Effect of atropine, orthokeratology and combined treatments for myopia control: a 2-year stratified randomised clinical trial

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ABSTRACT

Purpose To investigate the 2-year efficacy of atropine, orthokeratology (ortho-k) and combined treatment on myopia. To explore the factors influencing the efficacy.

Methods An age-stratified randomised controlled trial. Children (n=164) aged 8–12 years with spherical equivalent refraction of −1.00 to −6.00 D were stratified into two age subgroups and randomly assigned to receive placebo drops+spectacles (control), 0.01% atropine+spectacles (atropine), ortho-k+placebo (ortho-k) or combined treatment. Axial length was measured at baseline and visits at 6, 12, 18 and 24 months. The primary analysis was done following the criteria of intention to treat, which included all randomised subjects.

Results All interventions can significantly reduce axial elongation at all visits (all p<0.05). Overall, the 2-year axial elongation was significantly reduced in combined treatment than in monotherapies (all p<0.05). After stratification by age, in the subgroup aged 8–10, the difference between combined treatment and ortho-k became insignificant (p=0.106), while in the subgroup aged 10–12, the difference between combined treatment and atropine became insignificant (p=0.121). A significant age-dependent effect existed in the ortho-k group versus the control group (p for interaction=0.013), and a significant age-dependent effect existed in the ortho-k group versus the atropine group (p for interaction=0.035), which indicated that ortho-k can achieve better efficacy in younger children.

Conclusions Atropine combined with ortho-k treatment can improve the efficacy of myopia control compared with monotherapy in children aged 8–12. Younger children might benefit more from ortho-k.

Trial registration number ChiCTR1800015541.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Both atropine and orthokeratology (ortho-k) can slow myopia progression. Combined treatment can get better efficacy than ortho-k in 1 year. However, long-term randomised controlled trials including all four interventions (spectacle, atropine, ortho-k and combined treatment) were lacking.

WHAT THIS STUDY ADDS

⇒ In the long term, atropine combined with ortho-k treatment can improve the efficacy of myopia control compared with monotherapy. Age-dependent effect is potentially crucial in myopia management.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In the practice of myopia control, adopting combined treatment can improve long-term efficacy compared with monotherapy. When using monotherapy, younger children might benefit more from ortho-k.

INTRODUCTION

Myopia has been widely recognised as an important public health issue that leads to a significant loss of vision and increases the risk of developing a range of serious ocular conditions.[1] Among the interventions for myopia control, orthokeratology (ortho-k) and low-concentration atropine eye drops have been validated to be the most promising treatments with negligible side effects.[2 3] However, the efficacy was accompanied by significant individual variability both in ortho-k and atropine treatments.[4–10] There are still quite a number of children with poor efficacy under ortho-k or atropine treatment alone.[4 10 11]

Among the causes of poor efficacy, age has been validated as a crucial factor during ortho-k or atropine treatments in many studies.[8–10] However, no literature has carried out an age-stratified design to compare the efficacy among atropine, ortho-k and combined treatments.[12–17] Therefore, in the current randomised controlled trial (RCT), to balance the age distribution, the age-stratified randomised design was applied.

The preliminary results of the current atropine combined with orthokeratology (ACO) study have been published,[18] whose design has been evaluated in a meta-analysis.[13] The results demonstrated that ACO treatment can get better efficacy than atropine at the 1-month visit.[18] Several previous studies reported that the combined treatment can get better efficacy than monotherapy at 1-year visit.[12 15 19 20]

However, until now, long-term RCTs including four interventions (spectacle, atropine, ortho-k and ACO) were lacking.[13] Only one 2-year study reported that the combined therapy may be more effective for slowing axial length (AL) elongation

than ortho-k,[16] but this study included only two groups (ortho-k monotherapy and ACO treatment). Hence, considering long-term outcomes, how should clinicians make treatment options? To answer this clinical question, an RCT comparing the long-term efficacy among these four interventions is indispensable.

The current 2-year age-stratified RCT study was aimed at comparing the long-term efficacy among atropine, ortho-k and combined treatment. The age-stratified design can provide more solid evidence of the age effect on these interventions, which can help clinicians make a better choice for myopia control.

METHODS

Study design and participants

This was a stratified RCT, which was conducted at Zhongshan Ophthalmic Centre, Sun Yat-Sen University, Guangzhou, China.

