HIGH MYOPIA – PARTIAL REDUCTION USING ORTHOKERATOLOGY (HM-PRO)

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High Myopia - Partial Reduction using Orthokeratology (HM-PRO)

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Certificate of Originality

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_____ (Signed)

_Charm Chi Foon_____(Name of student)

Abstract

PURPOSE

The High Myopia Partial Reduction Orthokeratology (HM-PRO) study was a 2-year, single-masked, randomized clinical study which assessed the clinical performance of partial reduction using orthokeratology (ortho-k) and myopic progression in high myopic children after two years of lens wear.

METHODS

Children (8 to 11 years old) with spherical equivalent refraction 5.75D or above were recruited and randomly assigned into PR (partial reduction) ortho-k and control groups. PR ortho-k group used a custom made 4-zone ortho-k lenses (DreamLite, Procornea, The Netherlands) of target 4.00D to reduce the refractive errors. Residual refractive errors were corrected with a pair of glasses. Control subjects were fully corrected with single vision spectacles. Axial length (AL) was monitored with the IOLMaster during the treatment period. Complete ocular biometric data were collected at 6-month intervals. Analysis was performed on data from the right eye only.

RESULTS

During the study, 79 children were screened, and 52 (66%) were eligible and enrolled. Half of the subjects were randomly assigned to PR ortho-k group and the other half to the control group. In PR ortho-k group, the median (range)

myopic reduction and residual myopia were 3.75D (2.25D to 5.00D) and 2.75D (1.50D to 5.25D) respectively after 1-month lens wear. Residual refractive errors were corrected by a pair of spectacles and no significant difference was found in BCVA after stabilization of treatment at the 1-month visit. Pigmented arc was found in 32% of subjects after one month of lens wear. Observations of fluorescein staining of the cornea (less than Grade 2) were noted in some subjects at the 1-month visit.

Twelve PR ortho-k and 16 control subjects completed this 2-year study. At the end of the study period, the median reduction in myopia was 4.50D (range: 2.75D to 6.25D) in the PR ortho-k group. Compared to the residual refractive errors at the 1-month visit (after lens stabilization), the median change in residual non-cycloplegic myopia at the 24-month visit was 0.13D (range: -0.75 to 1.00D). In the control group, the median increase in myopia was 1.00D (range: 0.50 to 2.50D). No significant change in astigmatism was observed in both groups. Corneal staining was observed in both groups of subjects at each visit but the frequency was generally higher in the PR ortho-k treated subjects At the end of the 2-year monitoring period, the mean±SD increases in AL were 0.19±0.21mm for the PR ortho-k group and 0.51±0.32mm for the control group ($p=0.005$). AL elongation was 63% slower in PR ortho-k treated children when compared to children wearing spectacles.

CONCLUSIONS

This study showed that PR ortho-k with spectacles for correcting residual refractive errors is safe and can be offered to high myopic children who wish to undergo ortho-k treatment for myopic control. This mode of treatment can retard myopic progression in high myopic children.

Key Words: myopia control, orthokeratology, high myope, myopic progression, partial correction

Publications arising from this thesis

Journal Articles

Charm J and Cho P (2012). High Myopia-Partial Reduction Orthokeratology (HM-PRO): Study design. (Submitted).

Charm J and Cho P (2012). High Myopia-Partial Reduction Orthokeratology (HM-PRO): 2-year result. (Submitted).

Conference papers

Charm J and Cho P (2010). Partial reduction orthokeratology for high myopic children - methodology and preliminary results. Poster presented at the 7th Asia Cornea and Contact Lens Conference, Philippines.

Charm J and Cho P (2010). Partial reduction orthokeratology for high myopic children: 6-month result. Poster presented at the 13th International Myopia Conference, Germany.

Charm J (2011). High myopia – partial reduction orthokeratology (HM-PRO) study: recruitment and one year result. Presented at the British Contact Lens Association 35th Clinical Conference and Exhibition, Manchester, UK.

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Abbreviations

AC	Alignment Curve
BCVA	Best Corrected Visual Acuity
BOZR	Back Optic Zone Radius
Dk	Oxygen permeability
HM-PRO	High Myopia - Partial Reduction Orthokeratology
K	Corneal Curvature
LZA	Landing Zone Angle
Ortho-k	Orthokeratology
PC	Peripheral Curve
RC	Reverse Curve
RZD	Reverse Zone Diameter
SD	Standard Deviation
SER	Spherical Equivalent Refraction
TLT	Tear Lens Thickness

Chapter 1. Literature review and background of study

1.1 Introduction

Myopia is a refractive error of the ocular system. The image, refracted by parallel light, is focused in front of the retina due to high corneal refractive power or a long eyeball. Concave lenses, either spectacles or contact lenses, bring the image back to the retina (Goss 1987; Grosvenor et al. 1987).

This chapter reviews the prevalence of myopia, the philosophy, design and assessment and clinical efficacy of orthokeratology (ortho-k). Some major published myopic control studies are discussed and this is followed by a brief discussion on the use of ortho-k on high myopes.

1.1.1 Prevalence of myopia and myopic progression

Myopic progression in children is of great concern in Asian countries because the prevalence of myopia in Asia is high and may be increasing (Fan et al. 2004; Cheng et al. 2007). The prevalence of myopia for Singapore children (Saw et al. 2000) aged 3 to 7 was 8.6% while Lam and Goh (1991) reported it was 30% in Hong Kong children aged 6 to 7. Lam et al. (1999) reported a 2-year longitudinal study in

children aged 6 to 17 years and the prevalence of myopia in this study increased from 52% to 63% within 2 years. Fan et al. (2004) reported, in their cross-sectional study, that the prevalence increased from 17% at age 7 to 53% at age 11 in Hong Kong.

The annual myopic shift was reported to be −0.46D in myopic children (age 6 to 17) in 1999 (Lam et al. 1999) and it was −0.63D (age 5 to 16) in 2004 (Fan et al. 2004) in Hong Kong.

Fan et al. (2004) reported that the prevalence of severe myopia (spherical equivalent refraction≤−6.00D) was 1.19% in Hong Kong. The annual myopic shifts were −0.63D and −0.71D for low (−0.50 to −2.99D) and high (spherical equivalent refraction≤−6.00D) myopic groups respectively. High myopes have also been reported to show a faster myopic progression (Lam et al. 1999; Saw et al. 2000; Fan et al. 2004). Degenerative changes of the vitreous, glaucoma and myopic degeneration are complications associated with high myopia (Curtin and Karlin 1970; Grossniklaus and Green 1992; Mitchell et al. 1999), and many researchers are still investigating techniques to retard myopic progression. Hence, researchers have investigated the underlying physiology and ways to control myopic progression for many years, but have failed to put forward a feasible method. However, in recent years,

ortho-k has been shown to have a potential for myopic control and interest in this treatment has greatly increased. Ortho-k has also been confirmed to correct mild to moderate myopia effectively. However, there is little information about safety and a success rate in correcting high refractive errors. Clinically, attempts at high myopic reduction could result in corneal staining, heavy lens binding and lens decentration (Chan et al. 2008a). Practitioners partially correct refractive errors using ortho-k in high myopes. The patients then wear spectacles to correct residual refractive errors to obtain clear daytime vision. However, myopic progression using this wearing mode is unknown.

1.2 Orthokeratology

1.2.1 Reverse geometry lens

Traditional ortho-k originated in the 1960s when an "orthofocus" procedure was first introduced by molding the cornea with conventional rigid lenses (Jesson 1962). The base curve of the PMMA lens was flattened by the amount of myopic reduction desired to flatten the cornea. The May-Grant philosophy (Grant and May 1970) suggested using a series of progressively flatter lenses, the first pair being 0.50D or 0.75D flatter than the flat K of the eye. The Tabb technique (Coon 1982) was introduced in the early 1980s whereby the optic zone diameter was

varied to induce a reduction in lens sag as the cornea flattened. The treatment using traditional ortho-k was inefficient because the user needed to wear the lenses during the daytime (as an overnight wear material was not available), the amount of myopic reduction was small (about 1.00D), the time taken to induce this small reduction could be up to several months, and a series of lenses, on average 6 pairs, were required to achieve this small amount of myopic reduction (Brand et al. 1983). Hence, ortho-k was little used for many years until the early 1990s. Ortho-k was reintroduced with the introduction of computerized corneal topography (McMonnies and Boneham 1997; Swarbrick 2006), lens materials with a high oxygen permeability (Dk) (Haque et al. 2007; Lum and Swarbrick 2011) and innovative contact lens designs (Dave and Ruston 1998; Caroline 2001; Mountford et al. 2004; Sorbara et al. 2005).

