Combined Orthokeratology with Atropine for Children with Myopia: A Meta-Analysis

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\textbf{Keywords} Myopia · Orthokeratology · Atropine · Axial length · Combination therapy

\textbf{Abstract}

\textbf{Background:} Myopia has become a worldwide public health issue, which is occurring at a younger age, leading to an increased risk of high myopia. Ocular complications associated with high myopia can lead to irreversible vision loss. It is urgent and critical to explore effective treatment to slow down or even stop the progression of myopia in young children.

\textbf{Objective:} The aim of the study was to evaluate the additive effects of orthokeratology (OK) and 0.01\% atropine ophthalmic solution for myopia in children. \textbf{Methods:} We searched PubMed, Cochrane Library, EMBASE, MEDLINE, Web of science, Ovid, EBSCO host, CNKI, and CBM to collect eligible studies. Efficacy and safety were evaluated in terms of the axial length (AL), uncorrected distant visual acuity (UCVA), corneal endothelial cell density (CECD), and intraocular pressure (IOP). We calculated the weighted mean difference (WMD) and the 95\% confidence intervals (CIs) of all outcomes and plotted on forest plots. \textbf{Results:} Four studies were ultimately included, involving a total of 267 subjects. This meta-analysis revealed that the mean AL of the subjects in the experimental group was 0.09 mm less than that of subjects in the control group (WMD = −0.09, 95\% CI [−0.15, −0.03], \(p = 0.003\)). There was no significant difference in UCVA, CECD, and IOP between the 2 groups (WMD was −0.01 [95\% CI: −0.03, 0.01], 11.75 [95\% CI: −4.09, 27.58], 0.12 [95\% CI: −0.40, 0.63], respectively). None of the studies reported severe adverse events. \textbf{Conclusion:} Our study suggests that the combination of OK and 0.01\% atropine is more effective in slowing axial elongation than OK monotherapy in children with myopia in a relatively short duration of treatment. In addition, the combination therapy has no negative influence on UCVA, CECD, and IOP.

\textbf{Introduction}

Myopia has become a worldwide public health issue, particularly in some eastern Asian areas, where the prevalence in children is as high as 90\% [1]. It is estimated that the global prevalence of myopia and high myopia will show a significant increase, affecting nearly 5 billion people and 1 billion people, respectively, by 2050 [2]. In addition...
to a huge socioeconomic burden, ocular complications associated with high myopia such as cataract, glaucoma, retinal detachment, and myopic maculopathy, can lead to irreversible vision loss, which seriously affects the quality of patients’ life [3]. Myopia is occurring at a younger age, leading to an increased risk of high myopia [4]. Therefore, it is urgent and critical to explore effective treatment to slow or even stop the progression of myopia in young children.

The progression of myopia in children is mainly caused by axial elongation, so controlling axial elongation is important to prevent high myopia [5]. Current popular methods for controlling the progression of myopia include optical, pharmaceutical, and behavioral interventions [6]. It is possible that an additive effect could exist if the treatments with different mechanisms of action are combined. Orthokeratology (OK) is custom-designed rigid contact lens, which canreshape the cornea to reduce refractive error and allow clear unaided vision during the day [7]. A number of prospective clinical trials and meta-analyses have demonstrated that OK could inhibit axial eye growth and myopia progression [8–13]. Atropine has also been shown to ameliorate the myopia progression in children. The mechanism of action may be a direct effect of atropine on the eyeball to stop eyeball elongation or an indirect effect by relaxing the focusing muscles of eyes [4]. Efficacy and adverse effects of atropine in myopia with children have been becoming a focus of attention. A 2011 meta-analysis [4] showed better efficacy at higher doses, but included only 6 studies, and evaluated only the moderate and high doses of atropine, without the low dose. In 2017, a meta-analysis of 3,137 children younger than 18 years with myopia found no difference in the efficacy of atropine at different concentrations (low dose, 0.01%; moderate dose, >0.01%–<0.5%; and high dose, 0.5%–1.0%), whereas the adverse effects were dose dependent, which supported the use of low dose atropine (0.01%) to reduce the progression of myopia in children [14]. However, several randomized control trials have demonstrated that atropine eye drops are effective in the control of myopia in a dose-dependent manner. Chia et al. [15] showed that a dose-related response on myopia was found among the 3 treatment arms (0.5%, 0.1%, and 0.01% atropine treatment arms), although differences between treatment arms were clinically small. Their 5-year clinical trial [16] found that 0.01% atropine eye drops were more effective in slowing myopia progression with less visual side effects than higher doses of atropine. In addition, they found that a myopic rebound was greater in eyes that had received 0.5% and 0.1% atropine after atropine was stopped. In contrast, the 0.01% atropine had less myopic rebound, and the effect was more modulated and sustained [17]. A randomized, placebo-controlled, double-masked trial [18] also showed the 0.05%, 0.025%, and 0.01% atropine reduced myopia progression along a concentration-dependent response. Similarly, some studies clearly confirmed the dose-dependency on axial length (AL) growth and spherical equivalent refractive error (SER) [6, 19]. It can be seen that the relationship between atropine effect and dose in controlling myopia progression is still disputable. However, considering the adverse effects and rebound effects of atropine in different doses, 0.01% atropine combined with OK could be an optimal treatment option.