The inclusion criteria of this study included age between 8 years and 12 years, spherical equivalent refraction (SER) of −1.00 to −6.00 D in both eyes, astigmatism of no more than 1.50 D, and anisometropia of no more than 1.50 D; a best-corrected visual acuity (BCVA) of no worse than 20/25 in both eyes; and normal intraocular pressure and binocular function. The exclusion criteria included having ocular pathology (eg, strabismus, allergic conjunctivitis and dry eye), undergoing other treatment to prevent myopia progression (eg, ortho-k lenses, atropine, multifocal lenses and bifocal lenses), having a systemic disease that can influence vision development or having difficulties to complete the measurements or follow-up in this research. All the participants used single-vision spectacles for optical correction or remained uncorrected before enrolment.

Study protocol

The flow of patients through the study is shown in online supplemental figure 1. The stratified enrolment was performed before the randomisation. Participants were stratified into two age subgroups (8.0 (inclusive) to 10.0 (inclusive) years vs 10.0 (exclusive) to 12.0 (inclusive) years) and two SER subgroups (−1.00 to −3.00 D vs −3.01 to −6.00 D) in a 1:1:1:1 ratio. Then, the participants in each strata were randomised into four groups (control, atropine, ortho-k and ACO). The random allocation sequences were computer-generated and implemented by a hospital technician who was not otherwise involved in the trial. Study personnel was not aware of the allocation sequences or patient allocation. All observers were blinded to patient groupings. Age-stratified results of AL changes among the four groups were presented in the current study.

The subjects in the control group used single-ion spectacles and placebo solution eye drops once every night. The subjects in the atropine group used spectacles+0.01% atropine drops once every night. The ortho-k group used the overnight ortho-k+placebo drops once every night. The ACO group used overnight ortho-k lens+0.01% atropine drops once nightly. All the children were instructed to place one drop of their ophthalmic solution (placebo or 0.01% atropine solution) in each eye 10 min before wearing the ortho-k lens. The placebo was 0.9% sodium chloride (0.5 mL unit concentration, preservative-free). The parents or guardians, children and study investigators were kept masked to the assigned ingredient of the trial medications.

Disposable packaging was used for trial medications, which were prepackaged and prelabelled with the subject number, which was of similar appearance. Trial medications consisted of 0.01% atropine (Shenyang Xingqi Pharmaceutical Co., China). The ortho-k lenses used in the study were four-zone reverse-geometry lenses (Euclid Systems OK; Euclid System Corp., Herndon, USA) with BOSTON EQUALENS II (Oprifocona) and a nominal Dk of 127×10^{-11} (cm^2/s) (mL O_2/mL_mm Hg) (ISO/Fatt). Lens fitting was performed according to the manufacturer's fitting guidelines. For the atropine and control groups, spectacle prescriptions were given based on manifest refraction after cycloplegia with corrected visual acuity of 20/25 or better in both eyes.

Outcomes

The primary outcome was the AL change. Other ophthalmic parameters, including cycloplegic SER, Sim K flat, Sim K steep, distance uncorrected visual acuity (UCVA), distance BCVA, central cornea thickness (CCT), anterior chamber depth (ACD) and lens thickness (LT) were monitored. During each visit, subjects and parents were given an open-ended opportunity to report any medical illness or side effects. They were also specifically asked about ocular or systemic conditions at every visit. Any adverse events, regardless of whether they appeared relevant to atropine or ortho-k, were documented.

Measurements

Cycloplegia was induced by three drops of 0.5% tropicamide at 5 min intervals. Then, cycloplegic autorefraction and corneal keratometer were determined using an autorefractor (KR8800; Topcon Corp., Tokyo, Japan). At each inspection, the average result of five readings, which should be less than 0.25 D apart, was obtained. Keratometer readings were Sim K flat and Sim K steep. SER was defined as sphere plus half-cylinder power. Distance UCVA or BCVA logarithm of the minimum angle of resolution was assessed using the ETDRS chart. Ocular biometrics, including AL, CCT, ACD and LT, were measured using a non-contact biometer (Lenstar LS 900; Haag Streit AG, Koeniz, Switzerland). Five consecutive measurements were collected from each subject for each measure, and the values were averaged.

