

Long-Term Effect of Overnight Orthokeratology on Axial Length Elongation in Childhood Myopia: A 5-Year Follow-Up Study

Takahiro Hiraoka,¹ Tetsubiko Kakita,² Fumiki Okamoto,¹ Hideto Takahashi,³ and Tetsuro Oshika¹

PURPOSE. Our prospective study was conducted to compare axial length elongation in myopic children receiving long-term overnight orthokeratology (OK) treatment to those wearing spectacles as controls.

METHODS. There were 59 subjects enrolled in this study. The OK group comprised 29 subjects who matched the inclusion criteria for OK. The control group comprised 30 subjects who also matched the inclusion criteria for OK, but preferred spectacles for myopia correction. Axial length was measured periodically for 5 years using an IOLMaster device, and the time course of changes was evaluated and compared between the groups.

RESULTS. A total of 43 subjects (22 and 21 in the OK and control groups, respectively) completed the 5-year follow-up examinations. At baseline, the mean age \pm SD was 10.04 ± 1.43 and 9.95 ± 1.59 years, the spherical equivalent refractive error was -1.89 ± 0.82 and -1.83 ± 1.06 diopters (D), and the axial length was 24.09 ± 0.77 and 24.22 ± 0.71 mm in the OK and control groups, respectively, with no significant differences between the groups. The increase in axial length during the 5-year study period was 0.99 ± 0.47 and 1.41 ± 0.68 mm for the OK and control groups, respectively, and the difference was statistically significant ($P = 0.0236$, unpaired *t*-test). The annual increases in axial length were significantly different between the groups for the first ($P = 0.0002$), second ($P = 0.0476$), and third years ($P = 0.0385$), but not for the fourth ($P = 0.0938$) and fifth ($P = 0.8633$) years. There were no severe complications throughout the study period.

CONCLUSIONS. The current 5-year follow-up study indicated that OK can suppress axial length elongation in childhood myopia. (*Invest Ophthalmol Vis Sci.* 2012;53:3913-3919) DOI: 10.1167/iovs.11-8453

The prevalence of myopia is estimated to be between 20% and 50% in older adults of Europe and the United States,¹⁻⁶ while 60-90% of young adults in Asian countries report having

myopia.^{4,7-9} Furthermore, the prevalence of myopia is increasing rapidly in several countries.^{9,10-13} Of particular concern is the fact that patients who are diagnosed initially at a younger age are more likely to have more severe myopic-associated side effects later in life.¹³⁻¹⁵ Myopia is a predisposing factor for retinal detachment, macular degeneration, and glaucoma, which can contribute to loss of vision and, ultimately, blindness.¹⁶⁻¹⁹ The associated risk of these complications developing increases with the severity of myopia and axial length.^{4,19} The World Health Organization identified myopia as one of the five leading causes of blindness and visual impairments in the world.²⁰

Dependence on continuous refractive correction and the associated deterioration of visual function in patients with severe myopia creates questions of quality of life (QOL) standards for the physicians and their patients. Several studies showed that QOL is compromised in individuals with high refractive error compared to those with low or moderate myopia.^{21,22} Thus, prevention or retardation of myopic progression is of notable public health significance.

Myopia also causes a remarkable impact on the socioeconomic health of a given population. Javitt and Chiang estimated that the annual cost for eye examinations and corrections by spectacles and contact lenses in the United States was approximately \$4.6 billion.²³ Furthermore, the complications associated with severe myopia impact individuals significantly at a time when they are active economically. If interventions to retard the progression of myopia are successful, effects on the socioeconomic health of a given population could be reduced profoundly.