In recent years, several prospective randomized clinical trials [20–22] have been conducted to investigate the additive effects of OK and 0.01% atropine ophthalmic solution in slowing the progression of myopia. The results of these studies were similar, suggesting that combined treatment with atropine and OK was more effective in slowing axial elongation than OK monotherapy in children with myopia. We conducted this meta-analysis to better evaluate whether the combination of OK and 0.01% atropine has an additive effect in slowing the progression of myopia in children.

**Methods**

**Search Strategy**

We searched PubMed, Cochrane Library, EMBASE, MEDLINE, Web of science, Ovid, EBSCO host, CNKI, and CBM to obtain relevant studies from their inception to March 2020 in all languages, using Medical Subject Headings and free words combined with myopia, refractive errors, OK, and atropine. We also carefully screened the reference lists of published reviews to identify applicable studies.

**Eligibility Criteria**

We selected the studies according to the following criteria: (1) the type of study included was randomized controlled trial (RCT), (2) the participants were younger than 18 years and definitively diagnosed as myopia, (3) the experimental group was treated with OK and 0.01% atropine, while the control group was treated with OK or 0.01% atropine alone, and (4) at least 1 outcome that we were interested in was reported in the studies, including the changes in AL, uncorrected distant visual acuity (UCVA), corneal endothelial cell density (CECD), and intraocular pressure (IOP). The followings were excluded: conference abstracts, case reports, duplicate publications, letters, and reviews, and studies without complete data or with inconsistent or erroneous data, incorrect random methods, or intervention methods.
Data Extraction and Quality Assessment
Two researchers (S.Z.W. and J.W.) independently screened titles and abstracts of the retrieved literatures, and then they read the full text carefully to determine which studies were eventually included. Disagreements were resolved by discussion. Two researchers independently extracted the required data from each eligible study, including first author, publication year, country or area, sample size, age, intervention and control, duration of treatment, and outcomes.

We assessed the qualities of the included literature for the following 7 aspects according to the Cochrane Collaboration’s tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each entry was evaluated at "low risk of bias," "high risk of bias," or "unclear risk of bias." Discrepancies were resolved by discussion.

Statistical Analysis
The Review Manager (version 5.3; Cochrane Collaboration) was used for data analysis. We used the weighted mean difference (WMD) with 95% confidence intervals (CIs) in AL, UCVA, CECD, and IOP to assess myopia progression as well as adverse effects. Heterogeneity was assessed by means of $I^2$ statistics. If $I^2 \geq 50\%$, the random-effect model was used for meta-analysis, otherwise the fixed effect model was chosen. A sensitivity analysis was performed to investigate the sources of heterogeneity. There were not sufficient studies ($n < 10$) to analyze publication bias.

Results

Literature Search and Characteristics of Included Studies
A total of 643 records were initially identified through database searching. 453 records were screened after duplicates removal. Among them, 430 records were excluded due to irrelevance, and then, 23 of full-text articles were assessed for eligibility. Ultimately, 4 studies were included in meta-analysis after reading the full text. The screening process of eligible studies is shown in the flow diagram in Figure 1.

