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Original Article

Efficacy of atropine, orthokeratology, and combined atropine with orthokeratology for childhood myopia: A systematic review and network meta-analysis

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KEYWORDS
Myopia;
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Abstract *Background/Purpose:* Orthokeratology (Ortho-K), atropine eye drops and combined atropine with Ortho-K are proven to be effective ways to prevent myopic progression in many studies, but there is scarce evidence regarding the comparative efficacy of different dosages of atropine,Ortho-K, and combined atropine with Ortho-K for childhood myopia.
Methods: We performed a network meta-analysis (NMA) to assess the relative efficacy of the aforementioned interventions for myopic progression; moreover, we calculated the surface under cumulative ranking area (SUCRA) to determine the relative ranking of treatments.
Results: We identified 19 randomized controlled trials (3435 patients). NMA revealed that 0.01%—1% atropine, Ortho-K, and 0.01% atropine combined with Ortho-K inhibited axial elongation (AL) over one year. For refractive change, SUCRA analysis revealed that the hierarchy was high-dose (0.5%—1%), moderate-dose (0.1%—0.25%), and low-dose (0.01%—0.05%) atropine. Regarding AL, SUCRA analysis revealed the following hierarchy: Ortho-K combined with 0.01% atropine, high-dose atropine, moderate-dose atropine, Ortho-K, and low-dose atropine.
Conclusions: In conclusion, we found that atropine (0.01%—1%), Ortho-K, and 0.01% atropine combined with Ortho-K could significantly slow down myopia progression. The atropine

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efficacy followed a dose-related pattern; moreover, Ortho-K and low-dose atropine showed similar efficacy. There was a synergistic effect of using 0.01% atropine combined with Ortho-K, and it showed comparable efficacy to that of high-dose atropine.

Introduction

Myopia is a worldwide public health concern with a significant socioeconomic burden that affects 80%—90% of young adults, especially in East Asia.[1—9] Holden et al.[10] predicted that myopia may affect 50% of the world's population by 2050. Moreover, 9.8% of these cases will have high myopia, which causes severe sight-threatening complications, including retinal detachment, myopic macular degeneration, and glaucoma.[11—14] Therefore, there is a need to develop effective methods for slowing down myopia progression in children.[15]

Among the current myopic interventions, atropine eye drops and orthokeratology (Ortho-K) are considered effective at inhibiting myopia progression.[15] A global survey of myopia management attitudes and strategies among eye care practitioners reported that Ortho-K was perceived as the most effective method for controlling myopia, followed by pharmaceutical approaches.[16] Recent studies have shown that the combined use of atropine with Ortho-K is a promising treatment strategy for patients with rapid myopic progression[17]; generally, atropine is considered to slow the progression of myopia by a pharmaceutical mechanism and Ortho-K by an optical mechanism. Combining treatments with different mechanisms of action may be more effective than monotherapy in slowing the progression of myopia. However, there remains a need for further research.

Although previous meta-analyses[18—20] have reported the efficacy of 0.01%—1% atropine in myopia control, there have been few head-to-head trials among different atropine doses. Moreover, the dose-related atropine efficacy remains unclear. Several meta-analyses[21,22] have reported that Ortho-K has significantly greater efficacy in controlling axial elongation (AL) compared with spectacle correction. However, only two retrospective studies[23,24] have compared the efficacy of Ortho-K and atropine; moreover, the combined use of Ortho-K and 0.01% atropine was found to be more effective than Ortho-K alone in inhibiting AL.[17,25] It remains unclear whether this intervention is superior to 0.01% atropine or other atropine dosages. Therefore, there is a need to further assess treatments for better understanding and to compile current evidence.

This study conducted a network meta-analysis (NMA), which allows direct and indirect comparisons even for strategies that have not been directly compared. Further, this method allows the integration of relevant data without losing the randomization strength in individual randomized controlled trials (RCTs). This study aimed to evaluate the comparative efficacy in myopia control among different atropine dosages, Ortho-K, and combined use of atropine with Ortho-K. This information may facilitate decision-making in clinical practice.

Methods

Study design

We performed a systematic review of studies regarding atropine and Ortho-K for myopia control in children aged <18 years. Moreover, we conducted a NMA to investigate the comparative efficacy of different atropine doses and Ortho-K. This study was performed following the recommendations of the Preferred Reporting Items for a Systematic Review and Meta-analysis — Network Meta-analysis statement (Appendix 1). The protocol registration application for this study was performed (PROSPERO [International Prospective Register of Systematic Reviews] registration number: CRD42021255088).