Progression of youth-onset myopia is attributed widely to axial length elongation, which cannot be compensated by reductions in the corneal and crystalline lens power; however, the detailed mechanisms involved in the etiology of myopia remain unclear.^{10,24-26} As no current treatments can reverse the structural changes of pathologic myopia, the scientific community seeks effective means to slow or arrest the development of myopia in children to decrease the severity of associated myopic complications.²⁷ Topical application of tropicamide,²⁸ atropine,²⁹⁻³⁴ pirenzepine,³⁵⁻³⁷ and ocular hypotensive agents failed to prevent myopic progression effectively when adjusted for efficacy, safety, economic feasibility, and mode of application.^{38,39}

In recent years, the possibility of overnight orthokeratology (OK) for retarding the progression of myopia has been recognized. The efficacy of OK for myopia control now has been demonstrated in a number of different studies, although all have been limited to 2 years to-date.⁴⁰⁻⁴² Given that a large number of children continue OK treatment for more than 2 years, it is crucial to elucidate the long-term effect of OK. Therefore, we conducted our prospective study to investigate the long-term effect of OK on axial length elongation in

From the ¹Department of Ophthalmology, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan; ²Kakita Eye Clinic, Chiba, Japan; and ³Epidemiology and Biostatistics, School of Medicine, University of Tsukuba, Ibaraki, Japan.

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Corresponding author: Takahiro Hiraoka, Department of Ophthalmology, Institute of Clinical Medicine, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba, Ibaraki, 305-8575 Japan; thiraoka@md.tsukuba.ac.jp.

TABLE 1. Inclusion Criteria

1. Ages from 8–12 years at baseline
2. No history of orthokeratology or the use of contact lenses
3. Noncycloplegic autorefraction (spherical equivalent) from -5.00 to -0.50 D in both eyes
4. Astigmatism (noncycloplegic autorefraction) ≤ 1.50 D in both eyes
5. Anisometropia (noncycloplegic autorefraction) ≤ 1.50 D
6. Best-corrected visual acuity ≥ 0.00 logMAR units in both eyes (Snellen equivalent to 20/20)
7. No strabismus by a cover-uncover test either with or without refractive correction
8. Birth weight ≥ 1500 g
9. No known ocular, systemic or neurodevelopmental deviations that might affect refractive development
10. No use of medications that might affect refractive development.

children. This 5-year study was designed to evaluate how OK slows the progression rate of childhood myopia when compared to the use of single vision spectacles.

MATERIALS AND METHODS

Our survey was conducted between November 2002 and December 2010 at Kakita Eye Clinic. Upon completion of our previous 2-year study, many subjects wanted to continue OK.⁴² These subjects, who also fulfilled our new inclusion criteria (Table 1) and agreed to undergo subsequent examinations for three more years, were enrolled in this study. The inclusion criteria established for this study were different from our previous study in terms of age (≤ 12 years) and spherical equivalent refraction (≥ -5.00). Additional new subjects, who matched the inclusion criteria and consented to the 5-year follow-up schedule, also were recruited. As a result, 12 subjects from the previous study and 17 new subjects, for a total of 29 subjects (14 boys and 15 girls), were enrolled in the OK group. Ten subjects from the previous study and 20 new subjects, for a total of 30 subjects (13 boys and 17 girls), were recruited as controls. The control subjects also matched our inclusion criteria for OK, but preferred to use spectacles rather than OK for correction of their myopia. This study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Ethics Committee of Kakita Eye Clinic. Written informed consent was obtained from all participants and their guardians following an explanation of the nature and possible consequences of the study.

OK lenses used in this study were four-zone reverse geometry lenses (Emerald Lenses; Euclid Systems Corp., Herndon, VA), which are manufactured using Boston XO material (Polymer Technology Corp., Wilmington, MA) with a nominal oxygen permeability (Dk) of 100×10^{-11} (cm^2/sec)($mL O_2/mL \cdot mm Hg$). The nominal central thickness of the lenses was 0.22 mm and the diameter was 10.6 mm. The subjects were fitted with the lenses according to the manufacturer's fitting recommendations. After lens dispensing, the subjects were advised to wear their OK lenses every night for at least 7 consecutive hours.

The subjects in the control group wore single-vision spectacles, which were prescribed by a certified ophthalmic technician and modified according to any refractive changes throughout the follow-up period.

The OK group returned for examinations every 3 months and underwent slit-lamp examinations for any adverse events. The OK lens fit was evaluated at each visit. The control group also returned for examinations every 3 months. OK lenses and spectacles were replaced if visual acuity was found to change by more than 0.30 logMAR units during this follow-up period.

The axial length was evaluated by noncontact optical biometry (IOLMaster; Carl Zeiss Meditec, Dublin, CA) by a single examiner, who

was blinded to the original refractive status and subjects' group assignment. At each visit, five successive measurements were taken, and their average was used as a representative value. The measurements were performed between 3 and 6 o'clock in the afternoon to minimize the influence of diurnal variation.

