Clinical Research

Efficacy of long-term orthokeratology treatment in children with anisometropic myopia

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Abstract

• **AIM**: To explore the efficacy of the orthokeratology lens for anisometropic myopia progression.

• **METHODS:** A retrospective study was performed. Cycloplegic refraction and axial length (AL) were collected from 50 children ($10.52\pm1.72y$) who visited Peking University Third Hospital from July 2015 to August 2020. These children's one eyes (Group A) received monocular orthokeratology lenses at first, after different durations ($12.20\pm6.94mo$), their contralateral eyes (Group B) developed myopia and receive orthokeratology as well. The data in 1-year of binocular period were recorded. AL growth rate (difference of follow-up and baseline per month) were compared between two groups by paired *t* test. Interocular differences of AL were compared by Wilcoxon test.

• **RESULTS:** During monocular period, the AL growth rate of the Group A ($0.008\pm0.022 \text{ mm/mo}$) was significantly slower than that of the Group B ($0.038\pm0.018 \text{ mm/mo}$; *P*<0.0001). However, during binocular period, the AL growth rate of the Group A ($0.026\pm0.014 \text{ mm/mo}$) was significantly faster than that of the Group B ($0.016\pm0.015 \text{ mm/mo}$; *P*<0.0001). The AL difference between both eyes was 0.6 (0.46) mm, then significantly decreased to 0.22 (0.39) mm when started binocular treatment (*P*<0.0001). However, it was significantly increased to 0.30 (0.32) mm after a year (*P*<0.0001), but still significantly lower than baseline (*P*<0.0001).

• **CONCLUSION:** The orthokeratology lens is efficient for control the AL elongation of monocular myopia eyes and reduce anisometropia. For the condition that the contralateral eyes develop myopia and receive orthokeratology lens later, there is no efficiency observed on control interocular difference of AL during binocular treatment.

• **KEYWORDS:** orthokeratology; anisometropia; myopia; axial length; children

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INTRODUCTION

nisometropia is defined as the interocular difference of refraction. Anisometropia tends to occur over the course of a life span, namely, after birth, at the onset of myopia, and at the onset of presbyopia^[1]. Among school-aged children, the prevalence of anisometropia with a spherical equivalent refraction (SER) >0.5 diopter (D) is 34%, and it is 1%-10% when SER >1 $D^{[2-6]}$. Also, the prevalence of myopic anisometropia is significantly higher than that of emmetropic anisometropia^[3,7]. Both the prevalence and severity of anisometropia increase with increasing degree of myopia^[8-9]. Binocular vision can be impaired even with moderate refractive differences between eyes, including stereoacuity and contrast sensitivity^[10-12]. Anisometropia is thought to be closely related to aniseikonia and amblyopia^[1,13]. Without intervention, the difference between the two eyes will continue to increase in both mild and severe anisometropia among school-aged children^[14-16]. Thus, treating myopia and anisometropia at same time is seriously important.

An overnight orthokeratology (ortho-k) lens flattens the cornea by reverse geometry, which corrects the refractive error and provides clear vision during the daytime. Moreover, the ortho-k lens has been proven to be efficient in reducing myopia progression by nearly 45%^[17], especially in patients with a higher degree of myopia^[18-19]. Although there is a risk of microbial keratitis, ortho-k lenses are thought to be a safe clinical option^[20].

Few studies have explored the effectiveness of ortho-k lenses under certain circumstance. For example, in some children, after monocular ortho-k treatment, contralateral emmetropic eye develop myopia, too. Children with anisometropic myopia receive ortho-k treatment in the sequence of monocular and binocular. Our study was aim to analyze whether the ortho-k lens effect on the control of axial anisometropic myopia, especially the condition mentioned above. This study will contralaterally compare the axial length (AL) elongation characteristic under monocular and binocular ortho-k treatment, and find if there is an ocular parameter that related with the AL elongation of the eye myopic later.

SUBJECTS AND METHODS

Ethical Approval This study was in accordance with the ethical standards formulated in the Helsinki Declaration. All subjects signed an informed consent before treatment.