Search strategy

We identified RCTs describing the efficacy of different atropine doses and Ortho-K in myopia control published before August 2021 in the PubMed, Embase (Ovid), and Cochrane Library databases. There were no language restrictions. The keywords "atropine," "myopia control," and "orthokeratology," "combined atropine with orthokeratology, " as well as their synonyms and derivatives, were used. Appendix 2 presents the details regarding the search strategies. The "related articles" option in PubMed was used to broaden the search results; moreover, two independent authors (H.T. and T.C.) reviewed all abstracts, studies, and retrieved citations. Furthermore, we assessed the reference sections of the retrieved articles to identify more relevant studies.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) RCTs; (2) treatment modalities including placebo, atropine eye drops, Ortho-K, or combined use of Ortho-K and atropine eyedrops for slowing myopic progression; (3) participants with a myopia diagnosis who were aged <18 years; (4) mean follow-up period ≧ 1 year; (5) outcomes of interest including mean annual change in standardized equivalent refractive error (SER) (diopter/year) or AL (millimeters/year). We excluded studies if (1) they were review articles, case reports, case series, animal or laboratory studies, or conference abstracts and (2) if they lacked the required outcome measures.

Data extraction

Two authors (H.T. and T.C.) independently screened the titles and abstracts; moreover, they assessed the remaining full articles based on the eligibility criteria. Subsequently, the following items were extracted: first author, year of publication, number of eyes, baseline SER, baseline AL, follow-up period, details regarding the treatment arm, and mean progression in the SER and AL within one year. Given that the most objective evidence for evaluating the effect of Ortho-K is the decrease in the rate of globe AL, we mainly assessed treatments involving Ortho-K based on its AL inhibition effect.[26,27] The control group was comprised patients who received single vision spectacle lens and tropicamide eyedrops.[28] In case specific aspects required clarification, efforts were made to contact the corresponding authors for further information. For studies that did not report the standard deviation, we calculated the standard deviation using formulas described in the Cochrane handbook for systematic reviews of interventions.[29]

Quality assessment

The methodological quality of RCTs was evaluated using the Cochrane Collaboration's Risk of Bias Assessment tool (RoB v.2.0)[30] by two reviewers (H.T. and T.C.), with disagreements being resolved through discussions with two other reviewers (C.C. and J.W.).

Data synthesis and statistical analysis

Statistical analyses were performed using the statistical software package Stata, version 17 (StataCorp, Texas, USA) and R (version 4.0.5). The effect size is presented as the mean difference (MD) with 95% confidence intervals (CIs) for continuous outcome measures (SER and AL). Frequentist random-effects models of the NMA were conducted to evaluate each outcome. We conducted a contrast-based NMA through a network module based on the mvmeta command for multiple treatment comparisons using the restricted maximum likelihood approach.[31] Global inconsistency was evaluated using the design-by-treatment interaction model.[32] Potential local inconsistency between the direct and indirect evidence within the network was analyzed using the loop-inconsistency model and node-splitting method.[33,34] Further, we used the R package netmeta to generate a node-splitting plot for visualizing the aforementioned comparison in each pairwise. Additionally, we used the SUCRA curves to rank treatments for each outcome of interest.[35] The SUCRA scores ranged from 1 to 0, where 1 and 0 mean that the treatment ranks first and last, respectively, most of the time. Sensitivity analyses were performed to test the robustness of the findings by excluding studies with high bias; subsequently, we conducted NMA on all the remaining studies to determine whether the results are consistent. We adopted the comparison-adjusted funnel plot and Egger's tests to examine potential publication biases based on their point estimate. In Egger's test, P-value < 0.1 was assumed to indicate publication bias. Furthermore, we performed subgroup analysis by stratifying the atropine dosage into high-dose (0.5%—1%), moderate-dose (0.1%—0.25%), and low-dose (0.01%—0.05%); additionally, we conducted NMA to evaluate the dose-related atropine efficacy.

Results

Study selection

Fig. 1 presents a PRISMA flow diagram showing the process of obtaining eligible trials. We identified 838, 1262, 205, and 62 articles from PubMed, Embase, Cochrane library, and trial register website, respectively. After eliminating 570 duplicate articles, there were 1797 remaining articles. After screening for titles and abstracts, 1712 articles were excluded. Among the remaining 85 articles, 66 articles were excluded after the full-text review.

Study characteristics

Appendix 3 summarizes the trial characteristics. Among the 19 trials, two studies[36,37] had four arms, two studies[38,39] had three arms, and the remaining studies were two-armed. All studies were conducted in the Asian region. Regarding the follow-up period, six RCTs[39—44] followed-up for 2 years while the remaining RCTs[36—38,45—53] followed-up for 1 year. Notably, Zhao[52] separated the patients into the high and low myopic groups; moreover, we extracted data in each group through an individual pairwise comparison.

Quality of studies

Appendix 4 shows the quality assessment results. There were several concern across articles,[36—39,41,42,44,49—53] including lack of descriptions about the randomization methods and blinding of the participants or outcome assessors. Regarding missing outcome data, several articles[40,47] reported a high drop-out rate; therefore, they were considered to have a high risk of bias. Generally, most studies were rated as having some concern in the domain of overall bias.