Modern ortho-k, which uses reverse geometry lenses, is known as "accelerated orthokeratology" (Wlodyga and Bryla 1989; Harris and Stoyan 1992) as the reverse geometry lenses required fewer lenses to effect a larger myopic reduction. The responses are faster and the amount of myopic reduction is greater when compared to traditional orthokeratology. High oxygen permeable materials were introduced with Dk 100 or above, allowing an overnight wearing modality, which reduces

lens sensation, improves comfort and convenience as users only need to wear the lenses at night and can be spectacle- or contact lens-free in the daytime (Barr et al. 2003; Soni and Nguyen 2006). The high Dk materials also optimize clinical outcomes in terms of visual acuity, myopic reduction and ocular health (Haque et al. 2007; Lum and Swarbrick 2011).

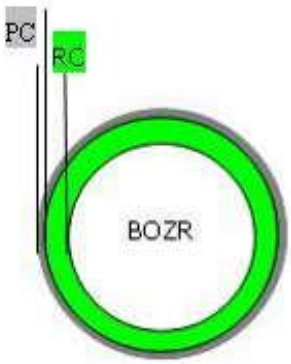
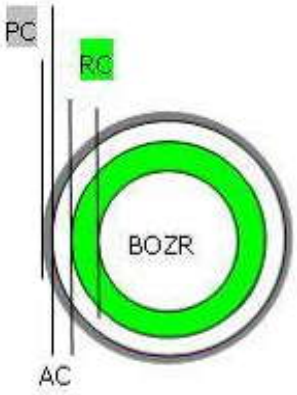
The introduction of computerized corneal topography allows practitioners to analyse and monitor the whole corneal profile (Cho et al. 2008) during treatment. Keratometers only measure the curvature of the central 3mm cornea whereas corneal topographer measures >90% of the corneal surface. Computerized corneal topography leads to a marked improvement in first-fit success and helps in refining the fit to correct adverse outcomes because practitioners can closely monitor changes in corneal topography.

The following sections of this chapter review ortho-k philosophy, mechanism, its efficacy, clinical implications and limitations.

1.2.2 Reverse geometry lens designs

A conventional rigid gas permeable lens has a back optic zone radius (BOZR) and a peripheral curve (PC). However, a reverse geometry lenses has at least three zones – BOZR, reverse curve (RC) and PC (Guillon and Sammons 1994; Mountford et al. 2004; Swarbrick 2006; van der Worp and Ruston 2006) (Table 1.1). The RC is also called the fitting curve and this is steeper than the BOZR. For 4- and 5-zone reverse geometry lens designs, the RC is surrounded by one or more outer peripheral curves (alignment curve (AC)) which align the mid peripheral cornea. Corneal changes induced are not only dependent on the BOZR, but also on the combination of BOZR and RC used.

Table 1.1. Different reverse geometry lens designs

Curves	3-zone	4-zone	5-zone
BOZR	✓	✓	✓
RC	✓	✓	✓
AC	--	✓	✓ (2 alignment curves)
PC	✓	✓	✓
			

With the reverse geometry lens on the eye, the tear layer formed behind the lens provides an applanation force to redistribute the corneal tissues. Changing the BOZR does not affect the lens fitting (Guillon and Sammons 1994; Mountford et al. 2004; Swarbrick 2006; van der Worp and Ruston 2006).

The tear reservoir behind the RC radically alters the efficacy of treatment and provides a relief area for tissue redistribution (Guillon and Sammons 1994; Mountford et al. 2004; Swarbrick 2006; van der Worp and Ruston 2006). It appears green when fluorescein is instilled because the tear layer thickness is above 20µm (Coon 1984; Mountford

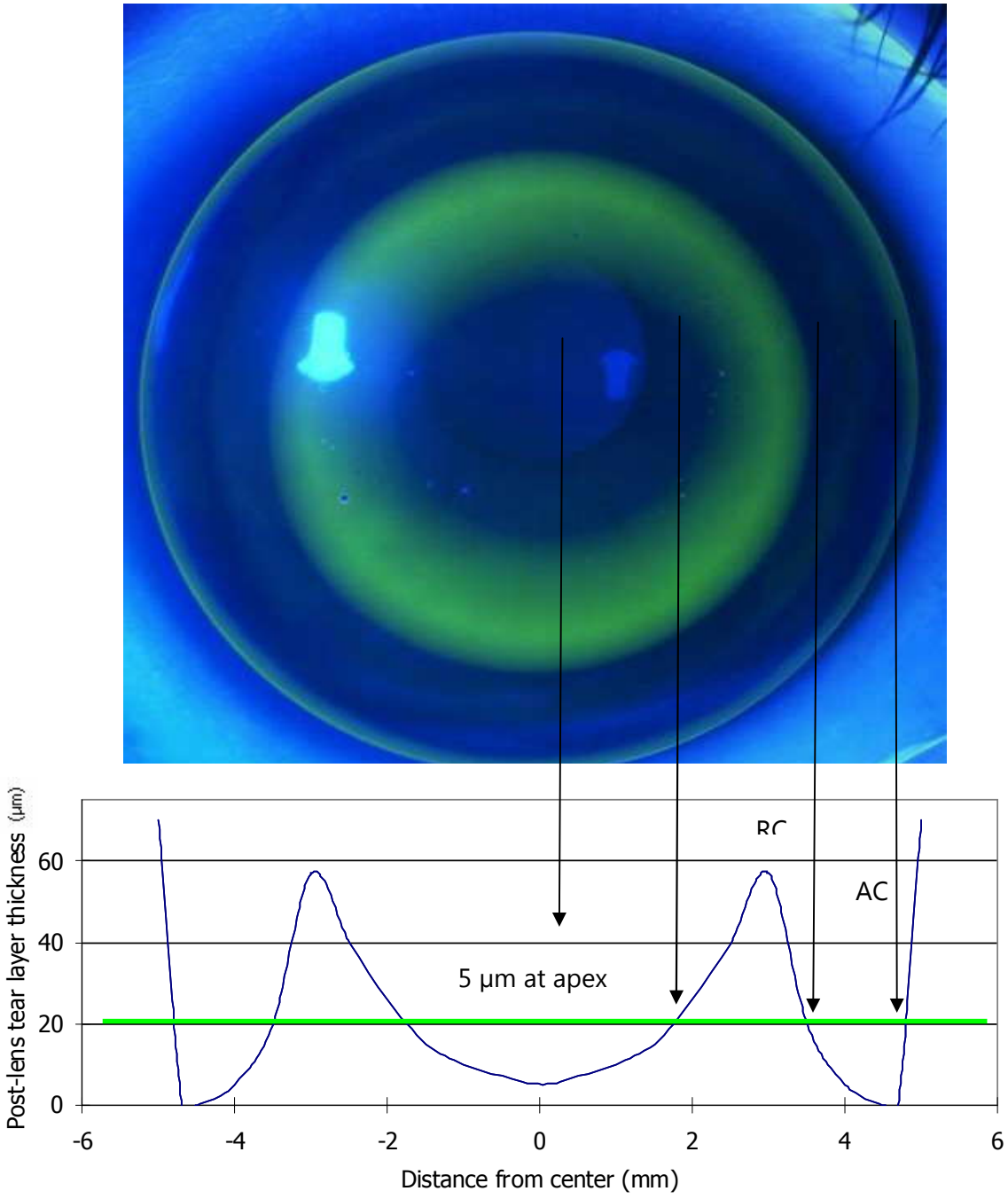
et al. 2004; 2005) (Figure 1.1). Fluorescein can only be visualized when the thickness of the tear layer is over 20μm (Mountford et al. 2004; 2005).

The AC aligns the peripheral cornea and controls lens centration (Guillon and Sammons 1994; Mountford et al. 2004; Swarbrick 2006; van der Worp and Ruston 2006). It shows bearing when fluorescein is instilled. The 5-zone lenses have two curves (AC1 and AC2) while 4-zone lenses have only one AC.