Subjects This retrospective cohort study included children who visited Peking University Third Hospital for refraction correction from July 2015 to August 2020. Subjects met the following inclusion criteria: aged between 8-18y; monocular best corrected visual acuity not worse than 20/20 for both eyes; one eye with myopia (SER \leq -1.0 D) received ortho-k lens; the other eye being relatively emmetropic (SER \leq ±0.5 D); after sometime of monocular ortho-k lens, the contralateral eye developed myopia (SER \leq -1.0 D) too and began binocular ortho-k lens treatment. And the exclusion criteria are: astigmatism \geq 2.0 D; history of corneal contact lens; history of atropine drops; eye disease or surgery; discontinuation of ortho-k lens use; ocular or systemic conditions that might affect.

Materials The ortho-k lenses used in this study were Paragon CRT lenses (Paragon Vision Sciences, USA) and LK lenses (Lucid, Korea). Ortho-k lenses were fitted to every subject according to the manufacturer's recommended procedure. Lenses were selected by experienced optometrists based on corneal topographic variables and adjusted under sodium fluorescein and cobalt blue lighting. After treatment began, each subject was told to wear a lens overnight for approximately 8h and visit the hospital regularly and whenever ocular complaints occurred.

Measurement and Technique All the subjects received baseline examinations, including autorefraction (RM 8800, Topcon, Japan), cycloplegic refraction (compound tropicamide eye drops, Sinqi, China), AL measurement (IOLMaster-500, Carl Zeiss, Germany), and corneal topography (Pentacam HR; Oculus, Germany). After no less than 3mo of treatment, the AL and corneal topography were evaluated at every 3mo or anytime subjects wanted.

Data Analysis Continuous variables are expressed as the means±standard deviation or median (interquartile range).

Multiple linear regression was used to estimate the relationship between several independent ocular variables and the AL growth rate of emmetropic eyes at monocular period. The baseline characteristics and the average elongation of AL per month were evaluated by paired t test. The comparation for interocular differences of AL were evaluated by Wilcoxon test. Statistical analysis was performed using the SPSS software package (SPSS for Windows, version 24, Chicago, IL, USA). The level of statistical significance was considered to be 0.05 (two-sided).

RESULTS

General Results A total of 50 children participated in this observation, 18 of whom were boys and 32 of whom were girls. The average age was $10.52\pm1.72y$. At baseline, they only had one myopic eye (SER -1.80±0.82 D), and were applied with ortho-k lenses. The degree of SER anisometropia was 1.56 ± 0.97 D (95%CI: 1.29, 1.84) at baseline. After different durations of monocular treatment, 12.20 ± 6.94 mo (95%CI: 10.23, 14.17), the contralateral eyes of these children developed myopia (SER -1.56±0.43 D) and applied with ortho-k lens, too. Then the patients started binocular ortho-k treatment.

For convenience, the eye that received the ortho-k lens first was regarded as Group A, and the other eye which received the ortho-k lens later was regarded as Group B. The AL and SER of the two groups of eyes at the baseline and endpoint of monocular period are shown in Table 1.

During the whole treatment, there were no serious adverse events among these subjects.

Factors Corelated with the Axial Length Growth of the Untreated Eyes The average elongation of the AL per month (mm/mo) was calculated as the AL growth rate, as well as the difference of follow-up and baseline AL (mm) divided by duration (mo). In monocular period, the AL growth rate of Group B, untreated eyes, is 0.038±0.018 mm/mo (95%CI: 0.033, 0.044). To explore the relationships, nine baseline factors were taken, including age, SER, mean corneal curvature (Km), anterior chamber depth (ACD), and AL of both eyes. In the multiple linear regression analysis, it was independent of observations (Durbin-Watson=1.901), and there was no multicollinearity. This regression model was statistically significant (F=3.879, P=0.001, adjusted $R^2=0.346$). As shown in Table 2, among these factors, age (P=0.005; B: -0.004; 95%CI: -0.007, -0.001), SER of Group A (P=0.03; B: 0.013; 95%CI: 0.001, 0.024), AL of Group A (P=0.006; B: 0.032; 95%CI: 0.01, 0.055), and AL of Group B (*P*=0.011; *B*: -0.035; 95%CI: -0.062, -0.009) were statistically significant.