Axial length

Fig. 2a presents a network of eligible comparisons for AL. Data regarding the AL inhibition effects over one-year period were available from 16 studies with 2712 patients. The predominant pairwise comparison comprised of 0.01% atropine with placebo or Ortho-K. As shown in Fig. 3a, all treatments showed significant AL inhibition effects within one year, including 1% atropine (mean difference [MD] = −0.35, CI = [−0.48, −0.21]), Ortho-K + 0.01% atropine (MD = −0.29, CI = [−0.43, −0.15]), 0.05% atropine (MD = −0.25, CI = [−0.42, −0.09]), 0.5% atropine (MD = −0.22, CI = [−0.35, −0.09]), 0.1% atropine, (MD = −0.22, CI = [−0.40, −0.04]), Ortho-K (MD = −0.18, CI = [−0.27, −0.10]), 0.02—0.025% atropine (MD = −0.17, CI = [−0.29, −0.05]), and 0.01% atropine (MD = −0.13, CI = [−0.20, −0.06]). As shown in Table 1a, 1% atropine

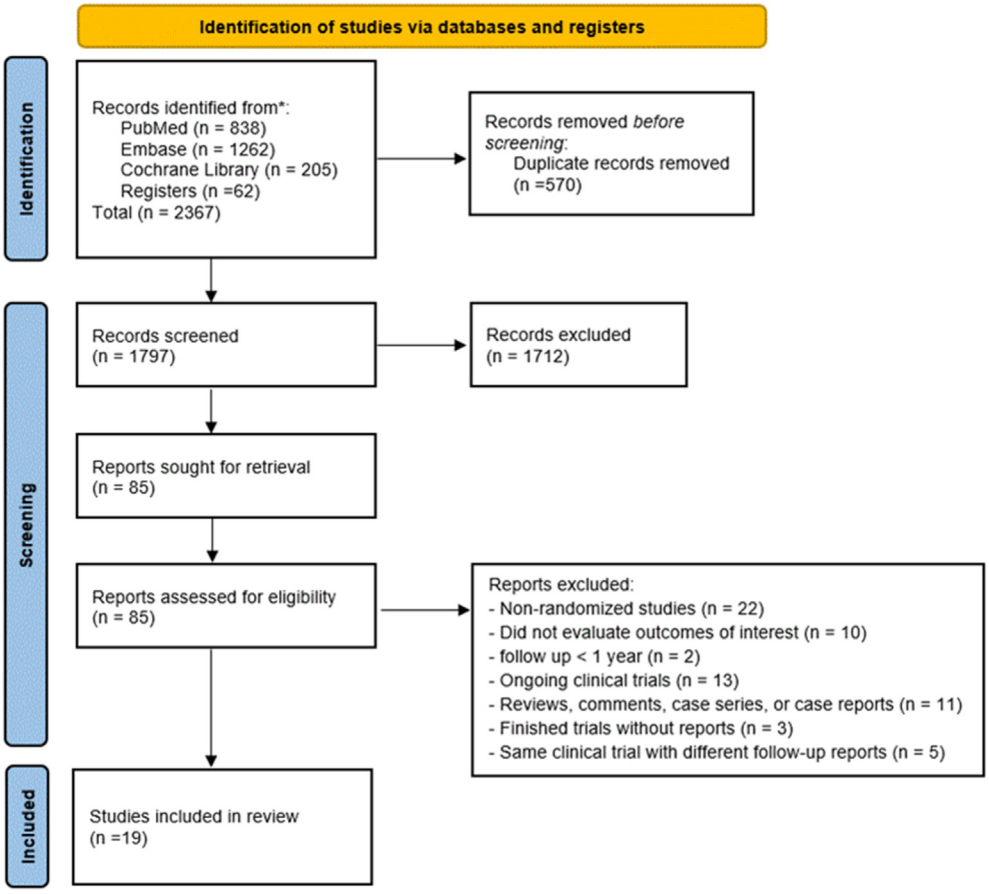

Figure 1 PRISMA flow diagram.

showed superior efficacy compared with 0.01% atropine (MD = −0.22, CI = [−0.37, −0.07]) and Ortho-K (MD = −0.16, CI = [−0.32, −0.01]). Additionally, Ortho-K + 0.01% atropine showed a higher efficacy compared with 0.01% atropine (MD = −0.17, CI = [−030, −0.04]) and Ortho-K (MD = −0.11, CI = [−0.22, −0.00]). The surface under the cumulative ranking (SUCRA) evaluation (Fig. 4a.) revealed that 1% atropine (SUCRA 90.5%) was ranked first, followed by Ortho-K + 0.01% atropine (SUCRA = 79.3%), 0.05% atropine (SUCRA 66.7%), 0.5% atropine (SUCRA 57.2%), 0.1% atropine (SUCRA 54.1%), Ortho-k (SUCRA 42.9%), 0.02—0.025% (SUCRA 38.2%), and 0.01% atropine (SUCRA 20.9%).