Previous reports showed that corneal thinning can be stabilized by the end of the first week of orthokeratology treatment,⁴³ or continues for 1 or 2 months.^{44,45} Therefore, axial length was measured 3 months after the start of OK and was used as the baseline data for axial length. For measures of refraction and visual acuity, data obtained before starting OK were used for these baseline measurements. In the control group, axial length, refraction, and visual acuity were measured once the subject began wearing spectacles. OK or spectacle use continued for 5 years, and axial length, refraction, and visual acuity were measured periodically until the end of the 5-year study period.

Changes in axial length were evaluated prospectively for the two groups and also compared across groups. Repeated-measures ANOVA was used to examine the difference between groups in time courses of changes over the five-year treatment period. An unpaired *t*-test was used to compare annual increases in axial length between the groups. The slopes of the regression lines, which demonstrate the relationship between axial elongation and baseline age, were compared between the OK and spectacle groups by analysis of covariance (ANCOVA). Similarly, slopes representing the relationship between axial elongation and baseline refractive errors for the two groups also were compared. All analyses were child-based. Continuous measures, such as refraction, visual acuity, and axial length, were averaged between the subjects' two eyes, with the exception of one OK-treated patient, who had myopia only in the right eye, while the left eye had emmetropia. In this case, only the right eye data for this patient were included in our analyses. The statistical software program, StatView 5.0 (SAS Institute Inc., Cary, NC), was used for our statistical analyses, which considered $P < 0.05$ to be statistically significant.

RESULTS

Among the 29 subjects who initially were enrolled in the OK group, 22 (10 boys, 12 girls) completed the 5-year follow-up examinations successfully. Their ages ranged from 8 to 12 (mean \pm SD 10.04 ± 1.43) years. At baseline, their spherical equivalent refractive errors ranged from -0.75 to -4.13 (-1.89 ± 0.82) diopters (D), their logMAR uncorrected visual acuities were 0.30–1.15 (0.70 ± 0.24), and their axial lengths ranged from 22.05–25.46 (24.09 ± 0.77) mm (Table 2). Of seven subjects (24%) in the OK group who dropped out of the study, three failed to complete follow-up examinations, three desired to switch to daily-wear contact lenses, and one was dissatisfied with their visual outcomes. The mean age of the subjects was 10.39 ± 1.34 years, mean spherical equivalent refractive error was -2.08 ± 0.82 D, mean logMAR uncorrected visual acuity was 0.74 ± 0.28 , and mean axial length was 24.66 ± 0.62 mm. No significant differences existed between the profiles of the subjects who dropped out of the study and those who completed the study ($P > 0.05$, unpaired *t*-test, for all 4 parameters).

Among the 30 subjects in the spectacle control group, 21 (8 boys, 13 girls) completed the 5-year follow-up examinations successfully. Their ages ranged from 8–12 (9.95 ± 1.59) years. At baseline, their spherical equivalent refractive errors were between -0.75 and -4.63 (-1.83 ± 1.06) D, logMAR uncorrected visual acuities ranged from 0.34–1.40 (0.73 ± 0.30), and axial lengths ranged from 22.70–25.50 (24.22 ± 0.71) mm (Table 2). Nine subjects (30%) in the control group dropped out of the study due to lack of follow-up examinations and five subjects desired to switch to daily-wear contact lenses. Their mean age was 10.16 ± 1.25 years, mean spherical equivalent refractive error was -1.93 ± 0.80 D, mean logMAR

TABLE 2. Baseline Characteristics of Subjects Who Completed 5-Year Follow-Up Examinations in the OK and Spectacle Groups

	Mean ± SD		P Value
	OK (n = 22)	Spectacle (n = 21)	
Age (years)	10.04 ± 1.43	9.95 ± 1.59	0.8412*
Sex	Male 10, female 12	Male 8, female 13	0.7244†
Spherical equivalent refractive error (D)	-1.89 ± 0.82	-1.83 ± 1.06	0.8468*
Uncorrected visual acuity (logMAR)	0.70 ± 0.24	0.73 ± 0.30	0.7443*
Axial length (mm)	24.09 ± 0.77	24.22 ± 0.71	0.5524*

There were no significant inter-group differences or variations in distribution patterns at the baseline in age, sex, spherical equivalent refractive error, uncorrected visual acuity, or axial length.

