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Adjunctive effect of orthokeratology and low dose atropine on axial elongation in fast-progressing myopic children—A preliminary retrospective study

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ABSTRACT

Purpose: To investigate the adjunctive effect of orthokeratology (ortho-k) and low-dose atropine eye drops on axial length elongation in fast-progressing myopic children.

Methods: Axial elongation in 60 eyes of 60 subjects who completed two years of ortho-k treatment was retrospectively reviewed. They were aged between 5.6–11.6 (mean, 8.3 ± 1.5) years old when they started ortho-k treatment. During their first year of ortho-k treatment (Phase One), they all demonstrated a faster than 0.25 mm/yr axial elongation rate. They were then treated with nightly 0.01% atropine in addition to ortho-k treatment for another year (Phase Two). Annual axial elongation rates before and after atropine treatment were compared.

Results: Baseline spherical equivalent refractive error was −2.65 ± 1.08 DS and axial length was 24.34 ± 0.92 mm for the study cohort. The mean axial elongation rate was 0.46 ± 0.16 mm/yr during Phase One, being significantly faster in younger children ($t = -4.920$, $P < 0.001$). When atropine was added, annual axial elongation rate significantly decreased to 0.14 ± 0.14 mm/yr ($t = -11.988$, $P < 0.001$), and those who were fast progressors in Phase One had a greater reduction in the rate of axial elongation during Phase Two ($t = -8.052$, $P < 0.001$).

Conclusions: Axial elongation rate is faster in younger children undergoing ortho-k treatment. For fast myopia progressors, low dose atropine may significantly slow axial elongation in addition to ortho-k's treatment effect. Those who have faster axial elongation after ortho-k treatment will benefit more from the addition of low dose atropine, regardless of their refractive error and age.

1. Introduction

Juvenile myopia is a disorder typified by an over-elongated eye and decreased unaided distance visual acuity typically starting at childhood or adolescence and progressing in severity until adulthood. The prevalence of juvenile myopia has reached alarming levels around the world, being most significant in East Asian countries like China [1]. Fast myopia progression and eye elongation is associated with a marked increase in the risk of myopia related complications such as retinal detachment and macular degeneration [2]. Multiple interventional methods including pharmaceutical and optical treatments have been proposed to retard myopia progression in children and juveniles with varied treatment effect [3].

Orthokeratology (ortho-k) is a technique using a reverse-geometry designed rigid gas-permeable contact lens worn while sleeping to temporarily reshape the cornea in order to correct low to moderate refractive error and improve unaided visual acuity during the day [4]. Aside from its vision-correcting function, ortho-k has been shown to slow axial elongation when compared to single vision lens wear in children, with an average control effect of approximately 41.7% across different studies [5].

Axial elongation rate after ortho-k treatment, however, varies significantly among individuals. The patient's age [6,7], initial refractive error [7–9] and pupil size [6,10] have all been proposed to be

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influencing factors on the myopia control effect of ortho-k, with younger children of lower refractive error being most likely to experience faster axial elongation during ortho-k treatment. Methods are therefore needed to address these fast progressors to yield more effective slowing of myopia progression and axial elongation.

Atropine is a non-selective muscarinic receptor antagonist that has a strong and sustainable cycloplegic effect when applied as an eye drop [11]. When used nightly in high dose (1%), it has been shown to slow axial elongation in children in the short-term, however cessation of the eye drop could cause a significant rebound in myopia progression in those eyes. The resultant overall change in spherical equivalent refractive error (SERE) in the atropine-treated eyes was −1.37 ± 0.78 D in comparison to −1.56 ± 0.89 D in the placebo-treated eyes at 36 months [11]. In contrast, lower dose (e.g., 0.01%) atropine eye drop has much fewer side effects when compared to higher doses and less rebound effect when medication is withdrawn [12]. In a five-year study, Chia et al showed that low dose atropine to be a safe and effective method for myopia control [13].

Since ortho-k from the optical arm and atropine from the pharmaceutical arm both serve as myopia control modalities, there may be an adjunctive treatment effect when used in combination. This preliminary study was designed to investigate the adjunctive effect of ortho-k and low dose atropine on myopia control in a group of Chinese children.