Standardized equivalent refractive error

Fig. 2b shows a network of eligible comparisons for changes in the standardized equivalent refractive error (SER). 14 studies on 2689 patients reported the SER inhibition effects. The predominantly pairwise comparison comprised of 0.01% atropine, 0.5% atropine, and 1% atropine with placebo. As shown in Fig. 3b, the following treatments showed significant SER inhibition effects over one year: 1% atropine (MD = 0.90, CI = [0.60, 1.20]), 0.5% atropine (MD = 0.78, CI = [0.54, 1.03]), 0.25% atropine (MD = 0.51, CI = [0.04, 0.98]), 0.1% atropine (MD = 0.52, CI = [0.16, 0.88]), 0.05% atropine (MD = 0.59, CI = [0.15, 1.04]), 0.02—0.025% atropine (MD = 0.39, CI = [0.07, 0.72]), and 0.01% atropine (MD = 0.34, CI = [0.15, 0.54]). As shown in Tables 1b and 1% atropine showed superior efficacy compared with 0.01% atropine and 0.02—0.025% atropine. The SUCRA evaluation (Fig. 4b) revealed 1% atropine (SUCRA 92.4%) was ranked best among the 8 treatments, followed by 0.5% atropine (SUCRA 83.3%), 0.05% atropine (SUCRA 59.1%), 0.1% atropine (SUCRA 51.4%), 0.25% atropine (SUCRA 49.7%), 0.02—0.025% (SUCRA 35.5%), and 0.01% atropine (SUCRA 28.3%).

Sensitivity analysis

We excluded studies with high biased studies[40,46,47]; subsequently, we performed NMA. Compared with controls, most interventions did not show significant changes in the effects; moreover, there was no significant change in the intervention ranking (Appendix 5).

Subgroup analysis

Table 2 Shows the NMA results after stratifying the atropine dosages into the low-dose (0.01 %—0.05%), moderate-dose (0.1%—0.25%), and high-dose (0.5%—1%) groups. Regarding AL (Table 2a.), Ortho-K + 0.01% atropine showed superior efficacy compared with low-dose atropine (MD = −0.16, CI = [−0.29, −0.03]). Additionally, high-dose atropine

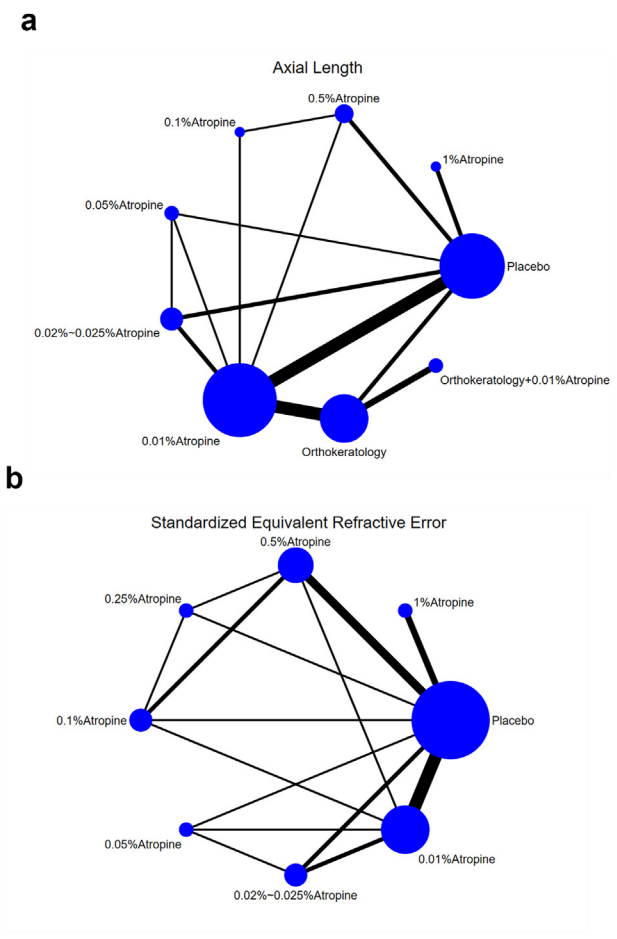

Fig. 2 **a.** Network plot for the mean annual change in the axial length. **b.** Network plot for the mean annual change in the standardized equivalent refractive error.

demonstrated greater efficacy compared with low-dose atropine (MD = −0.14, CI = [−0.24, −0.03]). SUCRA analysis (Appendix 6a) revealed the following hierarchy: Ortho-K + 0.01% atropine (SUCRA 84.4%), high-dose atropine (SUCRA 78.8%), moderate-dose atropine (SUCRA 67.8%), Ortho-K (SUCRA 44.7%), and low-dose atropine (SUCRA 24.1%). Regarding SER (Table 2b.), high-dose atropine demonstrated greater efficacy compared with low-dose atropine (MD = 0.44, CI = [0.19, 0.68]). Based on the SUCRA analysis, the hierarchy for inhibiting SER progression was high-dose (SUCRA 97.5%), moderate-dose (SUCRA 64%), and low-dose atropine (SUCRA 38.5%) (Appendix 6b).