The PC provides the desired edge (lift or clearance) to facilitate tear exchange behind the lens (Guillon and Sammons 1994; Mountford et al. 2004; Swarbrick 2006; van der Worp and Ruston 2006).

A contact lens which contacts the cornea directly will lead to corneal insult. It has been suggested that, in ortho-k, about a 5μm post-lens tear layer is required at the corneal apex (Mountford et al. 2004). This will exert a tear film squeeze pressure to manipulate the required refractive change. The tear layer thickness (TLT) under a reverse geometry lens is minimal at the corneal apex and maximal at the BOZR/RC junction. It is close to zero under the area where the

alignment curve aligns the peripheral cornea. Figure 1.1 shows the variation of the post-tear layer across a reverse geometry lens.



AC - Alignment Curve; RC - reverse Curve

Figure 1.1 An example of the post-lens tear layer profile behind a reverse geometry lens

Available lenses in the market are designed based on two philosophies, namely the Jessen factor philosophy and the Sag philosophy (Mountford et al. 2004). Lenses employing the Jessen factor philosophy include DreamLens (Procornea Ltd., Netherlands), DreimLens (DreimLens Taiwan, Taiwan Macro Vision Chroup, Taiwan, China), Emerald (Euclid Systems Co, Herndon, VA, USA); eLens (E&E Optics Ltd., Hong Kong SAR, China) and Menicon Z Night Lens (Menicon Ltd., Japan). Jesson (1962) proposed that the tear lens acted as correcting factor in the rigid gas permeable lens. However, with a reverse geometry lens, since the patients will not wear the lenses in the daytime, an additional factor called "compression factor" is taken into account because there may be some regression by the end of the day. The purpose of the compression factor is to over-correct the myopia to allow for such regression. Some studies (Mountford 1998; Nichols et al. 2000; Rah et al. 2002) reported about 0.25D to 0.75D day regression in adult Caucasian ortho-k wearers while there was less regression (median: 0.0D, range: 0.75D to −0.75D) reported in Chinese ortho-k wearers (Chan et al. 2008a). Most lens designs use 0.50D or 0.75D as the compression factor. The BOZR in a reverse geometry lens is determined by the amount of refractive change required (Target) and the compression factor of the lens design (Mountford et al. 2004; Chan et al. 2008b). The equation is as follows:

BOZR = Flat K (D) – Target (D) – compression factor (D).

Chan et al. (2008b) found that the compression factor underestimated the intended target of myopic reduction in Chinese subjects. Based on their results, they proposed that for lenses employing the Jessen philosophy, the equation should be:

BOZR = Flat K (D) – (1.23 target reduction + 1.27).

However, since their study was a retrospective analysis and the data were quite scattered when the myopic reduction exceeded 4.50D, they suggested a further clinical trial to validate this formula.

A commercially available reverse geometry lens employing the sag philosophy is the BE Retainer (BE Enterprises, Vancouver, Canada). A specific tear layer is introduced between the lens and cornea (Figure 1.2). When the lens curvature fits optimally on the cornea, this tear layer manipulates a squeeze film force to modify the corneal curvature. The sag of a five-zone reverse geometry lens is shown below:

Sag of lens $= x_0 + x_1 + x_2 + x_3$

= Corneal sag + tear lens thickness

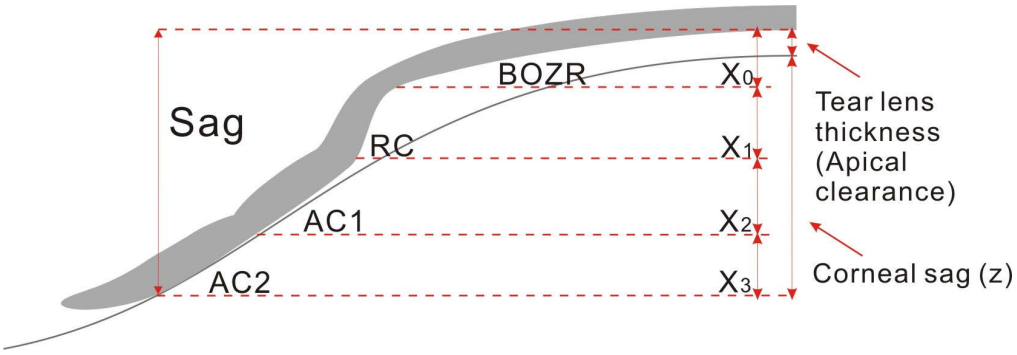


Figure 1.2 Sagittal height of a five-zone reverse geometry lens

Sagittal height of the cornea:

$$z = \frac{R_0 - \sqrt{(R_0^2 - py^2)}}{p}$$

z = corneal sag

R_0 = apical radius

y = half chord

p = shape factor

The calculation of sag for a multicurve reverse geometry lens is:

$$\text{Sag} = R_1 - \sqrt{R_1^{\,2} - (\frac{D_1}{2})^2} \; + \left[R_2 - \sqrt{R_2^{\,2} - (\frac{D_2}{2})^2} \right] - \left[R_2 - \sqrt{R_2^{\,2} - (\frac{D_1}{2})^2} \right] + \ldots\ldots \left[R_n - \sqrt{R_n^{\,2} - (\frac{D_n}{2})^2} \right] - \left[R_n - \sqrt{R_n^{\,2} - (\frac{D_{n-1}}{2})^2} \right]$$

R_1 = Back Optic Zone Radius D_1 = Back Optic Zone Diameter

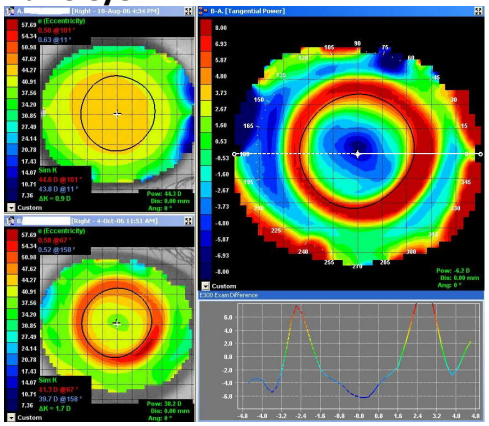
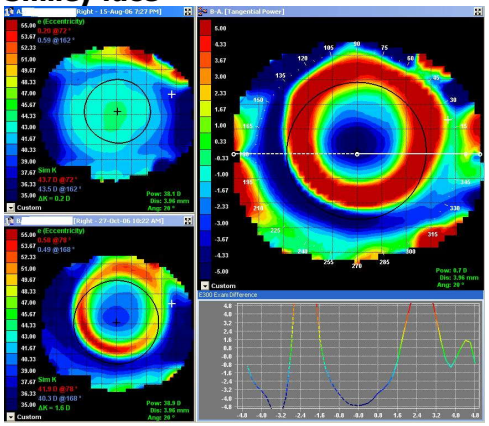
R_2 = 2nd Back Peripheral Radius D_2 = 2nd Back Peripheral Diameter

R_n = nth Back Peripheral Radius D_n = nth Back Peripheral Diameter

1.3 Assessment of lens fit

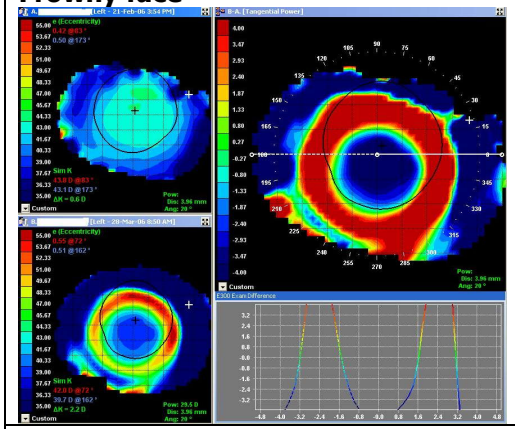
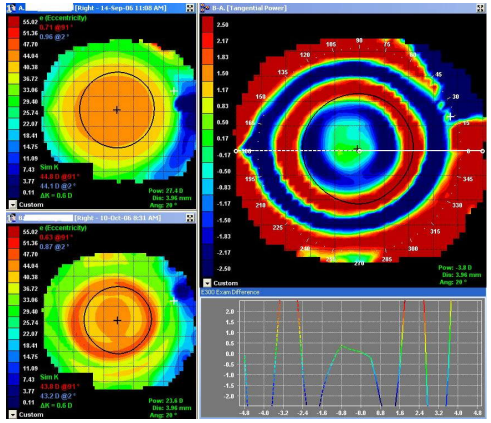
The preliminary lens fitting is based on the fluorescein pattern and overnight lens response. The responses are basically classified as bull's eye, smiley face, frowny face, true central island, smiley face with fake central island and lateral displacement. The possible causes of these responses and remedies to lens fit are presented in Table 1.2.