Table 1 shows the characteristics of 4 eligible studies. A total of 267 children were enrolled in this meta-analysis (age range from 6 to 16 years old). 1 study (Tan et al. [21]) was performed in Hong Kong, China, 1 (Kinoshita et al. [22]) in Japan, and the remaining 2 (Shi [23], Shi et al. [24]) in mainland China. The time to intervention ranged from 1 to 12 months. All studies concentrated on children with low to moderate myopia ($<-6.00\mathrm{D}$). The 0.01% atropine was self-prepared in all studies. In Kinoshita et al. [22] study, the atropine 0.01% ophthalmic solution was specially prepared by diluting Nitten ATROPINE Ophthalmic
Solution 1% with physiological saline at a ratio of 1:99 in a sterile manner. The 0.01% atropine used in Tan et al. [21] study was single-dose and preservative-free. The other 2 studies did not describe the preparation methods in detail.

**Risk of Bias Assessment**

Figure 2 shows the risk of bias of the included studies. Two of the included studies [22, 23] explicitly pointed out the randomization methods, while the remaining 2 studies [21, 24] did not completely report all outcome data. Furthermore, the other 2 studies did not describe the preparation methods in detail.

**Change in AL**

Four studies all reported and analyzed the changes in AL in the OK and 0.01% atropine combination group and the OK monotherapy group. We extracted the data from these 4 studies for a meta-analysis. The combined results showed that the mean AL of the 128 subjects in the experimental group was 0.09 mm (95% CI: −0.15, −0.03) less than that of 134 subjects in the control group, as Table 1.

**Table 1. Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country/region</th>
<th>Study type</th>
<th>Sample size (E/C)</th>
<th>Age, years</th>
<th>SER, D (E/C)</th>
<th>Intervention</th>
<th>Duration of treatment, months</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinoshita et al. [22]</td>
<td>Japan</td>
<td>RCT</td>
<td>20/21</td>
<td>8–12</td>
<td>−2.81±1.43/−2.95±1.43</td>
<td>OK + 0.01% atropine</td>
<td>OK</td>
<td>12</td>
</tr>
<tr>
<td>Tan et al. [21]</td>
<td>Hong Kong, China</td>
<td>RCT</td>
<td>33/35</td>
<td>6–11</td>
<td>−2.7±0.91/−2.88±0.92</td>
<td>OK + 0.01% atropine</td>
<td>OK</td>
<td>1</td>
</tr>
<tr>
<td>Shi [23]</td>
<td>China</td>
<td>RCT</td>
<td>31/33</td>
<td>9–14</td>
<td>−3.27±0.82/−3.29±0.89</td>
<td>OK + 0.01% atropine</td>
<td>OK</td>
<td>12</td>
</tr>
<tr>
<td>Shi et al. [24]</td>
<td>China</td>
<td>RCT</td>
<td>47/47</td>
<td>9–16</td>
<td>−1.50−6.00</td>
<td>OK + 0.01% atropine</td>
<td>OK</td>
<td>6</td>
</tr>
</tbody>
</table>

E/C, experiment group/control group; SER, spherical equivalent refractive error; AL, axial length; UCVA, uncorrected distant visual acuity; CECD, corneal endothelial cell density; IOP, intraocular pressure; OK, orthokeratology; RCT, randomized controlled trial.

E/C, experiment group/control group; SER, spherical equivalent refractive error; AL, axial length; UCVA, uncorrected distant visual acuity; CECD, corneal endothelial cell density; IOP, intraocular pressure; OK, orthokeratology; RCT, randomized controlled trial.
shown in Figure 3. There was statistical heterogeneity between the 2 groups (p < 0.00001, I² = 89%). We performed sensitivity analysis (removal of a study 1 by 1) to investigate the sources of heterogeneity. By omitting the Tan et al. [21] study, heterogeneity was reduced from 89% to 9% and the overall effect was not inversed (Table 2). The WMD in the change of AL was 0.12 mm (95% CI: 0.09, 0.14; p = 0.33, I² = 9%).

**Change in UCVA**

Three studies involved the changes in UCVA. We combined the data from these 3 studies to obtain the results. There were 81 participants in the experimental group and 87 participants in the control group. The pooled results indicated that there was no significant difference in UCVA between the 2 groups (95% CI: −0.03, 0.01), as shown in Figure 4. There was no statistical heterogeneity between the 2 groups (p = 0.99, I² = 0%).

**Change in CECD**

Two studies reported the changes in CECD between the combination group and monotherapy group. The combined results indicated that there was no statistical difference in CECD between the 2 groups (95% CI: −4.09, 27.58), as shown in Figure 5. There was no significant between-study heterogeneity (p = 0.49, I² = 0%). It should be noted that the high variability of CECD in the Kinoshita et al. [22] study led to a disputable conclusion. The value of meta-analysis for CECD is limited.