Publication bias and inconsistency assessment

Generally, there was no significant funnel plot asymmetry, which indicated the absence of small-study effects in the network. Furthermore, the Egger test revealed no significant publication bias in AL (p = 0.91) but in SER (p < 0.1) (Appendix 7).

The design-by-treatment interaction models revealed no evidence regarding global inconsistency in the efficacy outcomes (In AL, Higgins p = 0.95; In SER, Higgins p = 0.99). Appendix 8 presents the results of direct and indirect estimates using the node-splitting method. The loop-specific model revealed no significantly inconsistent loops (In AL p = 0.84; In SER p = 0.72).

Discussion

There are four major findings in this NMA and review. First, regarding AL, 0.01%—1% atropine, Ortho-K, and the combined use of 0.01% atropine with Ortho-K showed significant AL inhibition effects over one year. Regarding SER, 1% atropine, 0.5% atropine, 0.25% atropine, 0.1% atropine, 0.05% atropine, 0.02%—0.025% atropine, and 0.01% atropine showed significant effects in controlling SER progression. Second, the efficacy of atropine follows a dose-related pattern. This phenomenon was more prominent after stratifying the atropine dosage into the low-dose, moderate-dose, and high-dose groups as measured using SER and AL. Third, Ortho-K showed inferior efficacy compared with that of 1% atropine and 0.01% atropine combined Ortho-K in terms of inhibiting AL. Moreover, SUCRA analysis revealed that Ortho-K and low-dose atropine had similar efficacy. Fourth, combined use of Ortho-K and 0.01% atropine inhibited AL to a significantly greater extent than did 0.01% atropine and Ortho-K alone; additionally, its efficacy was comparable to that of high-dose atropine according to our SUCRA analysis.

Several meta-analyses[18–20] have assessed the dose-related atropine efficacy in controlling myopia; however, there are significant variances in these studies. Gong et al.[19] assessed 19 studies and stratified the atropine dosage into 0.01%, >0.01%—<0.5%, and 0.5%—1.0%. Notably, a wide dosage range of atropine (0.01%—0.5%) was included in the moderate group, which could have led to uncertain results regarding the efficacy of this dose range. Moreover, mostly retrospective studies were included; further, the dose-related AL inhibition effect was not assessed due to the rarity of relevant evidence. Zhao et al.[18] included 10 RCTs and only assessed three different atropine dosages (0.05%, 0.5%, 1%) with respect to myopia control. Although there were within-group differences in the subgroup analysis, there was missing evidence regarding low-concentration atropine. Song et al.[20] observed a dose—response effect using meta-regression after including six studies (atropine dosage: 0.25%—1%); however, this effect was only found in SER progression and the study had a small sample size. Huang et al.[28] conducted a NMA comparing different interventions for slowing down myopia progression and classified atropine doses into three groups: high-dose (1% and 0.5%), moderate-dose (0.1%), and low-dose atropine (0.01%) and they found no among-group differences. However, this previous study evaluated the low-dose atropine only based on indirect evidence; moreover, it did not include other low atropine dosages, including 0.05% or 0.025%. The advantage of our study was that we included 19 mostly high-quality clinical trials combined with the NMA techniques. Besides, we compared various atropine doses, including 1%, 0.5%, 0.25%, 0.1%, 0.05%, 0.02%—0.025%, and 0.01%, as well as performed ranking analysis to inform clinical decision-making. Furthermore, we stratified 0.01%—0.05%, 0.1%—0.25%, and