Table 1.2 Different orthokeratology outcomes with possible causes and remedies to lens fit

Conditions	Descriptions	Possible causes	Remedies to lens fit
Bull's eye 	• Ideal pattern • Lens sag = corneal sag + TLT • Good centration, with good alignment at peripheral cornea • 'Red-ring' centered with respect to pupil	• N/A	• N/A
Smiley face 	• Flat fitting lens • 'Red-ring' decenters superior-temporally with respect to pupil • The flatter the fit, the more superior the 'red-ring'	• Under-estimated lens sag (TLT=0) because of ❖ Under-estimated corneal sag, or ❖ Over-estimated eccentricity	• Increase lens sag ❖ Steepen AC (eLens, Emerald, OK series, DriemLens) ❖ Steepen RC/BOZR (Emerald) ❖ Increase RZD, LZA or BOZR (CRT) ❖ Decrease cone angle (Menicon Z Night Lens, BE Retainer)

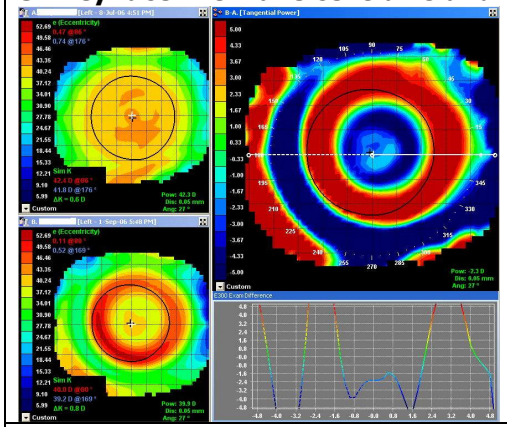
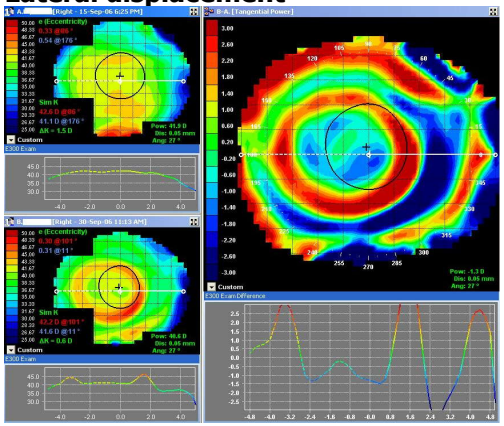
AC: alignment curve, RC: reverse curve, RZD: reverse zone diameter, LZA: landing zone angle, TLT: tear lens thickness

Table 1.2 Different orthokeratology outcomes with possible causes and remedies to lens fit (Con't)

Conditions	Descriptions	Possible causes	Remedies to lens fit
Frowny face 	• Slightly steep fitting lens • 'Red-ring' decenters inferiorly with respect to pupil • The steeper the fit, the more inferior the 'red-ring'	• Over-estimated lens sag (actual TLT>10 μm) because of ❖ Over-estimated corneal sag, or ❖ Under-estimated eccentricity • Small total lens diameter may cause lateral decentration as well	• Reduce lens sag ❖ Flatten AC (eLens, Emerald, OK series, DriemLens) ❖ Flatten RC/BOZR (Emerald) ❖ Reduce RZD, LZA or BOZR (CRT) ❖ Increase cone angle (Menicon Z Night Lens, BE Retainer) • Increase total lens diameter
True central island 	• Steep fitting lens • 'Red-ring' perfectly centers (as in Bull's Eye) but with the presence of a central area of steepening • The steeper the fit, the steeper the island	• Over-estimated lens sag (actual TLT>10 μm) because of ❖ Over-estimated corneal sag, or ❖ Under-estimated eccentricity	• If central cornea is flatter than original value and the island is small (less than 1.00D), wait for self-resolution, which usually takes 1 week • If the island is unresolved (In this case, it is usually steeper than the original cornea), refit lenses with reduced lens sag (* same as FROWNY FACE)

AC: alignment curve, RC: reverse curve, RZD: reverse zone diameter, LZA: landing zone angle, TLT: tear lens thickness

Table 1.2 Different orthokeratology outcomes with possible causes and remedies to lens fit (Con't)

Conditions	Descriptions	Possible causes	Remedies to lens fit
Smiley face with fake central island 	• Flat fitting lens • 'Red-ring' decenters superiorly with a relatively steepened area at the center	• Heavy bearing ➔ epithelial damage ➔ distorted images of the placido rings of the topographer	• Increase lens sag (*same as in Smiley face)
Lateral displacement 	• 'Red-ring' decenters either nasally or temporally	• Small total lens diameter	• Increase total lens diameter
		• Asymmetrical corneal curvature or decentred corneal apex	• Adjust the alignment curves accordingly

1.4 Clinical efficacy of orthokeratology in low myopes

Ortho-k is effective for reducing myopia under 4.00D (Nichols et al. 2000; Swarbrick 2006). Most studies reported that at least 80% myopic reduction could be achieved for a low to moderate amount of myopia (Table 1.3) (Nichols et al. 2000; Potapova et al. 2004; Sorbara et al. 2005; Swarbrick 2006; Cheung et al. 2007; Chan et al. 2008a). Some patients cannot achieve full myopic reduction due to poor lens centration, poor corneal response or higher initial refractive errors. Hence, myopic reduction can vary from individual to individual.

Table 1.3 A review of previous overnight orthokeratology studies

Study	Age±SD (years)	Initial SER ±SD (D)	Myopic reduction ±SD (D)	Reverse geometry lens used (study period)
Mountford (1997)	28	−2.19±0.8	2.19±0.57	Cortex
Nichols et al. (2000)	25.9±3.9	−1.84±0.81	1.83±1.23	Cortex (2 months)
Rah et al. (2002)	--	OD: −2.37±0.93 OS: −2.43±0.92	OD: 2.08±1.11 OS: 2.16±1.05	Fargo/CRT (3 months)
Alharbi and Swarbrick (2003)	22-29 [range]	−2.63±0.68	2.63±0.57	BE (3 months)
Joslin et al. (2003)	34.4±10.5	−3.33±1.26	3.08±0.93	CRT (1 month)
Tahhan et al. (2003)	18-35 [range]	−2.25±0.77	~2.00	Various lens designs (1 month)
Walline et al. (2004b)	10.5±1.1	−2.44±1.38	2.48±1.57	CRT (6 months)
Cho et al. (2005a)	9.6±1.5	−2.27±1.09	2.09±1.34	Various lens designs (12 months)
Chan et al. (2008a)	9 [median]	−3.56±1.49	~3.79	Various lens designs (6 months)
Kang and Swarbrick (2011)	11-16 [range]	−2.37±1.10	1.83±1.18	BE or BE-A (3 months)
Kakita et al. (2011)	12.0±2.6	−2.55±1.82	1.87	Euclid (2 years)

SER: Spherical Equivalent Refraction
SD: Standard Deviation

1.4.1 Myopic reduction

The largest amount of myopic reduction was reported to occur after the first night of overnight lens wear (Sridharan and Swarbrick 2003; Sorbara et al. 2005; Swarbrick 2006; Cheung et al. 2007; Chan et al. 2008a).

Myopia then continues to decrease for the next 7 to 10 days with overnight lens wear, but at a slower rate. By about 14 days, the reduction rate will reach a plateau. About a 98% reduction was achieved after one month of lens wear (Sridharan and Swarbrick 2003; Sorbara et al. 2005; Swarbrick 2006; Cheung et al. 2007; Chan et al. 2008a). This is generally true for all ortho-k lens designs currently available in the market for low myopia (about 4.00D).