**Change in IOP**

The changes in IOP between the 2 groups were reported by 2 studies. The combined results revealed a WMD of 0.12, 95% CI (−0.40, 0.63), which suggested there was no significant difference in IOP between the 2 groups, as shown in Figure 6. There was no statistical heterogeneity between the 2 groups (p = 0.51, I² = 0%).

**Adverse Event**

No severe adverse events were reported in our included studies. The most common ocular health issues were corneal stains and conjunctivitis. The incidence of central corneal staining reported by 1 study [21] was <10% in either group, which was consistent with previous studies. The authors analyzed that the corneal staining was mainly related to OK lens wearing rather than 0.01% atropine

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**Table 2. Sensitivity analysis**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental (mean SD total)</th>
<th>Control (mean SD total)</th>
<th>Weight, %</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nozomi K., 2018</td>
<td>0.09 0.12 20</td>
<td>0.19 0.15 20</td>
<td>18.5</td>
<td>−0.10 [−0.18, −0.02]</td>
<td></td>
</tr>
<tr>
<td>Qi T., 2019</td>
<td>−0.05 0.05 30</td>
<td>−0.02 0.03 34</td>
<td>28.7</td>
<td>−0.03 [−0.05, −0.01]</td>
<td></td>
</tr>
<tr>
<td>Shi M., 2018</td>
<td>0.12 0.07 31</td>
<td>0.22 0.08 33</td>
<td>26.7</td>
<td>−0.10 [−0.14, −0.06]</td>
<td></td>
</tr>
<tr>
<td>Shi Y., 2017</td>
<td>0.11 0.09 47</td>
<td>0.25 0.11 47</td>
<td>26.1</td>
<td>−0.14 [−0.18, −0.10]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 128 100.0  −0.09 [−0.15, −0.03]

Heterogeneity: τ² = 0.00, χ² = 28.34, df = 3 (p < 0.00001); I² = 89%
Test for overall effect: Z = 3.00 (p = 0.003)

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**Fig. 3.** Forest plot of the comparison of change in AL. AL, axial length; OK, orthokeratology; CI, confidence interval.

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eye drops. One case of brief episodes of conjunctivitis occurred in each group, which may be associated with contamination of the lens during insertion and increased eye rubbing. In another study [22], there was 1 case of corneal infiltration in the monotherapy group and 1 case of mild superficial punctate keratopathy in the combination therapy group, which were resolved after topical therapy.

Shi [23] reported that at follow-up a total of 47 (36.7%) of the patients in both groups had mild corneal staining, which were cured after treatment, and 4 cases (12.9%) presented mild outdoor photophobia in the combined treatment group, which did not affect normal study and life.
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Discussion

Our meta-analysis confirms that the combination of OK and 0.01% atropine is more effective in slowing axial elongation than OK monotherapy in children with myopia. Moreover, no significant difference was found in UCVA, CEC, and IOP between the combination group and monotherapy group, indicating that the combination therapy for children with myopia has no negative influence on clinical results. No severe adverse events were reported in our included studies. To our knowledge, this is the first overview of systematic reviews and meta-analysis on efficacy of the combined treatment of OK and 0.01% atropine for children with myopia.

OK is a clinical technique that uses specially designed rigid contact lenses to reshape the cornea to temporarily reduce or eliminate refractive error [25]. In recent years, a large number of studies have proved that OK can effectively delay the development of myopia in children, although the mechanism is still unclear [26–29]. A lot of scholars hold that wearing OK improves the defocus on the peripheral retina with increases in the higher order aberration through corneal epithelial redistribution in which the central cornea is thinned, and the mid-periphery is thickened [22]. Atropine is a nonselective muscarinic antagonist and has been widely studied in recent years to prevent the progression of myopia in children [30]. In addition to relaxing the focusing muscles of eyes, atropine may also block the muscarinic receptors in the retina and sclera that mediate axial elongation [31, 32]. 0.01% ATROPINE ophthalmic solution for children with myopia has been proved to be a safe and effective concentration with few vision-related adverse effects [16, 18]. Based on the different mechanisms of optics and pharmacology, combined OK with 0.01% atropine for children with myopia can produce better treatment effects, which our meta-analysis also proves.