Compare Axial Length Growth Rates Between Two Periods In order to explore the differences of AL changes between monocular and binocular periods, the AL of 12±1mo after beginning binocular ortho-k treatment was measured. The

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Parameters	meters Group A Group B		t	Р	
SER (D)	-1.80±0.82 (-2.05, -1.55)	-0.29±0.56 (-0.45, -0.14)	-10.725	< 0.0001	
SER ^a (D)	-	-1.56±0.43 (-1.69, -1.44)	-	-	
AL (mm)	24.53±0.78 (24.31, 24.75)	23.90±0.77 (23.68, 24.12)	10.356	< 0.0001	
AL ^a (mm)	24.64±0.78 (24.41, 24.86)	24.34±0.72 (24.13, 24.54)	5.619	< 0.0001	

Table 1 Characteristics at baseline and endpoint of monocular ortho-k treatment

Group A: The eyes received the ortho-k lens at first; Group B: The contralateral eyes; SER: Spherical equivalent refraction; AL: Axial length. ^aThe endpoint of monocular treatment.

Parameters	Р	Standardized coefficient B	Unstandardized coefficients B	95%CI for <i>B</i>
Age	0.005 ^b	-0.406	-0.004	-0.007, -0.001
Group A				
SER	0.030 ^a	0.617	0.013	0.001, 0.024
Km	0.461	0.433	0.005	-0.009, 0.019
ACD	0.541	-0.209	-0.022	-0.095, 0.05
AL	0.006^{b}	1.416	0.032	0.01, 0.055
Group B				
SER	0.539	-0.096	-0.004	-0.015, 0.008
Km	0.784	-0.163	-0.002	-0.015, 0.011
ACD	0.326	0.321	0.035	-0.036, 0.105
AL	0.011 ^a	-1.511	-0.035	-0.062, -0.009

Table 2 Associations (multiple analysis) between the ocular parameters and axial growth rate of emmetropic eyes in

Group A: The eyes received the ortho-k lens first; Group B: The contralateral eyes; SER: Spherical equivalent refraction; Km: Mean corneal curvature; ACD: Anterior chamber depth; AL: Axial length.

Parameters	п	Group A	Group B	t	Р
Monocular period	50	0.008±0.022 (0.002, 0.014)	0.038±0.018 (0.033, 0.044)	-8.251	< 0.0001
Binocular period	50	0.026±0.014 (0.022, 0.030)	0.016±0.015 (0.012, 0.021)	4.675	< 0.0001
t	-	-4.664	7.826	-	-
Р	-	< 0.0001	< 0.0001	-	-

Table 3 AL growing rate compared by t test

monocular ortho-k period

Group A: The eyes received the ortho-k lens first; Group B: The eyes that received the ortho-k lens later; Monocular period: The monocular ortho-k lens treatment; Binocular period: The binocular ortho-k lens treatment.

AL was $24.89\pm0.76 \text{ mm} (95\%\text{CI}: 24.68, 25.11)$ of Group A, and $24.51\pm0.71 \text{ mm} (95\%\text{CI}: 24.31, 24.72)$ of Group B. The AL growth rates per month were shown in Table 3, the paired *t* test was conducted. For the Group A, the AL growth rate was significantly lower in monocular period $(0.008\pm0.022 \text{ mm/mo})$ than in binocular period $(0.026\pm0.014 \text{ mm/mo}; t=-4.664, P<0.0001)$. For the Group B, the AL growth rate was significantly higher in monocular period $(0.038\pm0.018 \text{ mm/mo})$ than in binocular period $(0.016\pm0.015 \text{ mm/mo}; t=7.826, P<0.0001)$.