Sample size calculation

The sample size was calculated based on the primary outcome, 2-year cumulative increase in AL. The main assumption was that the combined treatment (ACO) was superior to the other three trial arms (atropine, ortho-k and control) simultaneously in primary outcome, which was a one-sided test at significant level of 0.05 with the minimum mean difference of 0.12 mm and common SD of 0.20 mm.[4 6] A sample size of 41 per trial arm was required to achieve 80% power, considering less than 15% loss to follow-up.[16] The sample size was calculated using G*power software V.3.1.[21]

Data analysis

The Pearson correlation coefficients between data from the right eye and data from the left eye were higher than 0.9. Thus, the statistical analysis was done using the data of the right eye unless otherwise indicated. For some main results, the analysis including both eyes was added based on generalised estimating equations. The statistical distribution of the participants' characteristics was descripted as mean (SD) or median (IQR) for continuous data and frequency (proportion) for categorical data. The overall baseline difference among trial arms was tested by analysis of variance (ANOVA) and χ^2 test for continuous data and categorical data, respectively. The normality of the primary parameters is confirmed by the Shapiro-Wilk test in four groups before the further analysis ($p>0.05$). The unadjusted difference between ACO and the other three trial arms in the 2-year AL

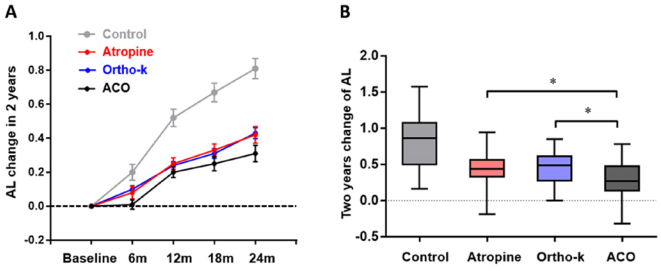


Figure 1 Change of AL in the four groups in the ITT set. (A) Line chart showing the change of AL for 2 years in the four treatment groups in the ITT set. Error bars represented the SE. (B) Box plot showing the 2-year AL elongation in the four treatment groups in the ITT set. Error bars represented the IQR. *P<0.05. The control group used single-vision spectacles+placebo eye drops once every night; the atropine group used single-vision spectacles+0.01% atropine drops once every night; the ortho-k group used overnight ortho-k lens+placebo drops once every night; the ACO group used overnight ortho-k lens+0.01% atropine drops once every night. ACO, atropine combined with orthokeratology; AL, axial length; ITT, intention to treat; ortho-k, orthokeratology.

increase is shown using a histogram and tested by two-sample t test. The factorial analysis of the primary outcome was based on the two-way ANOVA, and the interaction of these two factors (atropine and ortho-k) was calculated.

The primary analysis was done following the criteria of intention to treat (ITT), which included all randomised subjects. Sensitivity analyses were conducted conservatively by estimating that AL in the ACO group increased by 10% and 15% higher than the average level in the group, while that in the control and monotherapy group increased by 10% lower than the average level in the group. The adjusted trial effects, that is, the mean differences and the two-sided 95% CI between ACO and the other three trial arms in 2-year AL increase, were estimated by multivariable linear regression with adjustment of age, sex and baseline ophthalmic parameters. Per-protocol (PP) analysis, which only included subjects who completed the trial protocol, was also performed for the primary outcomes (online supplemental material 1).

The Pearson correlation coefficient reflected the association between annual AL change and potential variables. Then, the variables showing statistically significant associations (p<0.05) were included in the multivariate regression model. Grouped scatterplots depicting simple correlations between age and AL change were presented. The Pearson r was used for the analysis. To clarify the effect of age statistically, the analysis of covariance (ANCOVA) tests was performed among four groups, using age as the covariate and treatments as the main factors. Furthermore, the interactions between age and interventions were examined separately.[22]

All values are represented as the mean±SD in tables unless otherwise indicated. Statistical analyses were performed using SPSS Statistics software V.25.0.0.1 and the programme R V.4.0.3 (R Foundation for Statistical Computing). A p value of <0.05 was considered statistically significant.