A meta-analysis [33] reported that OK slowed the axial elongation more effectively for children with higher myopia than with lower myopia. In our meta-analysis, One [22] of the included studies also researched the effect of SER and age of children on the therapeutic outcomes, and found that the suppressive effect of OK monotherapy on axial elongation was affected by the SER rather than the age of children. The additive effect of the combination group in slowing axial elongation was greater in children with lower myopia, whereas the monotherapy group was as effective as the combination group in children with higher myopia. The authors’ point is that when OK therapy is for children with higher myopia, the amount of myopia correction becomes smaller, the defocus on the peripheral retina is not sufficiently improved by OK monotherapy for children with lower myopia, and then adding 0.01% atropine seems to be more effective. However, none of the included studies in our meta-analysis reported the peripheral refraction and higher order aberration, which is not convenient for us to further study the mechanism of combination therapy.

In our meta-analysis, heterogeneity arose between the 2 groups when the changes of AL were compared. Using of a random-effect model does not deal with heterogeneity. We identified the Tan et al. [21] study as the primary source of heterogeneity through sensitivity analysis. The study observed significant reductions in AL between the 2 groups of subjects after 1-month of treatment. AL was initially observed to be shortened after commencement of OK lens wear, which was consistent with previous studies [10, 34]. It has been suggested that the axial shortening may be due to choroidal thickening in response to myopic defocus or corneal thinning after OK lens wear [35–37]. Since subjects of both groups wore OK lenses in the study, the difference in the amount of axial shortening may have been due to atropine (0.01%). However, in the other 3 studies (≥6 months of treatment), axial shortening was not observed in either the experimental group or the control group, suggesting that the length of intervention time would affect the experimental results. In addition, the SER of subjects may also be a factor. In Tan et al. [21] study, the SER of subjects were −1.00 to −4.00 diopters (D), while these in the remaining studies were −1.00 to −6.00 diopters (D). Kinoshita et al. [22] study found that the additive effects of OK and 0.01% atropine in slowing axial elongation was greater in children with lower myopia, while OK monotherapy was as effective as combining combination therapy in children with higher myopia. In order to better evaluate the effect of combination therapy, subgroups of the subjects’ SER should also be made.

Our study has some limitations. We clearly realized that the small numbers of available studies and their short follow-up time are responsible for the limited validity of this early meta-analysis. First, only 4 RCTs meeting the requirements were found, and high-quality RCTs were relatively lacking, although we conducted an extensive and comprehensive search of the database. If more high-quality, large-sample RCTs were done, we could draw more reliable conclusions. Second, the duration of treat-
ment was relatively short. Controlling myopia treatment requires a long-term assessment. However, the duration of treatment in the studies we included ranged from 1 month to 12 months. Long-term additive effects of OK and 0.01% atropine to slow axial elongation in children with myopia is not yet fully established. Our study only confirms that the combination of OK and 0.01% atropine is more effective in slowing axial elongation than OK monotherapy in children with myopia in a relatively short duration of treatment. Larger sample size and longer study duration are warranted to confirm the real effectiveness of this combination treatment for children with myopia. Meanwhile it is also warranted to investigate long-term side effects and rebound phenomenon of OK and 0.01% atropine [38]. Third, all of included studies were conducted only in Asia. In order to obtain more scientific evidence, more large-scale, multi-ethnic, blinded, RCTs should be carried out in the future. Fourth, none of the included studies took into consideration the external factors such as outdoor activity time and near work time. Some studies have shown that outdoor light exposure is related to myopia incidence, and some evidence suggests outdoor light exposure slows myopic progression in individuals with myopia [39–43]. The influence of external factors on the progression of myopia should also be considered in future studies.

Conclusions

The combination of OK and 0.01% atropine is more effective in slowing axial elongation than OK monotherapy in children with myopia, and has no negative influence on UCVA, CEC, and IOP in a relatively short duration of treatment. The long-term efficacy and safety of the combination therapy of OK and 0.01% atropine in children with myopia will need to be further confirmed by more studies.

Statement of Ethics

All analyses were based on published studies, and thus, no ethical approval and informed consent are required. Nonetheless, the study adhered fully to the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funds were used in the conduct and completion of this study.

Author Contributions

S.W. and J.W. extracted data from published studies, analyzed the results, and drafted the manuscript. They contributed equally to the study. N.W. provided oversight for the extraction and analysis, and identified the accuracy of results and discussion presented in the manuscript.

Data Availability Statement

All data are within the paper and fully available without restriction.

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