2. Methods

2.1. Study design

Chinese children who visited the Fudan University Eye and ENT Hospital (Shanghai, China) between August 2017 and March 2018 and who met the following criteria were included in this retrospective study: 1) aged under 12 years; 2) initial myopic refractive error between −5.00 D and −1.00 D; 3) have undergone ortho-k treatment for 1 year but were still experiencing an annual axial elongation rate faster than 0.25 mm/yr (defined as fast progressors); 4) have had one more year of nightly low dose (0.01%) atropine eye drop therapy in addition to the ortho-k treatment after being identified as 'fast progressors'.

3. Study protocol

3.1. Phase one

All subjects had comprehensive screening tests before ortho-k treatment, including anterior segment biomicroscopy, fundus examination, non-cycloplegic manifest refraction, visual acuity, and corneal topography. They were fitted with either spherical or toric designed 4-zone ortho-k lenses (Euclid, USA) in both eyes. For the first trial lens selection, flat K and corneal eccentricity were used to determine the alignment curve radius. A proper fitting was established based on fluorescein pattern with contact lenses on the eye and corneal topography. Lenses were ordered upon over-refraction targeted at plano. Follow-up visits were scheduled to 1 day, 1 week, 1 month, 3 months, and every 3 months after ortho-k lens wear. During regular follow-up visits, if daily visual acuity after ortho-k treatment dropped below 20/25, over-refraction would be done on the original ortho-k lens and a new lens ordered to retain 20/20 or better visual acuity, otherwise lenses were replaced routinely every 12–18 months.

Axial length (AL) measurement using the IOL-Master (Carl Zeiss, Germany) was done in both eyes at baseline and every 6 months after ortho-k lens wear. Subjects who showed axial elongation greater than 0.25 mm in the first year of ortho-k treatment were given the option to use low dose atropine in addition to ortho-k treatment. Those who agreed to use atropine were eligible for study Phase Two.

3.2. Phase two

Subjects were prescribed low dose atropine eye drop (0.01%, Pharmaceutical Department, Fudan University Eye and ENT Hospital) applied once per night, 30 min before ortho-k lens insertion. Although no quantitative evaluation on pupil size and accommodative function were performed, subjects were requested to log any visual disturbances associated with atropine use, e.g., photophobia, reading difficulties, etc., during follow-up visits. AL measurement was done every 6 months after atropine use (baseline AL for Phase Two was equivalent to the end-point AL for Phase One).

A historical control group from one of the authors' previous studies was included [7]. In that study, 64 subjects completed the 2-year study where they were treated with ortho-k lenses only (no atropine use). Twenty-nine out of the 64 subjects had axial elongation of 0.25 mm or greater in the first year and were considered fast progressors. They were identified as the control group for this study.

4. Statistical analysis

Axial elongation over time was evaluated using repeated measures ANOVA. Baseline SERE and age were tested against axial elongation using stepwise linear regression analysis in Phase One. Axial elongation rates during Phase One and Phase Two were compared using paired-samples *t* test. Baseline SERE, age, and axial elongation rate during Phase One were tested against the difference between Phase One and Two using stepwise linear regression analysis. Difference in axial elongation rate between the second year and the first year was compared between this experimental group and the historical control group using independent samples *t* test. A $P < 0.05$ was considered to be statistically significant.

5. Results

A total of 60 eyes from 60 subjects (right eyes only) were included in this study. They were aged between 5.6 to 11.6 (mean, 8.3 ± 1.5) years old when they first started ortho-k treatment. Baseline SERE and axial length was −2.65 ± 1.08 D and 24.34 ± 0.92 mm for the subjects enrolled in this study. All subjects underwent uneventful ortho-k treatment in both phases and no subjects reported photophobia or near vision difficulties. Axial length changed over time during the 2-year study period ($F = 4.236$, $P = 0.002$; Fig. 1).

5.1. Phase one

After the first year of ortho-k treatment, the mean AL of the subjects increased to 24.80 ± 0.87 mm, with a mean axial growth of

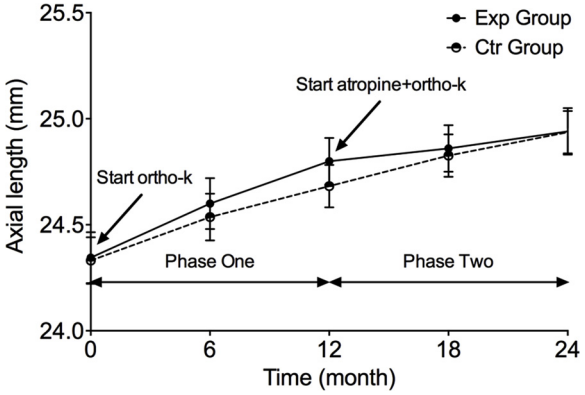

Fig. 1. Two-year axial growth of the subjects. Solid line stands for the current experimental group (Exp Group) and dashed line stands for the historical control group (Ctr Group).

