The effect of 0.01% atropine on ocular axial elongation for myopia children
A protocol for systematic review and meta-analysis
Yue Gao, MM⁴, Yan Yu, MM⁵,⁶,

Abstract
Background: Orthokeratology (OK) has a significant effect on the control of myopia progression, and has been accepted by doctors and patients. A small number of studies have shown that the combination of OK and atropine can enhance myopia control. However, owing to individual differences, research groups, drug concentrations, and research design differences, the safety and effectiveness of the combined treatment still need to be verified. Therefore, the present meta-analysis aimed to determine the effect of 0.01% atropine on ocular axial elongation in myopic children.

Methods: We searched the PubMed, Cochrane Library, and CBM databases from inception to March 1, 2022. Meta-analysis will be conducted using STATA version 14.0 and Review Manager version 5.3 softwares. We calculated the weighted mean differences (WMD) to analyze the change in ocular axial length (AL) between orthokeratology combined with 0.01% atropine (OKA) and OK alone. Cochran’s Q-statistic and I² test were used to evaluate the potential heterogeneity between studies. A sensitivity analysis was performed to evaluate the influence of single studies on the overall estimate. We will also perform subgroup and meta-regression analyses to investigate potential sources of heterogeneity. We will conduct Begger’s funnel plots and Egger’s linear regression tests to investigate the publication bias.

Results: This systematic review aimed to determine the effect of 0.01% atropine on ocular axial elongation in children with myopia.

Conclusions: These findings provide helpful evidence for the effect of 0.01% atropine on ocular axial elongation in myopic children.

Abbreviations: AL = axial length, OK = orthokeratology, OKA = orthokeratology combined with 0.01% atropine, WMD = weighted mean differences.

Keywords: atropine, meta-analysis, myopia, orthokeratology

1. Introduction
Myopia causes blurry vision when looking at distant object, which has become a worldwide healthy issue especially in some western Ascian area. There are approximately 1.406 billion myopia patients with myopia worldwide, accounting for 22.9% of the total population. It is estimated that there will be 4.758 billion myopia patients worldwide by 2050, accounting for 49.8% of the total population. Myopia causes not only a decline in vision, but also serious complications that can lead to irreversible vision loss, such as glaucoma, cataract, retinal detachment, retinal atrophy, and other eye diseases. The number of children with myopia has been increasing rapidly, particularly in recent decades. Children with myopia show an increasingly younger trend, thereby increasing the risk of high myopia. Therefore, it is imperative to explore appropriate treatments to control the progression of myopia in children.

Axial elongation is the main cause of myopia; therefore, controlling axial elongation is important for preventing high myopia. Current measures for controlling the progression of myopia include wearing glasses, orthokeratology (OK) lenses, low-concentration atropine, and behavioral interventions.
Atropine, a non-selective M receptor antagonist, has been shown to significantly control the development of myopia.[7] One study used 0.5%, 0.1%, and 0.01% concentrations and found that the higher the concentration, the more obvious the rebound, while the effect of 0.01% atropine on controlling the growth of myopia was sustained and stable.[8] A meta-analysis demonstrated the effect of atropine at different concentrations on myopia.[9] At present, 0.01% atropine is considered to have good curative effects, fewer adverse reactions, and more stability and less rebound than other concentrations of atropine after drug withdraw.[10] OK has proven to be an effective means of controlling the progression of myopia in adolescents.[11] The mechanism of controlling the progression of myopia is that the hydraulic pressure generated by the contact lens temporarily reshapes the cornea, aiming to correct the distant vision by changing the shape of the central cornea. Second, it makes the peripheral cornea steeper to make the image focus in front of the peripheral retina, reduce the refractive error, and achieve the best corrected vision.[12] OK has a significant effect on the control of myopia progression and has been accepted by both doctors and patients.[13] A small number of studies have shown that the combination of orthokeratology and atropine (OKA) can enhance myopia control.[14–16] However, owing to individual differences, research groups, drug concentrations, and research design differences, the safety and effectiveness of the combined treatment still need to be verified. Therefore, the present meta-analysis aimed to determine the effect of 0.01% atropine on ocular axial elongation in myopic children.

2. Methods

2.1. Literature search

We searched the PubMed, Cochrane Library, and CBM databases from inception to March 1, 2022. The following keywords and MeSH terms were used: ["orthokeratology"] and ["atropine"] and ["myopia"] (Table 1). We will also conduct a manual search to identify other potential articles.