1.4.2 Vision

Many studies have shown that in ortho-k, with full reduction of refractive errors, unaided vision under different contrast and luminance conditions were comparable to that before commencing

treatment (Swarbrick 2006; Johnson et al. 2007). Cheung et al. (2007) compared high and low contrast monocular visual acuities in 31 subjects with an initial myopia of −3.44±1.39D (mean±SD). Their subjects had at least one month of ortho-k lens wear history and did not wear spectacles during daytime. Their residual spherical equivalent refraction was −032±0.37D and −0.55±0.48D in the better and worse eyes respectively. The authors reported that, although uncorrected post-ortho-k visual acuity was comparable to the best corrected visual acuity (BCVA) of the spectacle wearers at high contrast levels, it was worst at low-contrast levels. They attributed the reduced low contrast unaided visual acuity to residual refractive errors. Indeed, blurred vision after ortho-k treatment was a major visual symptom reported in other ortho-k studies (Cho et al. 2003a; Lipson et al. 2005; Chan et al. 2008a). Hence, for ortho-k wearers with significant residual refractive errors, spectacles could be prescribed to correct the residual refractive errors to maintain good vision during daytime.

1.4.3 Corneal thickness

Swarbrick et al. (1998) and Alharbi and Swarbrick (2003) used the Holden-Payor optical pachometer to measure total corneal thickness and reported changes in central corneal thickness and midperipheral corneal thickness were -7.1 ± 7.1μm and $13.0 \pm$ 11.1μm respectively after one month of ortho-k treatment. The changes increased with the duration of lens wear. After 90 days of ortho-k treatment, the changes in central, nasal midperipheral and temporal midperipheral thickness were -19.0 ± 2.6μm, 14.4 ± 5μm and 7.6 ± 3.8μm (Alharbi and Swarbrick 2003). The variation in magnitude may be due to differences in the ortho-k lenses used and the subject pool in their studies, but the trend in these changes (central thinning and mid-peripheral thickening) was similar.

1.4.4 Safety of orthokeratology

Van Meter et al. (2008) extensively reviewed the safety of ortho-k. They evaluated related complications, including infectious keratitis, which were described in case reports and case series. However,

there existed discrepancies in the standards of different studies, and they suggested a further large well-designed cohort or randomized controlled studies to determine the safety of ortho-k wear.

Corneal staining is a common complication in ortho-k lens wear (Nichols et al. 2000; Cho et al. 2003a; Cho et al. 2003b; Walline 2004; Swarbrick 2006; Chan et al. 2008a). Cho et al. (2003b) found that the incidence of clinically significant corneal staining appeared to increase with the duration of ortho-k lens treatment from one month to 12 months. The staining was not correlated with refractive errors, unaided visual acuity or the age of the subjects. The Children's Overnight Orthokeratology Investigation (COOKI) study (Walline et al. 2004a) reported corneal staining after lens removal in more than half of their subjects during the 6-month study period. However, the staining was clinically insignificant and lens discontinuation was not required. Chan et al. (2008a) reviewed 108 children wearing ortho-k lenses for six months. About 84% of the corneal staining was clinically insignificant. The remaining 13% showed grade 2 and 3% showed grade 3 or 4 staining. These

subjects were required to cease lens wear until the corneas recovered. It was suggested that central corneal staining was common and practitioners should monitor patients carefully. The authors also noted a tendency for corneal staining when higher targets were aimed at.

Cho et al. (2003b) reported that 4 out of 61 children in their study had eye inflammations/infections which were diagnosed by optometrists and/or ophthalmologists during overnight ortho-k treatment. All recovered without any detrimental effect on their vision or corneal health. One of the children left the study as advised by an ophthalmologist while the remaining three resumed lens wear with no further difficulties. Although the incidence of eye inflammations or infections was low, close monitoring of ocular health in ortho-k treatment is essential to minimize unnecessary or preventable complications (Cho et al. 2008), especially when children are involved.

Microbial keratitis is of great concern when the corneal epithelium is not intact and overnight lens wear is considered to be a risk factor. A number of microbial keratitis cases have been reported since the introduction of modern ortho-k (Watt and Swarbrick 2005; Watt and Swarbrick 2007). Watt and Swarbrick (2007) studied the first 50 cases of microbial keratitis in association with overnight ortho-k. Eighty percent of the cases happened in Asia and 61% of patients were between 9 and 15 years old. The underlying risk factors included inappropriate lens care procedures, patient non-compliance with practitioner instructions, and persisting with lens wear despite discomfort. The majority (55%) occurred within the first 12 months of ortho-k lens wear and pseudomonas aeruginosa and acanthamoeba were the main pathogenic organisms reported (Table 1.4). Most cases happened in the year 2001 in China where there was a lack of supervision on fitting ortho-k (Van Meter et al. 2008). In the same year, ortho-k practice was banned from optical shops and practices and restricted to clinics with appropriate facilities, including an on-site ophthalmologist. The publicity from these cases also alerted

practitioners to the importance of proper aftercare for ortho-k patients. A later review showed a substantial reduction in the incidence of microbial keratitis in ortho-k (Song et al. 2011). Song et al. (2011) retrospectively reviewed the medical records of microbial keratitis on 76 children aged 16 or below. The majority of microbial keratitis cases (about 60%) were due to trauma. A Taiwanese study (Hsiao et al. 2007) reported that 10% of hospitalized microbial keratitis cases were due to ortho-k wear compared with 31% and 21% of cases due to soft contact lens wear and trauma respectively.

Table 1.4 Pathogenic organisms in microbial keratitis reported in orthokeratology patients

Studies	Number of cases of microbial keratitis	Pseudomonas aeruginosa	Acanthamoeba
Hsiao et al. (2005)	21	43%	5%
Watt and Swarbrick (2005)	50	52%	30%
Sun et al. (2006)	28	46%	29%
Hsiao et al. (2007)	8	50%	0%
Watt and Swarbrick (2007)	123	37%	33%

In overnight lens wear, eye closure may promote the growth of trapped organisms (Ramachandran et al. 1995). Also, the risk of microbial keratitis may be increased by central epithelial thinning in ortho-k which may compromise epithelial integrity (Swarbrick et al. 1998; Alharbi and Swarbrick 2003; Watt et al. 2007). Lens binding due to poor tear exchange, mechanical abrasion from the build-up of deposits on the back surface of lens and improper lens removal of a bound lens can result in corneal staining (Chan et al. 2008a) and increase the risk of microbial keratitis (Choo et al. 2009). Personal hygiene, the lens care regimen, non-compliant behaviors and improper fitting can also increase the risk of microbial keratitis (Lam et al. 2002; Watt and Swarbrick 2005; Watt et al. 2007; Watt and Swarbrick 2007). Hence, a high standard of practice which includes appropriate equipment such as a corneal topographer and diligent patient education and compliance (both from practitioners and patients) is necessary to minimise adverse events in ortho-k. A comprehensive guideline on patient selection, proper examination procedures and patient instruction to improve ortho-k practice has been published (Cho et al. 2008).

1.5 Parameters to monitor in myopic control

Since ortho-k alters the corneal profile to achieve myopic reduction, refractive errors measured during treatment do not reflect the actual amount of myopia. A change in axial length is closely related to myopic progression (Grosvenor 1987; Gonzalez Blanco et al. 2008) and comprising the axial length before and after a treatment is the gold standard for determining myopic progression. It was suggested that the anterior chamber depth may be affected by ortho-k or rigid gas permeable lens wear due to backward corneal displacement (Grosvenor et al. 1991) which would artificially give a shorter axial length measurement. However, anterior chamber depth was not significantly changed in ortho-k (Tsukiyama et al. 2008). Also, the change in vitreous chamber depth, the main component of axial length which is unaffected by corneal flattening or backward corneal displacement, has been shown to be similar to the change in axial length in the LORIC study (Cho et al. 2005a).