* Unpaired t-test.

† χ^2 test.

uncorrected visual acuity was 0.81 ± 0.21 , and mean axial length was 24.68 ± 0.65 mm. There were no significant differences between the subjects who dropped out of the study and those who completed the study ($P > 0.05$, unpaired t-test, for all 4 parameters).

Baseline characteristics of subjects who completed the 5-year follow-up examinations were balanced, with no statistically significant differences in age, sex distribution, spherical equivalent refractive error, uncorrected visual acuity, or axial length between the OK and the spectacle groups (Table 2).

In the OK group, spherical equivalent refractive error decreased significantly from -1.89 ± 0.82 D at baseline to -0.70 ± 0.45 D at 5 years after treatment ($P < 0.0001$, unpaired t-test). In the spectacle group, the spherical equivalent refractive error increased significantly from -1.83 ± 1.06 to -5.03 ± 1.83 D ($P < 0.0001$).

The time course of changes in axial length during the 5-year study is shown in Figure 1. There were significant differences in axial length between the OK and spectacle groups over the time course of the study ($P = 0.0085$, repeated measures ANOVA). Figure 1 shows the annual increase in axial length for each year of the study. Significant differences in the annual increase in axial length between the two groups were found

for the first ($P = 0.0002$), second ($P = 0.0476$), and third ($P = 0.0385$) years, but not for the fourth ($P = 0.0938$) and fifth ($P = 0.8633$) years.

Figure 2 shows the increases in axial length over the 5-year study period plotted against subject age at baseline for both groups. The slope of the linear regression line was -0.178 for the OK group and -0.359 for the spectacle group. The latter intergroup difference was statistically significant ($P = 0.033$, ANCOVA, Table 3).

Figure 3 shows the increases in axial length over the 5-year study period plotted against spherical equivalent refractive errors at baseline for both groups. The slope of the linear regression line was 0.174 for the OK group and -0.035 for the spectacle group. The latter intergroup difference was not statistically significant ($P = 0.303$, ANCOVA, Table 3).

During the 5-year study period, moderate superficial punctate keratopathy was observed in 3 subjects and mild corneal erosion was found in 1 subject in the OK group, but these conditions were recovered completely after discontinuation of lens wear for 1 week. All subjects resumed OK treatment thereafter. No other severe complications, such as corneal ulcer, were noted in the OK group and there were no adverse events in the spectacle group.

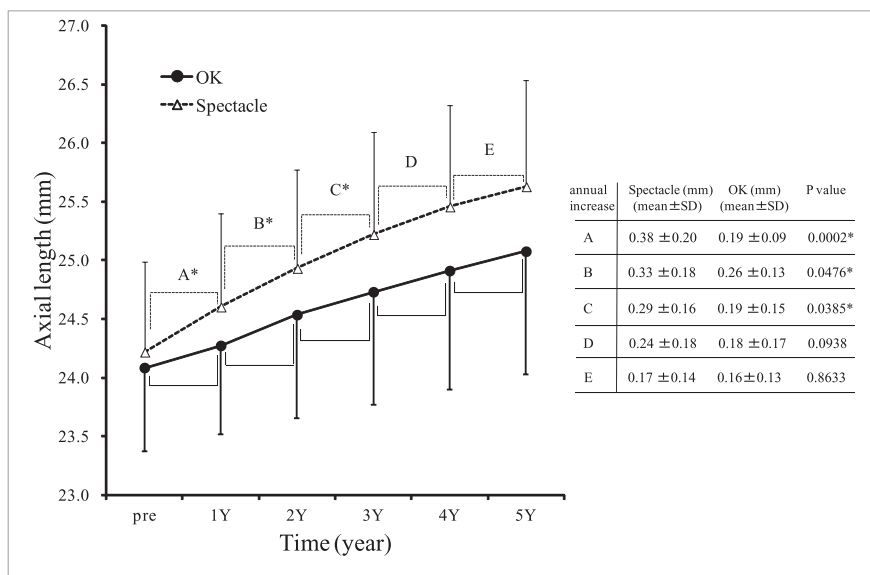


FIGURE 1. The time course of changes in axial length over the 5-year study period for OK and spectacle groups. There are significant differences in the time course of changes in axial length between the OK and spectacle groups ($P = 0.0085$, repeated-measures ANOVA). Data are expressed as the mean ± SD. Significant differences in the annual increase in axial length between the two groups also were found for the first, second, and third years, but not for the fourth and fifth years. *Statistically significant differences between the OK and spectacle groups were determined using an unpaired t-test.