RESULTS

As presented in online supplemental figure 1, 184 children were recruited between April 2019 and June 2019. After the assessments, 20 children were excluded. Before the randomisation, the participants were stratified into two age subgroups (8–10 years vs 10–12 years). Then, a total of 164 subjects including two age strata were randomly allocated into the four groups (control, atropine, ortho-k and ACO groups). The final follow-up was in June 2021. Eventually, all 164 subjects were involved in the ITT analysis, with 40, 42, 40 and 42 participants in the control, atropine, ortho-k and ACO groups, respectively. Meanwhile, 129 subjects (80.6%) who completed the 2-year treatments were involved in the PP analysis, with 30, 31, 34 and 34 participants in the control, atropine, ortho-k and ACO groups, respectively. Among the four groups, no significant differences in baseline characteristics were observed (all p>0.05) in the ITT set (online supplemental table 1). No significant baseline differences were found in the PP set (online supplemental material 1). The difference between the 129 individuals involved in the PP set and the 35 individuals who dropped out were insignificant (one-way ANOVA, all p>0.05) (online supplemental table 2).

Table 1 AL changes (mm) in 2 years among the control, atropine, ortho-k and ACO groups in the ITT set

	Control	Atropine	Ortho-k	ACO	Overall P value
6 months	0.20±0.26	0.08±0.19	0.10±0.11	0.01±0.20	<0.001
12 months	0.52±0.34	0.25±0.20	0.24±0.17	0.20±0.23	0.005
18 months	0.67±0.35	0.33±0.23	0.31±0.19	0.25±0.24	<0.001
24 months	0.81±0.35	0.42±0.23	0.43±0.22	0.31±0.23	<0.001

The control group used single-vision spectacles+placebo eye drops once every night; the atropine group used single-vision spectacles+0.01% atropine drops once every night; the ortho-k group used overnight ortho-k lens+placebo drops once every night; the ACO group used overnight ortho-k lens+0.01% atropine drops once every night.
Data are presented as mean±SD.
ACO, atropine combined with orthokeratology; AL, axial length; ITT, intention to treat.; ortho-k, orthokeratology.

AL changes in 2 years among the four groups

Figure 1 and table 1 show the AL change in the ITT set. The AL changed with time significantly in all groups for 2 years (all p<0.01) (figure 1A). The AL changes were significantly different among the four groups at visits of 6, 12, 18 and 24 months (all overall p<0.01), and the results of the ITT analysis were supported by PP analysis (online supplemental material 1). Compared with control, all interventions can significantly reduce the AL elongation at all time points according to the pairwise comparisons (all p<0.05) (online supplemental table 3).

According to the ITT analysis, figure 1B and the pairwise comparisons shown that the 2-year AL elongation was significantly reduced in the ACO group (0.31±0.23 mm) than the atropine group (0.42±0.23 mm) (p=0.036) or the ortho-k group (0.43±0.22 mm) (p=0.034) (online supplemental table 3). The analysis based on data including both eyes hardly changed these results (p=0.026 and 0.012).

On average, in the ITT set, 2-year AL elongation was slower by 63.4% in the ACO, 47.5% in the ortho-k and 48.7% in the atropine group compared with the control. The interaction effect of atropine and ortho-k was detected (p for interaction=0.004), indicating that the interinhibitive interaction may exist between atropine and ortho-k.

AL changes in 2 years stratified by age

According to the ITT analysis, in the two age subgroups, the AL changes were significantly different among the four groups (all overall p<0.01) (online supplemental table 4). In the younger subgroup aged 8–10 (n=81), the 2-year AL elongation was significantly reduced in the ACO group (0.42±0.20 mm) than in

Table 2 Multivariate regression analyses of the association between selected factors and AL change per year in the four groups in the ITT set

	Control		Atropine		Ortho-k		ACO	
	Adjusted β±SEM	Adjusted P value	Adjusted β±SEM	Adjusted P value	Adjusted β±SEM	Adjusted P value	Adjusted β±SEM	Adjusted P value
Age (year)	−0.127±0.025	**0.001***	−0.072±0.026	**0.010**	−0.041±0.012	**0.013**	−0.068±0.020	**0.004**
AL change at first or second year (year)	−0.155±0.072	**0.011**	−0.066±0.034	**0.045**	–	–	–	–
Baseline SER (D)	0.048±0.070	0.097	–	–	–	–	–	–
Intercept	1.883	–	0.919	–	0.686	–	0.832	–

The control group used single-vision spectacles+placebo eye drops once every night; the atropine group used single-vision spectacles+0.01% atropine drops once every night; the ortho-k group used overnight ortho-k lens+placebo drops once every night; the ACO group used overnight ortho-k lens+0.01% atropine drops once every night.
*The boldfaced p values indicated that the p value is significant (< 0.05).
ACO, atropine combined with orthokeratology; AL, axial length; ITT, intention to treat; ortho-k, orthokeratology; SER, spherical equivalent refraction.

the atropine group (0.55±0.16 mm) (p=0.021). However, the difference between the ACO and ortho-k groups was insignificant (p=0.106) (online supplemental figure 2 and online supplemental table 5). The analysis based on data including both eyes hardly changed this result (p=0.072).