Compare Axial Length Growth Rates Between Two Eyes The results are also shown in Table 3. As in Figure 1, during monocular period, the AL growth rate of the Group A (0.008±0.022 mm/mo) was significantly slower than that of the Group B

 $(0.038\pm0.018 \text{ mm/mo}; t=-8.251, P<0.0001)$. However, during binocular period, the AL growth rate of the Group A $(0.026\pm0.014 \text{ mm/mo})$ was significantly faster than that of the Group B $(0.016\pm0.015 \text{ mm/mo}; t=4.675, P<0.0001)$.

Compare Changes in Anisometropia of Axial Length The intraocular differences of AL were non-normally distributed. At beginning, it was 0.6 (0.46) mm. After monocular ortho-k treatment, it was significantly decreased to 0.22 (0.39) mm (Z=-5.402, P<0.0001). However, after a year around binocular ortho-k treatment, it was significantly increased to 0.30 (0.32) mm (Z=-4.086, P<0.0001), but still significantly lower than baseline (Z=-4.716, P<0.0001; Table 4).

DISCUSSION

Anisometropia is a special form of refractive error that is

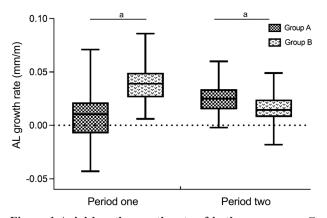


Figure 1 Axial length growth rate of both eye groups Group A: The eyes received the ortho-k lens first; Group B: The eyes that received the ortho-k lens later; Monocular period: The monocular ortho-k lens treatment; Binocular period: The binocular ortho-k lens treatment. Box and whiskers were shown in min and max. Statistical significance was assessed using paired *t* test (${}^{a}P < 0.0001$).

Table 4 Intraocular differences of axial length				
Paremeters	Intraocular difference of	Z		

Paremeters	axial length (mm)	Ζ	Р
Initial	0.60 (0.46)	-5.402 ^a	< 0.0001
Intermediate	0.22 (0.39)	-4.086 ^b	< 0.0001
Final	0.30 (0.32)	-4.716 [°]	< 0.0001

Initial: The baseline of monocular ortho-k treatment; Intermediate: The endpoint of monocular treatment; Final: The endpoint of binocular treatment. ^aInitial *vs* intermediate; ^bIntermediate *vs* final; [°]Initial *vs* final. Data were represented in median (interquartile range). Statistical significance was assessed using Wilcoxon test.

defined as refractive differences between two eyes that are spherical, cylindric or both, but the criterion for anisometropia varies among studies from 0.5 to 1.5 D^[6,14,21-22]. Since the ortho-k lens only applied to SER \leq -1.0 D, subjects in this study had anisometropia no less than SER 0.5 D, and the degree of anisometropia was SER 1.56±0.97 D at baseline. Although optical components such as corneal curvature, refraction of the crystalline lens, and AL all contribute to ocular refraction, AL is considered to be fundamental in creating interocular refraction differences^[3,14]. Thus, this study was to observe progression of axial anisometropia under ortho-k lens.

The multiple analysis between the parameters and axial growth rate of Group B in monocular period showed significant relation (P=0.001). Beside age (P=0.005), AL of Group A and Group B (P=0.006, P=0.011) were significantly related to axial growth rate before developing myopia. This is in accordance with previous studies showing that myopia progression varies with AL elongation, besides age growth^[23-24]. And SER of Group A showed significant, too (P=0.03). Which may suggest that the higher refractive error, the faster growth of the contralateral eye. During the monocular ortho-k lens period, the AL of the myopic eyes was prolonged by 0.008 ± 0.022 mm/mo, compared to 0.038 ± 0.018 mm/mo in the contralateral untreated eyes. Also, the interocular difference in AL was significantly smaller than that at baseline (*P*<0.0001).