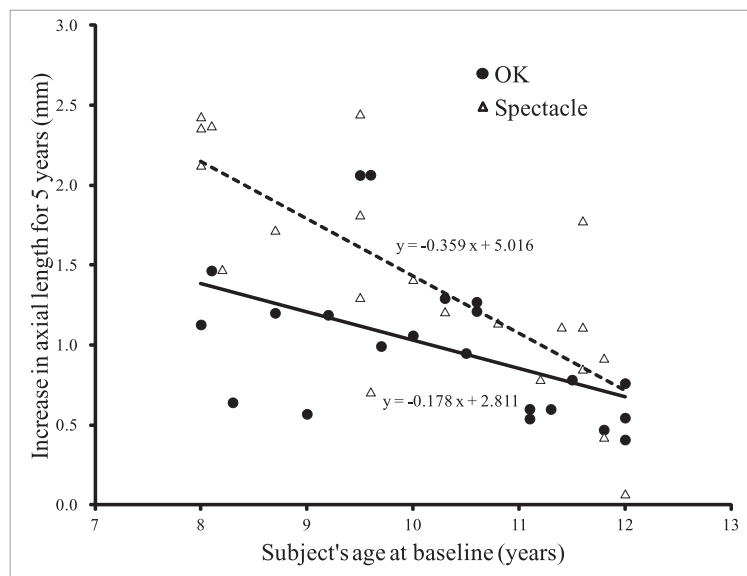


FIGURE 2. Scatterplots demonstrating increases in axial length for 5 years and subject's age at baseline in the OK and spectacle groups. The slope of the linear regression line was -0.178 for the OK group and -0.359 for the spectacle group, showing a significant intergroup difference ($P = 0.033$, ANCOVA).

DISCUSSION

To our knowledge, this is the first study to investigate the long-term effects of OK on axial length growth. Our results confirmed that OK treatment is effective in slowing the increase in axial length, with this effect being most noticeable over the first year of OK treatment and largely limited to the first 3 years of treatment.

In 2005, Cho et al. reported that axial length in children increased over a 2-year period by 0.29 ± 0.27 mm in an OK-treated group and by 0.54 ± 0.27 mm in a control group treated with spectacles.⁴⁰ In 2009, Walline et al. reported similar findings, whereby the mean increase in axial length after 2 years was 0.25 mm in the OK group and 0.57 mm in the control group.⁴¹ In 2011, Kakita et al. reported an increase of 0.39 ± 0.27 mm in the OK group versus 0.61 ± 0.24 mm in the control group.⁴² Although similar results were obtained in our study, our subjects showed a slightly greater increase in axial length after 2 years, which was 0.45 ± 0.21 mm in the OK group versus 0.71 ± 0.40 mm in the control group. This discrepancy in the amount of axial length elongation between studies may be related to differences in baseline refractions, because our subjects had a lower degree of myopia than those of other studies. It has been reported in a previous study that OK is less effective in slowing axial elongation in low compared to higher degrees of myopia.⁴² However, of importance is the fact that all of these studies demonstrated a therapeutic benefit of OK in retarding axial growth in

childhood myopia. Our study has two strengths compared to previous studies. The most important one was our longer study period compared to those of previous studies. Our use of an IOLMaster, a noncontact laser interferometer-based instrument, instead of a contact, ultrasound-based technique, has practical advantages, especially in measuring children, and offers good repeatability of axial length measurements.⁴⁶