In the older subgroup aged 10–12 (n=83), the 2-year AL elongation was significantly reduced in the ACO group (0.18±0.19 mm) than in the ortho-k group (0.37±0.23 mm) (p=0.029). However, the difference between the ACO and atropine groups was insignificant (p=0.121) (online supplemental figure 2 and online supplemental table 5). The analysis based on data including both eyes hardly changed this result (p=0.071).

Selecting factors associated with the efficacy

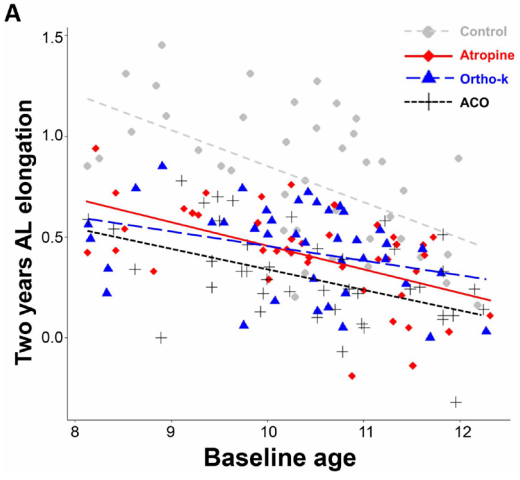
To explore the potential factors influencing efficacy, first, the univariate regression models were built to screen the factors associated with annual AL change (online supplemental table 6) in the ITT set. Second, the variables showing statistical significance (p<0.05) in the univariate analysis were included in the multivariate regression models, which included age, annual AL change at the first or second year, and baseline SER (table 2). The backward stepwise selection was subsequently performed to build the multivariate models.

In the multivariate regression models, older age was significantly associated with less AL elongation in the four groups (all p<0.05) (table 2). AL change during the second year was significantly associated with less AL elongation, while this association only existed in the control group (p=0.011) and the atropine group (p=0.045). Baseline SER was significantly associated with AL elongation only in the control group, while this association became insignificant after adjusting for age in the multivariate models (p>0.05) (table 2). To further analyse the effect of age, using treatments as main factors and SER as the covariate, we found no interaction between SER and interventions (p>0.05, online supplemental figure 3).

Age-dependent effect significantly influenced the efficacy

As shown in the multivariate models (table 2) and previous literature,[4 10] the effect of age held an important role in the efficacy of atropine or ortho-k. To further illuminate this age-dependent effect, the grouped scatterplots were performed. The age-dependent effect was observed in each treatment group: the younger the age, the poorer the efficacy (figure 2A). There were significant negative correlations between AL elongation and baseline age in the control (r=−0.611, p=0.001), atropine (r=−0.574, p=0.001), ortho-k (r=−0.31, p=0.033) and ACO (r=−0.530, p=0.002) groups.

To further validate the effect of age statistically, the ANCOVA test was performed using treatments as main factors and age as the covariate, which demonstrated that covariate age has a significant effect on AL change (p=0.001). Furthermore, the interactions between age and interventions were examined separately. Overall, a significant interaction effect (age×treatment group)



B

P values for interaction (age × treatment) based on pairwise comparison among the four groups

Pairwise comparison	*p* for interaction (age × treatment)
Control vs Atropine	0.112
Control vs Ortho-K	**0.013**
Control vs ACO	0.381
Atropine vs Ortho-k	**0.035**
Atropine vs ACO	0.463
Ortho-k vs ACO	0.072

Figure 2 Relationship between age and AL change among the four groups in the ITT set. (A) Scatter plot showing the relationship between 2-year AL elongation and age in the four groups in the ITT set. (B) Pairwise comparisons of the analysis of covariance tests among the four treatment groups in the ITT set. The control group used single-vision spectacles+placebo eye drops once every night; the atropine group used single-vision spectacles+0.01% atropine drops once every night; the ortho-k group used overnight ortho-k lens+placebo drops once every night; the ACO group used overnight ortho-k lens+0.01% atropine drops once every night. ACO, atropine combined with orthokeratology; AL, axial length; ITT, intention to treat; ortho-k, orthokeratology.

was detected (p for interaction=0.011), indicating the existence of an age-dependent effect.