Some similar studies also investigated the change in anisometropia with monocular ortho-k lens. Cheung et al^[25] described a case in which the AL of the eye fitted with an ortho-k lens increased 0.13 mm, while that of the other eye without vision correction increased by 0.34 mm over two years. Chen and Dai^[26] observed 56 adolescents with unilateral ortho-k lens for one year. The AL was increased by 0.14±0.10 mm and 0.32±0.14 mm in eyes with and without ortho-k lenses, respectively. Tsai et al[27] demonstrated that after 2y of ortho-k treatment in unilateral myopic children, the AL interocular difference (the authors named as aniso-AL) decreased from 0.83 ± 0.45 to 0.59 ± 0.49 mm. Na and Yoo^[28] observed 45 children with monocular ortho-k lenses for one year, and the AL increase in myopic eyes (0.07±0.21 mm) was smaller than that in nonmyopic eyes $(0.36\pm0.23 \text{ mm})$. Therefore, it has been confirmed that the ortho-k lens is efficient in diminishing interocular differences in monocular myopia.

It is considered that a greater baseline SER is related to a smaller AL elongation under ortho-k treatment^[29-30]. Lum^[31] described a case report of an Asian boy with progressive myopic anisometropia, where the aniso-AL increased from 0.76 to 0.91 mm before treatment but decreased to 0.84 mm after the same period of binocular ortho-k treatment. Long et al^[32] observed 98 anisometropic children fitted with binocular ortho-k lenses, and the aniso-AL decreased by 0.10±0.15 mm after one year. Zhang and Chen^[33] also found that the aniso-AL decreased from 0.72±0.34 to 0.56±0.38 mm after 2y of binocular ortho-k treatment in 49 children. However, Fu et $al^{[34]}$ reported another outcome from 25 anisometropic children with a one-year binocular ortho-k lenses. The elongation of the low myopic eyes (0.13±0.16 mm) showed no significant difference from that of the high myopic eyes (0.09±0.14 mm, P=0.36). They found that both eyes grew at the same rate and that the degree of anisometropia did not decrease.

In our study, after Group B (-0.29±0.56 D) developed myopia (-1.56±0.43 D), subjects received binocular ortho-k treatment. At the beginning of binocular period, although the true SER of Group A was difficult to measure, the AL of Group A (24.64±0.78 mm) was still significantly longer than the AL of Group B (24.34±0.722 mm; P<0.0001). During binocular period, the AL elongation of the Group B was 0.016±0.015 mm/mo, while that of the Group A was 0.026±0.014 mm/mo. Contrary to the expectation that the effect of ortho-k on myopia progression was dose-dependent,

the Group A were longer than the Group B (P < 0.0001). The reason might be that the functionality of the ortho-k lenses was reduced during usage and needs to be replaced. The peripheral myopia defocus generated by ortho-k treatment is considered to be a fatal signal in slowing myopia progression^[35]. When the AL lengthens, the visual signal on the retina may change, and the power of the ortho-k lens may decline. During binocular period, the Group A still fit with the old lenses, which may cause the control of myopia progression to be reduced. The AL growth rate of Group A between the two periods was also compared; monocular period (0.008±0.022 mm) was smaller than binocular period (0.026±0.014 mm), which suggested that the ortho-k lenses were worn out. In addition, the aniso-AL in final timing 0.30 (0.32) mm was significantly higher than that in intermediate timing 0.22 (0.39) mm (P<0.0001), but still significantly lower than initial one 0.60 (0.46) mm ($P \le 0.0001$). In other words, after the other eyes also developed myopia, just fitting these eyes with ortho-k lenses maybe not enough to treat axial anisometropia. The old lenses might need to be replaced. There are some limitations in the current study. First, although criteria were used to enroll subjects, data on some factors that may influence myopia progression, such as ethnic group, genetic differences, environmental differences, daily activities, and time spent outdoors, were not recorded. Second, the different durations of the untreated eyes developing myopia makes it difficult to compare the AL directly, thus we analyzed the growth per month, which may interfere the results. In the future, more well-designed prospective studies are needed.

In conclusion, the ortho-k lens is efficient for control progression of anisometropic myopia, because of inhibiting the AL elongation of monocular myopia eyes. For the condition that the contralateral eyes develop myopia and receive ortho-k lens later, there is no efficiency observed on control interocular difference of AL during binocular treatment. This study may suggest doctors to use ortho-k lens to treat monocular myopia children, and pay attention to the contralateral eyes of children with higher myopia or longer AL.

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