When comparing our results to those of previous studies involving different interventions, we took into account differences in the follow-up periods of the studies. The effects reported were not constant throughout the study period, and their magnitude usually was greater in the first year of follow-up.^{32,37,47} Thus, our results were compared to those of previous studies according to the observation period (Table 4). The inhibitory effect of OK on axial length elongation was superior to that of progressive addition lenses wearing⁴⁷ and topical administration of pirenzepine ophthalmic gel.^{36,37} On the other hand, Shih et al. reported a greater effect of atropine eyedrops with multifocal glasses.⁴⁸ Chua et al. also showed better results of topical atropine.³² Based simply on these findings and our results, it seems that the inhibitory effect of topical atropine is superior to that of OK. However, the age of the subjects included in the 2 topical atropine studies was lower than that of the subjects assessed in our study, because both former studies included 6- and 7-year-old children,^{32,48} who were excluded from our study. Further studies with age-matched subjects are needed to verify whether the inhibitory effect of OK actually is inferior to that of topical atropine.

A suggested mechanism underlying the effects of OK in retarding myopia progression involves the observation that the corneal morphology after OK can eliminate or decrease relative peripheral hyperopia.^{42,49,50} A study attempting to slow myopia progression, based on decreasing hyperopic blur of the peripheral retina with specially designed spectacle lenses, showed no significant effects (Table 4).⁵¹ Another study using dual-focus soft contact lenses showed that the mean increase in axial length over 10 months was significantly less by 0.11 mm than that in a control group of single-vision contact lens wearers (Table 4).⁵² Although this inhibitory effect was not as great as that observed in the present study with OK and in previous studies with atropine,^{32,48} the subjects were

TABLE 3. Results of ANCOVA

Factors	Parameter	Parameter Estimate	SE	P Value
Slope	OK	-0.178	0.072	0.032
	Spectacle	-0.359	0.097	0.033
Intercept	OK	2.811	0.738	0.007
	Spectacle	5.016	0.990	
Age				< 0.001

ANCOVA with age as a covariate revealed significant intergroup differences in axial elongation for 5 years.

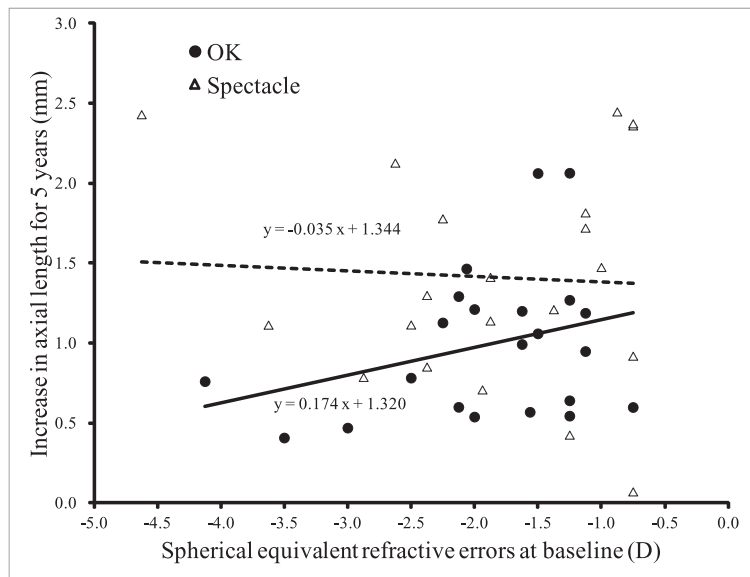


FIGURE 3. Scatterplots demonstrating increase in axial length for 5 years and spherical equivalent refractive errors at baseline in the OK and spectacle groups. The slope of the linear regression line was 0.174 for the OK group and -0.035 for the spectacle group, showing no significant intergroup difference ($P = 0.303$, ANCOVA).

much older than those of other studies. The effect of dual-focus contact lenses on axial elongation should be assessed in younger populations.

One of the most interesting findings of our study is that a significant difference in the annual increase in axial length between the OK and control groups was observed until the third year, but not in the fourth and fifth years. Axial elongation slows over time, as shown in Figure 1, thereby making it more difficult to detect a significant difference in later years, especially in a small sample size. The continuation of OK after 3 years appears to have some favorable effects along with maintaining previous benefits. Although a rebound phenomenon in myopia progression is observed in atropine-treated eyes after drug discontinuation, this does not negate completely the earlier positive effects of the treatment.³⁴ The potential for a

rebound or catch-up effect after OK discontinuation remains unknown. Further studies are necessary to address this question.