The pairwise comparisons were performed to compare these age-dependent interactions in pairs (figure 2B). A significant difference of age-dependent effect existed in the control group versus the ortho-k group (p for interaction=0.013). Interestingly, a significant difference of age-dependent effect existed in the atropine group versus the ortho-k group (p for interaction=0.035). The PP analysis supported these results (online supplemental material 1).

Adverse events

No severe complications like infectious keratitis or conjunctivitis were observed. One patient in the ACO group got mechanical corneal abrasion at the 1-year visit and thus suspended treatment for 1 month. The intervention was resumed after the normal ocular condition was confirmed by clinicians. Two individuals in the ortho-k group were thought to be with suspected superficial punctuate keratitis at visits of 1 and 6 months, respectively. Both cases resolved after 1-week lens wear suspension, and lens wear was resumed after the restoration of ocular surface condition confirmed by clinicians. At the 1-month visit, two individuals in the atropine group and one individual in the ACO group reported photophobia at bright backgrounds lasting about 15 min. Since these individuals claimed no obvious disturbance to their daily study or activity, no specific measure was taken and all of them continued with the treatment. No other adverse events were observed.

DISCUSSION

Previous 1-year studies and our previous works suggested the short-term efficacy of the ACO treatment.[13 18] To clarify the long-term efficacy and illuminate the age effect, the current age-stratified RCT study compared the 2-year efficacy among atropine, ortho-k and ACO treatments, which reconfirmed the long-term efficacy of the 0.01% atropine drops and ortho-k treatment. Compared with monotherapy, overall, ACO treatment can get better 2-year efficacy (figure 1).

However, in the subgroup aged 8–10, the efficacy of ACO treatment was similar to ortho-k (p=0.106). In the subgroup aged 10–12, the efficacy of ACO was similar to atropine (p=0.121). This result suggested the improvement of ACO treatment might be influenced by age.

The results that originated from RCTs can provide more solid evidence than other designs.[23] Hence, to compare the efficacy with previous studies, table 3 included all recent RCTs related to the 0.01% atropine drops, ortho-k or ACO treatment.[6 12 15–17] The 1-year outcomes of atropine or ortho-k treatment revealed in the current study were consistent with the previous results.[6 12 15–17] However, the 1-year AL elongation (0.20±0.23 mm) of ACO treatment in the current study was slightly more than the previous study (range from 0.07 mm to 0.14 mm) (table 3). The 2-year efficacy of monotherapies was consistent with previous results.[6 16 17] Meanwhile, the result of 2-year AL elongation in the current ACO treatment (0.31±0.23 mm) was similar to that of the previous study of Kinoshita *et al* (0.29±0.20 mm).[16] Furthermore, in the current study, the ACO treatment can get better efficacy than monotherapy in 2 years, which was in accord with the previous study.[12 15 16]

Although these treatments have been validated to be effective in myopia, both the current and previous studies have found that significant individual variation existed.[4 8–10] So which factors influence the efficacy? If the influential factors are revealed, how should clinicians make a better choice? Table 2 shows the answer to this issue.

As shown in table 2, age was the most influential factor associated with annual AL elongation in all four groups (all p<0.05) according to the multivariate models. The ANCOVA test validated the significant role of the covariate age was significant in efficacy (p=0.001), which was consistent with the previous study.[5] Furthermore, the pairwise comparisons based on the ANCOVA test illuminated that the age-dependent effect significantly differs in the control group versus the ortho-k group (p for interaction=0.013) and in the atropine group versus the ortho-k group (p for interaction=0.035) (figure 2B). Combined with figure 2A, we can hypothesise that compared with spectacles, the younger the age, the better the efficacy of the ortho-k treatment can be realised (p for interaction=0.013), which was in accord with previous studies.[4 8–10] Cho *et al* also reported that ortho-k can achieve better efficacy at a younger age, whose results were repeated by several studies.[16 24 25]

As for the atropine group, Li *et al* and Chia *et al* observed that low-concentration atropine can achieve better efficacy in older age, and younger age is associated with poor treatment response.[10 11] In the current study, the interaction between atropine and the control group was insignificant (p for interaction=0.112). This difference may be due to the narrower age range and a smaller sample size in the current study. However, the interaction between atropine and ortho-k group (p for interaction=0.026) demonstrated that atropine may get better efficacy in older age compared with ortho-k. The mechanism of the poorer efficacy of low-dose atropine in younger children is still unclear and deserves further investigation.[26] Age-dependent effect existed in all groups, which may be the reason why the younger children can get poorer treatment response.