Table 1
Mean ± SD of Age and SERE of the subjects who experienced ≥0.45 mm and < 0.45 mm axial elongation during the first year of ortho-k treatment.

1st year axial growth	≥0.46 mm (n = 28)	< 0.46 mm (n = 32)	P value
Age (y)	7.5 ± 1.2	9.0 ± 1.4	< 0.001
SERE (D)	−2.70 ± 1.10	−2.60 ± 1.04	0.647

0.46 ± 0.16 mm. Demographics including age and SERE of the subjects who experienced ≥0.46 mm and < 0.46 mm axial elongation during the first year were shown in Table 1. Axial elongation rate was significantly correlated with baseline age, being much faster in younger children ($t = -4.920$, $P < 0.001$) as compared to their elder counterparts. Baseline SERE did not significantly contribute to axial elongation rate in Phase One ($t = 0.198$, $P = 0.844$).

5.2. Phase two

After one year combined treatment of ortho-k and atropine, AL increased from 24.80 ± 0.87 mm to 24.94 ± 0.88 mm, with a mean axial growth of 0.14 ± 0.14 mm. Axial elongation rate in Phase Two was significantly slower than that in Phase One ($t = -11.988$, $P < 0.001$). Reduction in axial elongation rate during Phase Two was more significant in those who experienced faster axial growth in Phase One ($t = -8.052$, $P < 0.001$; Fig. 2), but was not correlated to baseline age ($t = 0.101$, $P = 0.920$) or SERE ($t = -1.136$, $P = 0.261$).

In the historical control group with 29 subjects, the baseline age and SERE were 8.8 ± 1.5 years and −2.50 ± 0.94 D, respectively. After ortho-k treatment, axial elongation was faster in the first year (0.35 ± 0.11 mm) compared to the second year (0.25 ± 0.08 mm) ($t = 8.362$, $P < 0.001$). However, the reduction in axial elongation rate from the first year to the second year was more significant in the experimental group (−0.31 ± 0.20 mm) when compared to the control group (−0.10 ± 0.06 mm; $P < 0.001$) (Fig. 3).

6. Discussion

In this retrospective study, the authors found that low dose atropine has an adjunctive effect on myopia control when used concurrently with ortho-k in fast myopia progressors, when compared to ortho-k treatment alone.

In this study cohort, the average axial elongation rate of 0.46 ± 0.16 mm/y during ortho-k treatment in Phase One is faster than that reported by most of the other studies [7,8,14,15]. This might not only be due to the fact that the enrolled subjects in this study were considerably younger (8.3 ± 1.5 years), but also because this study was retrospective in nature, and thus is subject to selection bias – all the

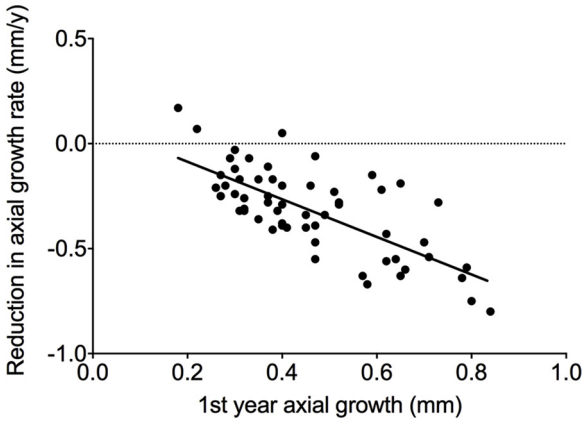

Fig. 2. Reduction in axial growth rate in Phase Two against first-year axial growth in Phase One.