2.2. Eligibility criteria

1. Type of study. This study included high-quality randomized controlled trials, cohort studies, and case-control studies.
2. Type of patients. The patients were children aged <18 years who had undergone myopia. We will not apply any restrictions on race, age, educational background, or economic status.
3. Intervention and comparison. This study compared OKA with OK for myopia control.
4. Type of outcomes. The primary outcome was ocular axial elongation.

2.3. Data extraction

Relevant data were systematically extracted from all included studies by two researchers using a standardized form. The following data were collected: first author’s surname, publication year, language of publication, study design, sample size, age, follow-up time, ocular axial length (AL), instrument, SER, and ocular axial elongation.

2.4. Quality assessment

The quality of the primary studies will be assessed using the Cochrane risk of bias tool[17] by two independent researchers and an additional investigator in the case of any conflicts. The risk of bias for each study was evaluated according to selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Each of these biases was classified as high-risk (score 0), low-risk (score 2), and unclear risk of bias (score 1). The total risk of bias was calculated by summation of all categories.

2.5. Statistical analysis

Review Manager 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark) and STATA version 14.0 (Stata Corp, College Station, TX) will be used for the meta-analysis. We calculated the weighted mean differences (WMD) with 95% confidence intervals (CIs) to analyze the change in AL between OKA and OK. Cochran’s Q-statistic and $I^2$ test were used to evaluate the potential heterogeneity between studies. If significant heterogeneity was detected ($Q$ test $P < .05$, $I^2$ test $> 50\%$), a random-effects model or fixed-effects model was used. A sensitivity analysis was performed to evaluate the influence of single studies on the overall estimate. We will also perform subgroup and meta-regression analyses to investigate potential sources of heterogeneity. We will conduct Begger’s funnel plots and Egger’s linear regression tests to investigate the publication bias.

2.6. Ethics and dissemination

Ethical documents will not be obtained because this study will be conducted based on data from the published literature. We expect that this study will be published in a peer-reviewed journal.

3. Discussion

The prevalence of myopia, the most common type of ametropia, is increasing every year.[18] The degree of myopia will continue to increase with age, seriously affecting children’s normal lives in the future.[19] As the loss of vision caused by high myopia is irreversible, myopia have become one of the main causes of untreated vision loss in the world.[20] Axis is an important monitoring index for myopia. Axial myopia occurs when the axis elongates beyond the normal value. There is a parallel relationship between the length of the axis and the progression curve of myopia corresponding to age.[21] Atropine, an alkaloid derived from belladonna, is a non-selective muscarinic acetylcholine receptor antagonist. Atropine eye drops act on antimuscarinic receptors of the retina, choroid, and sclera. It may increase choroidal thickness by regulating dopamine release, or it may regulate scleral fibroblasts, interfering with scleral remodeling in myopia. The effect of atropine on myopia progression is dose dependent.[22] Some studies have suggested that 0.01% atropine has a positive effect on controlling axial elongation.

### Table 1

| Number | Search strategy sample of PubMed. |
|--------|----------------------------------|
| 1      | Orthokeratology                  |
| 2      | Atropine                         |
| 3      | Myopia                           |
| 4      | 1–3                              |

| Search terms | 1 | 2 | 3 | 4 |
|--------------|---|---|---|---|
| Orthokeratology | ✓ | ✓ | ✓ | ✓ |
| Atropine | ✓ | ✓ | ✓ | ✓ |
| Myopia | ✓ | ✓ | ✓ | ✓ |
| 1–3 | ✓ | ✓ | ✓ | ✓ |
growth and suppressing myopia. The OK lens adopts a reverse geometric design and is composed of highly oxygen-permeable materials. The refractive power was changed by changing the shape of the central cornea. Studies of various mechanisms have confirmed that wearing OK devices is an effective way to control the progression of myopia.\(^{[23,24]}\) Therefore, the efficacy of OK combined with 0.01% atropine in the treatment of myopic children is a problem worth studying. At present, there is a lack of multicenter and large-sample research on this aspect. This study aimed to provide a comprehensive and reliable conclusion regarding the effect of 0.01% atropine combined with OK on ocular axial elongation in children with myopia.

**Author contributions**

Conceptualization: Yan Yu.

Data curation: Yan Yu, Yue Gao.

Methodology: Yan Yu.

Supervision: Yue Gao

Writing – original draft: Yue Gao.

Writing - review & editing: Yue Gao

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