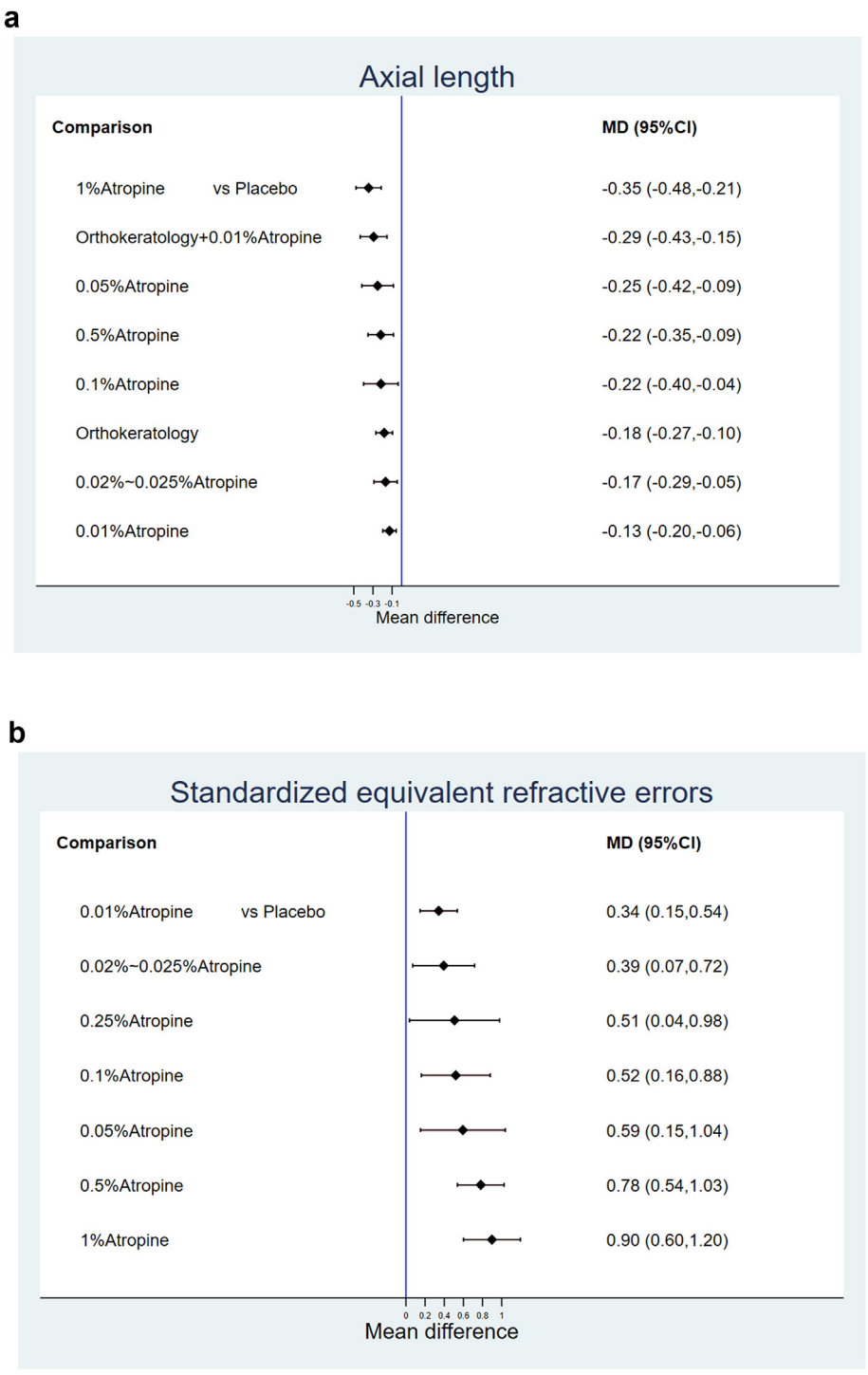

Fig. 3 **a.** Network meta-analysis of the mean annual change in the axial length, relative to that observed with placebo. MD, mean difference; CI, confidence interval. **b.** Network meta-analysis of the mean annual change in the standardized equivalent refractive error, relative to that observed with placebo. MD, mean difference; CI, confidence interval.

0.5%—1% atropine into the low-, moderate-, and high-dose groups and observed a dose-dependent effect within groups as measured by SER and AL. These findings may improve clinical practice given the varying responses to atropine eyedrops and present a strategy for stepwise increases in the concentration.

The Low-concentration Atropine for Myopia Progression (LAMP)[37,54] study demonstrated a concentration-dependent response for low-concentration atropine drops from 0.01% to 0.05%, with 0.05% conferring highest efficacy among the studied concentrations of up to 67% compared with the placebo group. Furthermore, young age is significantly

Table 1 League table of results from network meta-analysis. a. On the upper triangle, a mean difference of >0 favors the row-defining treatment. b. On the upper triangle, a mean difference of >0 favors the column-defining treatment.

a. Mean change in axial length progression over a 1-year period

Placebo	**−0.18 (-0.27,-0.10)**	**−0.13 (-0.20,-0.06)**	**−0.17 (-0.29,-0.05)**	**−0.25 (-0.42,-0.09)**	**−0.22 (-0.40,-0.04)**	**−0.22 (-0.35,-0.09)**	**−0.35 (-0.48,-0.21)**	**−0.29 (-0.43,-0.15)**
	Orthokeratology	0.06 (−0.01,0.13)	0.01 (−0.12,0.15)	−0.07 (−0.24,0.11)	−0.03 (−0.22,0.15)	−0.04 (−0.18,0.11)	**−0.16 (-0.32,-0.01)**	**−0.11 (-0.22,-0.00)**
		0.01% Atropine	−0.04 (−0.16,0.08)	−0.12 (−0.29,0.04)	−0.09 (−0.26,0.08)	−0.09 (−0.23,0.04)	**−0.22 (-0.37,-0.07)**	**−0.17 (-0.30,-0.04)**
			0.02%−0.025% Atropine	−0.08 (−0.26,0.09)	−0.05 (−0.26,0.16)	−0.05 (−0.22,0.12)	−0.18 (−0.36,0.00)	−0.12 (−0.30,0.05)
				0.05% Atropine	0.03 (−0.20,0.27)	0.03 (−0.17,0.24)	−0.09 (−0.31,0.12)	−0.04 (−0.25,0.17)
					0.1% Atropine	−0.00 (−0.17,0.17)	−0.13 (−0.35,0.10)	−0.08 (−0.29,0.14)
						0.5% Atropine	−0.13 (−0.31,0.06)	−0.07 (−0.26,0.11)
							1% Atropine	0.05 (−0.14,0.24)
								Orthokeratology + 0.01% Atropine

b. Mean change in standardized equivalent refractive error progression over a 1-year period