Clinically, axial length is measured by A-scan ultrasound biometry or IOLMaster. A-scan ultrasound biometry is an invasive tool which may cause corneal abrasion if patients do not fixate well. The IOLMaster (Carl Zeiss Meditec, Dublin, CA, USA) is a non-invasive instrument and does not cause corneal abrasion or infection. The axial length is measured by an interference signal when the light is reflected by the tear film and the retinal pigmented epithelium of the eye. The reliabilityand validity of IOLMaster was higher than A-Scan (Carkeet et al. 2004; Hussin et al. 2006). Axial length was performed using IOLMaster to monitor eye growth and refractive development in children in recent myopic control studies (Santodomingo-Rubido et al. 2011; Kakita et al. 2011; Cho 2012).

1.6 Myopic control studies

Spectacles and contact lenses have been shown to be ineffective for myopic control (Horner et al. 1999; Hasebe et al. 2008; Walline et al. 2008). Progressive lenses/bifocals and specially designed soft contact lenses have not been successful (Parsinnen et al. 1989; Jensen 1991; Fulk and Cyert 1996; Leung and Brown 1999; Shih et al. 2001; Edwards

et al. 2002; Fulk et al. 2003; Hasebe et al. 2008; Yang et al. 2009; Cheng et al. 2010; Anstice and Phillips 2011). Pharmaceutical agents (atropine and pirenzepine) have been reported effective in retarding myopic progression (Tan et al. 2005; Chua et al. 2006; Siatkowski et al. 2008; Tong et al. 2009), but side effects such as accommodation insufficiency and dilated pupils affected daily life activities (Chua et al. 2006; Tong et al. 2009). Research in the field of ortho-k has increased substantially in the last few years, especially after published reports of its potential for slowing myopic progression in children (Cho et al. 2005a; Walline et al. 2009; Kakita et al. 2011).

1.7 Myopic control with orthokeratology

Table 1.3 summarizes the results from different ortho-k studies. Most studies investigated the reduction of the spherical equivalent refraction rather than myopia because the majority of subjects were low to moderate astigmatic myopes (sphere≤4.00D and astigmatism≤1.50D). Most studies were able to achieve a full myopic correction and had good vision during the daytime. In general, ortho-k is effective in correcting

low to moderate myopes (sphere≤4.00DS). Most of the earlier studies involved adults, but more recently, researchers have shifted their focus to myopic control in children (Table 1.5).

Cheung et al. (2004) reported a retardation of myopic progression with ortho-k in a case report. An 11-year-old boy underwent unilateral ortho-k treatment in 1999. He had ortho-k treatment on the left eye (refractive error: −2.50/−0.50x170) and no lens wear on the right eye (refractive error: −0.25/−0.75x168). The axial lengths were recorded from 2001 to 2003. The increases in the left eye and right eye were 0.13mm and 0.34mm respectively during two years of ortho-k treatment. The increase in axial length in the right eye matched the increase in refractive error (0.75D in spherical equivalent refraction).

Table 1.5 Results from longitudinal studies using orthokeratology

Study	Cho et al. (2005a)	Walline et al. (2009)	Santodomingo- Rubido (2010)	Mok and Chung (2011)	Kakita et al. (2011)	Cho (2012)
Age group (years)	7-12	8-11	6-12	7-13	8-16	6-10
Study group	Various brands of ortho-k (4- or 5-zone lenses)	CRT, Paragon Vision Sciences, Mesa, Arizona	Menicon Z Night Lens	Dreimlens, E and E Optics, Hong Kong	Euclid Systems Corporations, Herndon, VA, USA	Menicon Z Night Lens
Control group	Spectacles	Soft single vision contact lens	Spectacles	Spectacles	Spectacles	Spectacles
Equipment to measure axial length	A-Scan	A-Scan	IOLMaster	-	IOL master	IOLMaster
Race	Chinese	Caucasian	Caucasian	Chinese	Chinese (Japanese)	Chinese
Myopia (D)	2.27±1.09 (ortho-k) 2.55±0.98 (control)	0.75-4.00	0.75-4.00	2.88±0.49 (ortho-k) 2.60±0.61 (control)	2.55±1.82 range: 0.50-10.00	0.75-4.00
Study duration	2 years	2 years	2 years	7 years	2 years	2 years
Changes in axial length	P = 0.012	P < 0.001	For 18 months, p<0.0001	-	P < 0.001	For 2 year, P=0.000
Study group (mm)	0.29±0.27	0.25±0.27	0.37±0.13		0.39±0.27	0.36±0.24
Control group (mm)	0.54±0.27	0.57±0.27	0.52±0.31		0.61±0.24	0.63±0.26
Changes in vitreous chamber depth	P = 0.005	P < 0.001	-	-	-	-
Study group (mm)	0.23±0.25	0.26				
Control group (mm)	0.48±0.26	0.46				
Limitations	Non-randomized study Control group: historical subjects	Non-randomized study Control group: historical subjects	Non-randomized study	Retrospective study No axial length data Non-cycloplegic refraction	Non-randomized study	-

Ortho-k has been shown to have a potential to retard myopic progression in non-randomized clinical studies. In the LORIC study (Cho et al. 2005a), anterior chamber depth, vitreous chamber depth and axial length measured with ultrasound A-scan in 35 children wearing spectacles (historical subjects from a progressive lens study (Edwards et al. 2002)) and compared with those parameters measured in 35 children undergoing ortho-k. Significant differences were found in vitreous chamber depth and axial length between the ortho-k and spectacle groups over two years of monitoring (Cho et al. 2005a). The increase in axial length (vitreous chamber depth) in ortho-k subjects was about 46% (52%) slower compared to the control group (Table 1.5).

Walline et al. (2009) conducted a two-year study (CRAYON study) to compare the annual rate of change in axial length between subjects wearing ortho-k and soft contact lenses (historical subjects from a contact lens study, CLAMP study (Walline et al. 2004b)). Increases in axial length and vitreous chamber depth in the ortho-k group were significantly less than those in soft contact lens wearers. Increase in axial length (vitreous chamber depth) was about 56% (43%) slower in

children wearing ortho-k lenses compared to those wearing soft contact lenses.

Santodomingo-Rubido et al. (2011) reported the 24-month results of their study (Myopia Control with contact lenses in Spain (MCOS)). The study compared the axial length change between 31 ortho-k subjects and 30 spectacle-wearing subjects. AL, measured using the IOLMaster, was shorter in the ortho-k group than in the control group. The increase in axial length was about 33% slower in children wearing ortho-k lenses compared to those wearing soft contact lenses after 24 months of lens wear.

Kakita et al. (2011) conducted a masked study on axial length measurements in ortho-k subjects. They measured axial length using IOLMaster for 45 and 60 subjects in ortho-k and spectacle (control) groups respectively. The increase in axial length was about 36% slower in subjects wearing ortho-k lenses compared to those wearing spectacles after two years.

Although axial length was measured differently (either using A-Scan or IOLMaster) in these four different studies, their results suggested a strong potential of ortho-k for myopic control. However, there is a need for a randomized masked study to confirm the results. A 2-year randomized, masked clinical trial (Retardation Of Myopia In Orthokeratology (ROMIO)) was commenced in 2008 in Hong Kong (Cho 2012). Children from 6 to 10 years old were recruited. Menicon Z Night Lenses (Menicon Ltd., Japan) and single vision spectacles were used in the study and control groups respectively to fully correct the myopia. Two year results (unpublished) showed an axial length increase of 0.36mm in the study group compared to 0.63mm in the control group ($p<0.001$) (Cho 2012). The retardation rate was about 43%, comparable to previous studies (Cho et al. 2005a; Walline et al. 2009; Santodomingo-Rubido et al. 2011; Kakita et al. 2011). The ROMIO study is on-going, but preliminarily results appear to confirm that ortho-k can retard myopic progression in children.

The above studies have shown that ortho-k has the potential for myopic control (Cho et al. 2005a; Walline et al. 2009). However, the subjects in

these studies were all low to moderate myopes who were mostly fully corrected by the ortho-k lenses. Most clinical studies limited refractive errors to 4.00D or less of myopia (Sridharan and Swarbrick 2003; Sorbara et al. 2005; Swarbrick 2006; Cheung et al. 2007; Chan et al. 2008a) because available lens designs in the market are mostly designed for this group of myopes.