The current 2-year RCT study included both atropine and ortho-k for the first time (table 3) and makes a direct comparison between them, which prompts that to realise better efficacy, younger children

Table 3 Previous RCTs related to the efficacy of 0.01% atropine drops, ortho-k or ACO treatment

	Baseline age (year)	Baseline SER (D)	1-year AL change (mm)				2-year AL change (mm)			
			Control	Atropine*	Ortho-k	ACO	Control	Atropine	Ortho-k	ACO
Tan *et al*[15]	6~11	−1.00 to −4.00	–	–	0.16±0.15	0.07±0.16	–	–	–	–
Kinoshita *et al*[16]	8~12	−1.00 to −6.00	–	–	0.21±0.13	0.12±0.08†	–	–	0.40±0.23	0.29±0.20
Chia *et al*[17]	6~12	−1.00 to −6.00	–	0.24±0.19	–	–	–	0.41±0.32	–	–
Yam *et al*[6]	4~12	≤−1.00	0.43±0.21 (0%)‡	0.35±0.24 (18.6%)	–	–	–§	0.59±0.38	–	–
Zhao and Hao[12]	5~14	−1.00 to −6.00	0.72±0.21 (0%)	0.24±0.12 (66.6%)	0.29±0.11 (59.7%)	0.14±0.08 (80.5%)	–	–	–	–
The current study	8~12	−1.00 to −6.00	0.52±0.34 (0%)	0.25±0.20 (51.9%)	0.24±0.17 (53.8%)	0.20±0.23 (61.5%)	0.81±0.35 (0%)	0.42±0.23 (48.1%)	0.43±0.22 (46.9%)	0.31±0.23 (61.7%)

Data are presented as mean±SD unless otherwise indicated.
*All subjects in the atropine group were given 0.01% atropine drops once every night.
†Subjects in the ACO group from Kinoshita *et al* had already received ortho-k for 3 months before ACO treatment.
‡Percentage of efficacy was calculated based on the control group (control group was considered as no efficacy).
§Subjects in the control group from Yam *et al* was switched to the atropine group owing to ethical considerations.
ACO, atropine combined with orthokeratology; AL, axial length; ortho-k, orthokeratology; RCT, randomised controlled trial; SER, spherical equivalent refraction.

might tend to be treated with ortho-k, while older children tend to be treated with atropine compared with ortho-k. The age cut point is potentially located between the age of 10 and 11 (figure 2). Few adverse events occurred in the combined treatment group or the monotherapy group. However, if patients consider the economic factors, younger children can take ortho-k monotherapy first for myopia control. This hypothesis needs to be validated in further study.

As for the limitations, at the final follow-up, the valid sample size was relatively small, although the criteria of sample calculation and subject recruitment were strictly observed. One reason is the increased drop-out rate caused by the COVID-19 pandemic, which was unanticipated at the beginning of the study.[27] Hence, some non-significant findings in analysis in the age subgroups may be the result of the lack of samples, and these findings should be verified by further study with a larger sample size. The unanticipated COVID-19 pandemic probably also affected the behaviour of children and intervened in myopia progression, and behavioural data were not collected in the current study. In addition, SER data are important in myopia progression. However, the reshape effect of ortho-k on cornea can cause obvious error in the evaluation of SER; hence, SER was not the primary outcome in this study. Lastly, the trial was conducted in a single centre. However, the trial protocol was highly standardised, and the trial was conducted in a highly specialised ophthalmic centre.[28] Further a multicentre RCT study with a larger sample size is favourable to validate the findings revealed in the current research.

In conclusion, the current stratified RCT study confirmed the long-term efficacy of the atropine and ortho-k treatment in children aged 8–12. Combined treatment can significantly improve the efficacy compared with monotherapy in children aged 8–12. However, this improvement was not still obvious in age subgroups. When using monotherapy, younger children might benefit more from ortho-k. Further multicentre RCT study with a larger sample size is favourable to validate this hypothesis.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was conducted at Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangzhou, China. The current study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Ethical Committee of Zhongshan Ophthalmic Center, Sun Yat-Sen University. Both written and verbal informed consent was obtained from the participants and their parents or guardians before the study.

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