Placebo	**0.34 (0.15,0.54)**	**0.39 (0.07,0.72)**	**0.59 (0.15,1.04)**	**0.52 (0.16,0.88)**	**0.51 (0.04,0.98)**	**0.78 (0.54,1.03)**	**0.90 0.60,1.20)**
	0.01% Atropine	0.05 (−0.27,0.37)	0.25 (−0.26,0.67)	0.18 (−0.19,0.55)	0.17 (−0.33,0.66)	**0.44 (0.16,0.72)**	**0.56 (0.20,0.91)**
		0.02%−0.025% Atropine	0.20 (−0.26,0.67)	0.13 (−0.34,0.59)	0.11 (−0.45,0.68)	0.39 (−0.01,0.78)	**0.50 (0.07,0.94)**
			0.05% Atropine	−0.07 (−0.63,0.48)	−0.09 (−0.73,0.55)	0.19 (−0.31,0.68)	0.30 (−0.23,0.84)
				0.1% Atropine	−0.01 (−0.52,0.49)	0.26 (−0.09,0.61)	0.38 (−0.09,0.84)
					0.25% Atropine	0.27 (−0.20,0.74)	0.39 (−0.17,0.95)
						0.5% Atropine	0.12 (−0.27,0.50)
							1% Atropine

a

Treatment	SUCRA	PrBest	MeanRank
1%Atropine	90.5	54.6	01.8
Orthokeratology+0.01%Atropine	79.3	23.4	02.7
0.05%Atropine	66.7	12.4	03.7
0.5%Atropine	57.2	02.0	04.4
0.1%Atropine	54.1	07.0	04.7
Orthokeratology	42.9	00.0	05.6
0.02%~0.025%Atropine	38.2	00.6	05.9
0.01%Atropine	20.9	00.0	07.3
Placebo	00.2	00.0	09.0

b

Treatment	SUCRA	PrBest	MeanRank
1%Atropine	92.4	64.2	01.5
0.5%Atropine	83.3	20.4	02.2
0.05%Atropine	59.1	09.2	03.9
0.1%Atropine	51.4	03.0	04.4
0.25%Atropine	49.7	03.2	04.5
0.02%~0.025%Atropine	35.5	00.0	05.5
0.01%Atropine	28.3	00.0	06.0
Placebo	00.4	00.0	08.0

Fig. 4 **a.** Surface under the ranking curve of the mean annual change in the axial length. SUCRA, surface under cumulative ranking area. **b.** Surface under the ranking curve of the mean annual change in the standardized equivalent refractive error. SUCRA, surface under cumulative ranking area.

Table 2 League table of subgroup analysis after stratifying into 0.01—0.05%, 0.1—0.25%, and 0.5—1% atropine. a. On the upper triangle, mean difference >0 favor the row-defining treatment. b. On the upper triangle, mean difference >0 favor the column-defining treatment.

a. Mean change in axial length progression over a 1-year period

Placebo	**−0.15 (-0.22,-0.08)**	**−0.26 (-0.44,-0.09)**	**−0.29 (-0.38,-0.19)**	**−0.20 (-0.29,-0.11)**	**−0.31 (-0.45,-0.17)**
	low-dose	−0.11 (−0.29,0.06)	**−0.14 (-0.24,-0.03)**	−0.05 (−0.12,0.02)	**−0.16 (-0.29,-0.03)**
		moderate-dose	−0.02 (−0.20,0.15)	0.06 (−0.12,0.25)	−0.02 (−0.26,0.17)
			high-dose	0.09 (−0.04,0.21)	−0.02 (−0.19,0.14)
				Orthokeratology	−0.11 (−0.22, 0.00)
					Orthokeratology +0.01%Atropine

b. Mean change in standardized equivalent refractive error progression over a 1-year period