The slope of the linear regression line comparing the relationship between axial elongation over 5 years and age was significantly flatter in the OK group than in the control group. The value of the slope in the OK group (-0.178) was approximately half of that found in the control group (-0.359). This finding suggests that the earlier OK treatment is initiated, the greater will be the inhibitory effect on axial growth. Prevention of side effects associated with myopia appears to be controlled best the earlier myopic children begin the OK treatment.

As is the case for any study, our study does exhibit some limitations. Although we confirmed the inhibitory effect of

TABLE 4. Comparison of Results between the Present OK and Previous Studies with Other Interventions in Terms of Inhibitory Effect on Axial Length Elongation

Study (Year)	Age Range	Intervention of Treatment and Control Group	Mean Increase in Axial Length for Whole Study Period	Inhibitory Effect (Difference between Groups)	Inhibitory Effect of the Present OK Study
Gwiazda et al. ⁴⁷ (2003)	6–11	Progressive addition lenses Single vision glasses	0.64 mm for 3 years 0.75 mm for 3 years	0.11 mm for 3 years	0.36 mm for 3 years
Tan et al. ³⁶ (2005)	6–12	Pirenzepine Placebo	0.20 mm for a year 0.33 mm for a year	0.13 mm for a year	0.20 mm for a year
Siatkowski et al. ³⁷ (2008)	8–12	Pirenzepine Placebo	0.28 mm for 2 years 0.40 mm for 2 years	0.12 mm for 2 years	0.26 mm for 2 years
Shih et al. ⁴⁸ (2001)	6–13	Atropine + multi-focal glasses Single vision glasses	0.22 mm for 1.5 years 0.59 mm for 1.5 years	0.37 mm for 1.5 years	0.23 mm for 1.5 years
Chua et al. ³² (2006)	6–12	Atropine Placebo	-0.02 mm for 2 years 0.38 mm for 2 years	0.40 mm for 2 years	0.26 mm for 2 years
Sankaridurg et al. ⁵¹ (2010)	6–16	3 novel spectacles to reduce peripheral hyperopic defocus Single vision glasses	0.31–0.36 mm for a year 0.36 mm for a year	0–0.05 mm for a year	0.20 mm for a year
Anstice et al. ⁵² (2011)	11–14	Dual-Focus soft contact lens Single vision contact lens	0.11 mm for 10 months 0.22 mm for 10 months	0.11 mm for 10 months	0.17 mm for 10 months

The difference in axial length elongation between treatment and control groups was calculated by the following subtraction: ([mean increase in axial length in control group] – [mean increase in axial length in treatment group]), which is considered to be an inhibitory effect of each treatment on axial length elongation.

long-term OK continuation on axial length elongation, we did not identify the optimal treatment duration. It is unknown whether a slower rate of axial length elongation will be maintained after OK cessation or whether a rebound phenomenon will occur. Further studies with an appropriate follow-up after treatment discontinuation are required to address these questions. Second, only low and moderate myopes were included in our study population. Thus, the efficacy and safety of this treatment option in subjects with a relatively high degree of myopia remain unknown. Third, the sample size of the current study was relatively small. A larger-scale study should be conducted to confirm the potential efficacy and limitations of long-term OK treatment. Fourth, the dropout rate was high in both groups (24% in the OK group and 30% in the spectacle group). In addition, approximately one-third of the subjects included in our study were recruited from subjects who already had completed a 2-year study,⁴² for which the follow-up period was extended to 5 years. Therefore, it is possible that the dropout rate of this study was underestimated. Moreover, it cannot be denied that the recruitment method may have introduced some bias into the current results. Another well-designed study should be conducted to confirm the present findings.

In conclusion, our study showed that OK treatment was effective in slowing axial length elongation over a 5-year treatment period and demonstrated a clinically acceptable safety profile in a population of patients aged 8 to 12 years. Considering the various adverse events and negative influences on visual function associated with topical atropine, OK may become the most promising intervention for slowing myopic progression, especially in children with low and moderate myopia. However, the optimal treatment duration and ideal starting age remain unclear. Further clinical studies are warranted to elucidate these issues.

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