RLRL therapy is more effective than traditional myopia treatments. The following evidence-based guideline conclusions can be drawn. First, RLRL, 0.01% AP, Ortho-k and 0.01% AP+Ortho-k effectively suppress AL and SE progression. Second, the efficacy of these interventions for inhibiting AL prolongation and SE progression decreased in the following order: RLRL>0.01% AP+Ortho-k>Ortho-k>0.01% AP.

Contributors Z-TZ was responsible for designing the protocol, writing the protocol and report, screening potentially eligible studies, extracting data, interpreting results. XJ contributed to data extraction and provided feedback on the report. R-XC extracted data, created tables and updating reference list. LD was responsible for designing the review protocol and providing material support. All the authors have read and approved the final manuscript.

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Patient consent for publication Not applicable.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All the data analysed during this study are included in this published article and its additional files.

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