Placebo	**0.36 (0.16,0.55)**	**0.53 (0.19,0.87)**	**0.80 (0.62,0.97)**
	low-dose	0.18 (−0.18,0.53)	**0.44 (0.19,0.68)**
		moderate-dose	0.26 (−0.07,0.60)
			high-dose

associated with poor treatment efficacy for low-concentration atropine. A greater rebound effect was associated with higher atropine concentration (0.05%) and younger age at treatment cessation.[55] In a recent report,[56] low concentration atropine induced a choroidal thickening effect along a concentration-dependent response and

associated with a slower SE progression and AL elongation among all the treatment groups (0.01%, 0.025% and 0.05% atropine). However, several studies[57,58] reported that 0.05% atropine induced significantly more anisocoria and loss of accommodation amplitude than 0.01% atropine in White children with lighter pigmented eyes that may be less tolerant of the side effects. Myopic children who have photophobia and blurry near vision after administration of higher-dose atropine may benefit with lower concentration atropine treatment. Several reviews[59,60] have recommended 0.01% atropine as the useful treatment for controlling myopia given that it could slow SER progression with minimal myopic rebound and side effects. Nevertheless, there have been inconsistent reports regarding its effect on AL inhibition.[37,38,43,48,50] Consistent with the findings in a recent meta-analysis[61] investigating the efficacy of 0.01% atropine for myopic progression, we found that 0.01% atropine could effectively inhibit myopia progression as measured using SER and AL. This finding may instill confidence in clinicians to administer this treatment modality.

Our study also provided novel evidence by comparing the efficacy of Ortho-K and different atropine doses in myopia control. Given the nature of both treatment modalities (optical and pharmaceutical), it may be difficult to conduct an RCT to compare them. Currently, only two retrospective studies[23,24] have compared the effects of Ortho-K and atropine in myopia control. These studies showed that Ortho-K might be superior to 0.125% and 0.02% atropine in inhibiting AL over a three- and two-year follow-up period, respectively, especially in patients with high baseline myopia. In present study, we observed a significant difference only between Ortho-K and 1% atropine; however, SUCRA analysis revealed that the hierarchy of Ortho-K in AL inhibition was similar to that of 0.01%—0.025% atropine over a one-year follow-up period. Unfortunately, we could not perform subgroup analysis according to baseline myopic degree given the rarity of evidence for forming a well-structured network. Therefore, our findings should be interpreted with caution; moreover, there is a need for further research upon compilation of more evidence.

Consistent with previous pairwise meta-analyses,[25,62] we found that the combined use of Ortho-K and 0.01% atropine was more effective against myopia progression and AL elongation than monotherapy with OK lenses or 0.01% atropine. The SUCRA analysis also revealed that this combination had similar efficacy to high-dose atropine. This is a novel finding and further supports the efficacy of this combinative treatment. The synergistic effect of Ortho-K combined with atropine has been observed in former studies.[63,64] Wan et al.[63] demonstrated that the potential mechanism on the combined effect of atropine treatment and OK lenses is that large pupil diameter increased retinal illumination which would lower the myopic shift in the peripheral retina and enhance the effect of OK lens. Besides, Vincent et al.[64] pointed out that the use of 0.01% atropine in OKA group caused a small but significant increase in pupil diameter which resulted in elevated levels of high order abberations compared to the OK group for a photopic pupil size. Elevated aberrations may provide a visual signal that slows eye growth and antimuscarinic effect of atropine act on the ocular tissues also involves in the regulation of eye growth. In addition, several studies[65—69] demonstrated that the mechanism of myopia may be related to AL elongation and subfoveal choroidal thickness (SFChT) thinning, Hao et al.[70] indicated that OK lenses, 0.01% atropine and their combination (OKA) could effectively retard AL elongation and increased SFChT. The increase in SFChT was best in OKA group, followed by OK group and 0.01% atropine group. The authors speculated that changes in SFChT may affect the oxygen supply and produce certain chemical substances to provide a sign of slowed axial elongation. One recent cohort study[70] demonstrated that those who had poor response to lower concentration of atropine may have the risk of faster progression, even with high concentration of atropine, and additional or alternative treatment might be considered. Coupled with our finding, we asserted that children with poor response to atropine might consider additive treatment of Ortho-K.

This study has several limitations. First, some treatments had small trial numbers and sample sizes, which could have resulted in wide CIs and uncertain results. For example, only one study evaluated the efficacy of 0.25% and 0.05% atropine. Second, we did not evaluate the long-term outcome or ortho-k combined with dosage of atropine other than 0.01% because the relevant data were yet to obtained, and the results of a disconnected network analysis may not be conclusive. Finally, caution should be applied when generalizing our findings to other ethnicities since all the studies were conducted in Asia, and a previous meta-analysis showed that atropine may slow myopia progression more in Asian countries than in other countries.[71]

In conclusion, we found that atropine (0.01%—1%), Ortho-K, and 0.01% atropine combined with Ortho-K could significantly slow down myopia progression. There is a dose-related pattern in the atropine efficacy for myopia control. Furthermore, the efficacy of Ortho-K alone in inhibiting AL was similar to that of low-dose atropine. There was a synergistic effect of combining 0.01% atropine and Ortho-k, which showed similar efficacy as high-dose atropine in inhibiting AL. This information could provide helpful guidance regarding the management of myopic progression.

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Data availability

All data is available upon request.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2022.05.005.

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