1.8 Peripheral defocus in orthokeratology

Axial elongation in the myopic eye has been associated with the visual feedback due to peripheral defocus (Norton and Siegwart 1995; Smith et al. 2005). The hypothesis is that, since there is a greater relative hyperopia in the periphery with respect to axial refraction in myopes compared to relative peripheral myopia in emmetropes and hyperopes, peripheral hyperopic defocus may promote axial myopia in humans. In ortho-k, the central cornea is flattened which reduces the myopia while the mid-periphery is steepened which leads to a ring of increased of peripheral myopia in myopic eyes. This may retard the visual feedback for eye elongation (Norton and Siegwart 1995; Smith et al. 2005;

Charman et al. 2006; Mathur and Atchison 2009; Smith et al. 2009; Kang and Swarbrick 2011). The change in refractive status, the reduction of myopia at central and induced ring of peripheral myopia induced by ortho-k lens wear, may be a likely mechanism for retarding myopic progression.

1.9 Definition of high myopia

Published reports have classified the magnitude of myopia into low, moderate and high according to the spherical equivalent refraction (Fan et al. 2004; Saw et al. 2005; Cheng et al. 2007). Spherical equivalent refraction was calculated as spherical power plus half negative cylinder power. High myopia was defined as spherical equivalent refraction at least −6.00D (Fan et al. 2004; Lam et al. 2005; Saw et al. 2005; Cheng et al. 2007).

1.10 Orthokeratology for high myopes

Published studies or reports on ortho-k for myopic reduction for high myopes are scarce. Ogur and Nishimura (2003) reported that of 8 eyes

of 5 high myopic patients (mean spherical equivalent refraction: −7.22D; range: −6.00D to −9.00D) (mean age 28.2 years) fitted with ortho-k, only 3 eyes (37.5%) achieved visual acuities of 20/20 after 1 year of treatment. However, they did not provide any details about ortho-k lens fit, wear or the ocular health of these subjects.

A pilot study (unpublished data) at the School of Optometry, The Hong Kong Polytechnic University, attempted to fit ortho-k on high myopes in Hong Kong in 2007. Significant corneal staining and lens decentation were found when the lens target was increased to 5.00D or above. This is in agreement with other published studies of the tendency towards an increased severity of corneal staining with higher target lenses (Cho et al. 2002; 2003a). Lens wear for these high myopes was terminated due to significant staining. In view of the problems with correcting high myopes with high targets using current lens designs, a more conservative approach is to partially correct high myopes by ortho-k (4.00D) and prescribe spectacles for the residual refractive errors to obtain a good visual acuity (Chan et al. 2008a).

Kakita et al. (2011) reported on a high myopic case partially corrected using ortho-k. A 12-year-old boy with initial myopia of 10.00D and 8.75D in the right and left eyes respectively, was partially corrected (target not stated). The increase in AL, at the end of 2-year lens wear, was 0.13mm and 0.27mm respectively in the right and left eyes. The axial length changes in this case were much smaller than those in their overall ortho-k group (0.39±0.27mm) in their study.

To our knowledge, there is no published study on the efficacy of partial reduction ortho-k for myopic control in children. Further clinical investigation is necessary to determine whether partial reduction ortho-k can indeed retard myopic progression.

1.11 Summary

The prevalence of myopia is increasing, especially in Asian countries. Modern ortho-k has been shown to be effective in correcting myopia in children with low to moderate myopia. Although most of studies demonstrated a certain degree of corneal complications using ortho-k,

most of these complications did not result in any significant impact on vision. In order to minimize adverse events in ortho-k, a thorough eye examination and follow up with proper patient instructions is essential. Ortho-k has also been shown to have the potential for myopic control in low and moderate myopes. For children with higher myopia, it may not be possible to achieve full reduction and clinicians and researchers are cautious about safety associated with the use of high targets (above 4.00D). Special lens designs may have to be developed to fully correct high myopes. In the meantime, partial reduction ortho-k for high myopes can be a relatively more conservative and safer treatment for high myopic children.

Chapter 2. Aim and methodology

2.1 Introduction

As discussed in the previous chapter, the prevalence of myopia is increasing, particularly in Asian countries (Section 1.1.1). A few published reports have shown the potential of modern ortho-k for myopic reduction and control in low and moderate myopes. However, clinicians are cautious with the use of full targets for myopic reduction in high myopes due to increased corneal staining and lens fitting problems (Section 1.10). Some investigators have reported successful cases of myopic control in high myopic children who were only partially corrected with ortho-k and who wore spectacles in the day time to correct their residual refractive errors. Partial reduction for high myopes with ortho-k is therefore a relatively more conservative and safer treatment for high myopic children. However, to date, there is no study assessing the effectiveness of partial reduction ortho-k for correcting high myopes.

This chapter presents the methodologies and criteria in conducting myopic control study on high myopes using partial reduction overnight ortho-k.

2.2 Aim

The aim of this study was to determine the effectiveness of partial reduction ortho-k with day time spectacles in slowing myopic progression in high myopic children over a 2-year period.

2.3 Method

2.3.1 Recruitment

Subjects were recruited via advertisements posted in local newspapers, and leaflets in the Optometry Clinic of the School of Optometry, The Hong Kong Polytechnic University. Eligible subjects and guardians were informed verbally and in writing about the nature, benefits and risks of the study. Ethics approval for this study was obtained from the Departmental Research Committee of the School of Optometry at The Hong Kong Polytechnic University

(Appendices 1 to 3). All procedures were performed under the tenets of the Declaration of Helsinki, as revised in 2002 and written informed consent was obtained before commencing the study.

This study was registered in clinical trial at www.clinicaltrial.gov with the identifier NCT00977236.

2.3.2 Inclusion criteria

Table 2.1 lists the inclusion criteria for this study. Only children aged 8 to 11 years, with spherical equivalent refraction (negative) of more than 5.50D and astigmatism (negative cylinder) not more than 1.50D, were recruited. Eligible subjects were randomly assigned to control (spectacle-wearing) and partial reduction ortho-k groups at the baseline visit, and those assigned to the partial reduction ortho-k group had their refractive errors partially reduced using ortho-k lenses and had to agree to wear spectacles to correct residual refractive errors in the daytime. Those who refused to comply with the grouping were excluded.

Table 2.1 Inclusion Criteria

Age	8 to 11 years of age on the date of recruitment
Refractive errors Spherical equivalent refraction (-ve, D) Astigmatism (-ve cylinder)	(Noncycloplegic manifest ocular refraction either eye) SER>5.50D ≤ 1.50D for axis 180±30
Visual acuity	Monocular Snellen 6/7.5 or better
Ocular health	No binocular vision problems No ocular conditions which might affect vision or vision development (for example, cataract and ptosis) No contraindications for overnight orthokeratology lens wear
General health	No systemic conditions which might affect vision or development of the refractive errors
Others	No previous experience in myopic treatment (e.g. refractive surgery, progressive add lens wear) Willing to wear orthokeratology lenses in accordance with instructions if assigned to partial reduction orthokeratology group Available for the monthly follow up at the PolyU Optometry Clinic for 12 months after treatment commences Willing to comply with the prescribed aftercare/data collection visits

2.3.3 Sample size

To estimate the sample size of this study, we aimed for 80% power based on the SD from the study of Cho et al. (2005a) and to detect a 0.3mm (about 0.75D) difference in axial length between the two groups. With the significant level of 0.05 (2-tailed), the sample size

should not be less than 14 in each group..To allow for 30% dropouts, at least 40 subjects should be recruited.

2.3.4 Lenses and solutions used

Partial reduction ortho-k subjects were fitted with ortho-k lenses (DreamLite, Procornea Ltd, The Netherlands) of target 4.00D. DreamLite (Procornea Ltd, The Netherlands) lens parameters were determined using the computer software (EyeLite, Procornea Ltd, The Netherlands) provided by the manufacturer. The software utilizes sagittal height data imported from corneal topography, and the spectacle prescription to calculate the parameters of the lens required. BOZR is determined based on the Jessen factor philosophy (Jessen factor of 0.75) (ie. the BOZR ordered is 0.75D flatter than the attempted target). Lens parameters can be modified as necessary to improve fit using the software. The study lens design is 4-zone (back optic zone curve, fitting curve, alignment curve and peripheral curve) reverse geometry. The lens parameters

generated can be spherical or toric (toric RC and/or AC), depending on corneal parameters according to their software.