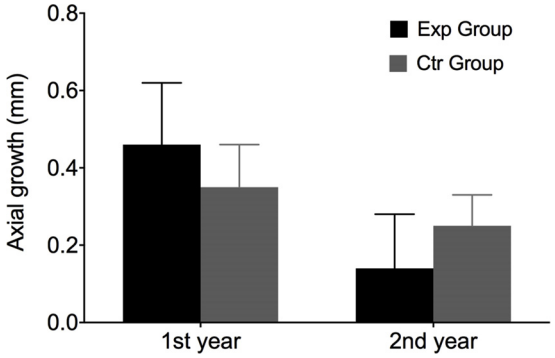

Fig. 3. Comparison of first year and second year axial growth in the current experimental group (Exp Group) and the historical control group (Ctr Group).

enrolled subjects were originally categorized as "fast myopia progressors". Nevertheless, The main goal of this preliminary study was to determine if adding low dose atropine to ortho-k treatment has the potential to produce an enhanced slowing of axial length growth over ortho-k alone in fast progressors. This initial data will serve as a basis for a future randomized controlled trial.

As noted, when low dose atropine was added in addition to ortho-k treatment, the axial elongation rate was slowed dramatically (0.46 ± 0.16 mm/y vs. 0.14 ± 0.14 mm/y). It could be argued that axial elongation slows over time with age, as indicated by the historical control group [7], but the difference between the two phases was much more significant in the treatment group than in the control group (−0.31 ± 0.20 mm vs. −-0.10 ± 0.06 mm), suggesting that the discrepancy could not be explained solely by age. Previous ortho-k studies have not observed similar significant slowing of axial elongation over time between the ages of 8–12 years [7,8,14–16], and thus this treatment effect could be largely due to the added atropine. The exact mechanism underlying this adjunctive effect is unknown, although different myopia control mechanisms have been proposed for ortho-k and atropine [17,18].

It has been hypothesized that ortho-k as an optical treatment shifts the retinal image profile to be favorable for myopia control, namely peripheral myopic defocus [17]. Atropine, on the other hand, has been hypothesized to either upregulate or downregulate muscarinic receptors in the retina and/or sclera, which in the downstream, alter the scleral remodeling process during myopia progression and axial elongation [18]. The adjunctive effect of the two treatment modalities suggests that they work through different mechanisms. One of the possible explanations for low dose atropine's complementary effect on ortho-k treatment might involve its mydriatic effect (reportedly approx. 1 mm enlargement in pupil diameter according to the ATOM study) [12], as previous studies have shown that the myopia control effect of ortho-k was affected by pupil size [6,10]. It has been suggested that children with larger pupil sizes would receive a greater proportion of peripheral myopic defocus associated with ortho-k lens wear, which in turn results in better myopia control [10]. This is a possible mechanism that warrants further investigation.

It should be noted that both ortho-k and high dose (1%) atropine use could cause choroidal thickening [19–21], which serves as a positive sign for long-term myopia retardation in animal studies [22–24]. On the other hand, change in choroidal thickness affects the measurement of AL, with the thickening of the choroid yielding a shallower vitreous chamber depth and shorter AL [19,25]. It is not clear whether low dose (0.01%) atropine would cause significant choroidal thickening as well, but it seems unlikely as Chia et al. [12] reported a remarkable AL shortening in children using atropine 1% but did not observe the same phenomenon in atropine 0.01%, suggesting that the AL measurement in Phase Two was unlikely to be affected by low dose atropine.

It has been shown by numerous studies that age is a significant

contributor to axial elongation during ortho-k treatment, with younger children progressing faster than their elder counterparts [7,8]. Similar results were found in Phase one of the current study. It is of equal clinical interest that once low dose atropine was added, age was no longer an influencing factor for axial elongation rate. On the other hand, reduction in axial elongation rate during Phase Two was found to be more significant in those who experienced faster axial growth in Phase One, regardless of baseline age or SERE. The underlying mechanism is unknown, although it can be argued that the "poor responders" for ortho-k treatment may well be the "good responders" for atropine. Nevertheless, this finding suggests that low dose atropine should always be considered as a supplementary treatment if ortho-k fails to control myopia progression to a favorable degree, e.g., less than 0.25 mm/yr, regardless of patient age or SERE.

One of the limitations of this study is its retrospective nature. A randomized clinical trial (RCT) is under way to further compare the treatment effect between single versus combined modalities. This RCT will also help answer the question of whether combined treatment for myopia control should be recommended for all progressive myopes or only those that are identified as fast progressors.

In conclusion, axial elongation is faster in younger children undergoing ortho-k treatment. For fast myopia progressors, low dose atropine may significantly slow axial elongation in addition to ortho-k's treatment effect. Those who have faster axial growth after ortho-k treatment will benefit more from the addition of low dose atropine, regardless of their refractive error and age.

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Conflict of interest

The authors have no conflict of interest to declare.

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