In this study, a lens diameter of 10.5mm was selected. Spherical trial lenses were also made available from an inventory set provided by the manufacturer. Back surface toric design lenses had to be ordered and shipped from the Netherlands. Stabilization of treatment was confirmed when changes in myopia and corneal curvatures at two consecutive visits (within one week) were not more than 0.50D. A second pair of lenses would be ordered after confirmation as a spare pair in case of damage or loss, or as an annual replacement pair where appropriate. The lens specifications are shown in Table 2.2. All lenses were made of Boston XO material. All subjects had to learn how to insert and remove their lenses using their fingers and without any assistance from their parents. No suction holder (lens remover) was prescribed.

Table 2.2 Specifications of DreamLite lens

Manufacturer	Procornea Ltd, Netherlands
Material	Boston XO
Design	4-zone (BOZR, RC, AC and PC) spherical or toric (toric RC and/or AC), depending on corneal parameters
Jessen factor	0.75
Oxygen permeability (Barrer)	100
Back optic zone radius (mm)	7.20 to 9.50 (0.05 each step)
Optic zone diameter (mm)	6.0
Total diameter	10.50
Lens central thickness (mm)	0.22
Wearing modality	Overnight
Replacement period	1 year
Remarks	Manufacturer's recommendation for this lens design is for target up to 4.50D myopia only

Partial reduction ortho-k subjects used Menicon O2 Care, MeniCare Plus (MPS), Menicon Progent (Menicon Co. Ltd, Japan) for daily cleaning, soaking and disinfecting, and weekly enzymatic cleaning respectively. Complimentary Menicon O2 Care (not available commercially in Hong Kong) was provided to the subjects to encourage them to use this daily cleaner for cleaning the lenses. All solutions and lens cases were replaced monthly. Ortho-k lenses were replaced yearly.

Procedures for cleaning the lenses and lens cases are shown in Appendices 4 and 5 respectively. Procedures for removing bound lenses are shown in Appendix 6.

2.3.5 Spectacles

For control subjects, single vision spectacles were prescribed with maximum plus which gave maximum visual acuity, and subjects were asked to wear the spectacles in the daytime during waking hours.

For partial reduction ortho-k subjects, residual refractive errors were corrected by a pair of single vision spectacles to be worn during daytime.

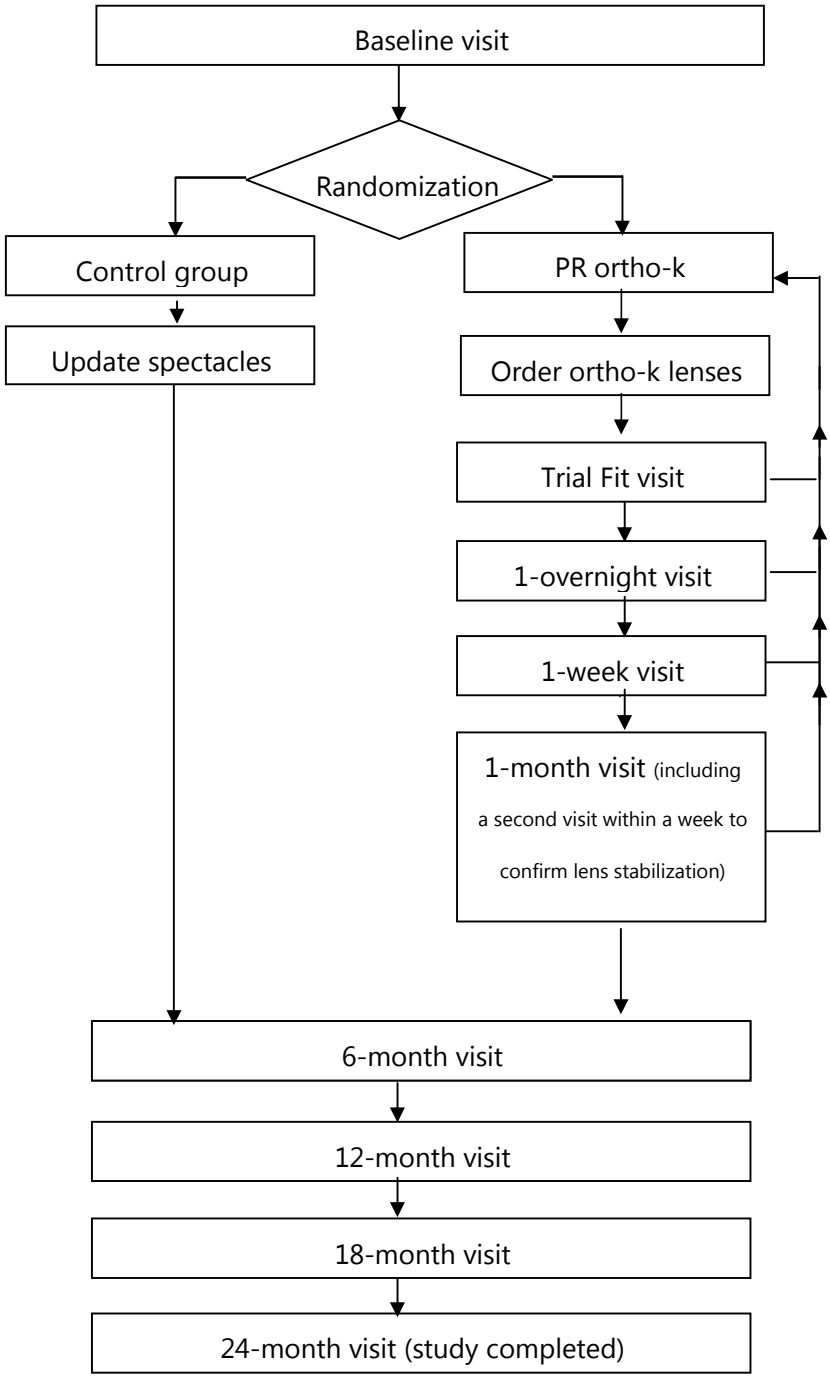
After the commencement of the study, the spectacle prescription would be updated at any subsequent visit for either group of subjects if a difference in residual refractive error (sphere or astigmatism) obtained at that visit exceeded 0.50D compared to the

stabilized refractive errors (i.e residual refractive errors after stabilization of treatment).

2.3.6 Examination schedules and procedures

All subjects who enrolled in this study were required to attend non-cycloplegic and cycloplegic examinations at baseline and every six months over two years. Partial reduction ortho-k subjects had to attend three extra visits (first morning after lens wear (1-overnight), one week (1-week) and one month (1-month)) after lens delivery to assess/confirm lens performance (Figure 2.1). Extra aftercare consultations would be provided as required during the study period (eg. in case of adverse events such as significant lens binding leading to corneal staining).

All measurements, excluding axial length measurements, were performed by the same examiner throughout the study. Axial length measurements were taken by a masked examiner.



PR ortho-k: partial reduction orthokeratology

Figure 2.1 Schedule of visits

2.3.6.1 Masking

This study was a single-mask design to eliminate any examiner bias on myopic progression. The masked examiner (not involved in this study) only measured and recorded the axial length.

2.3.6.2 Ophthalmic examination

Two types of examination were conducted during the study period: non-cycloplegic and cycloplegic examinations. Cycloplegic assessments included objective and subjective refraction, axial length measurement and fundus examination. These assessments were made at baseline and at every 6-month visit, and after the non-cycloplegic examination at the same visit (Table 2.3). One drop of 0.5% Proparacaine (Alcaine, Alcon-Couvreur, Puurs, Belgium) was first instilled, followed, one minute later, by one drop of 1.0% Tropicamide (Mydriacyl, Alcon-Couvreur, Puurs, Belgium), and, five minutes later, one drop of 1.0% Cyclopentolate (Cyclogy, Alcon-Couvreur, Puurs, Belgium) (Kleinstein et al. 1999). After 30 minutes, when no pupillary response was confirmed, and the

amplitude of accommodation was measured to be less than 2.00D, cycloplegic measurements were commenced.

Table 2.3 Data collection schedule

Data taking visits		Baseline	1-month visit	Every 6 months
Refraction	Pre-cycloplegic	X	X	X
(Subjective and objective)	Cycloplegic	X		X
Best corrected visual acuity	High contrast	X	X	X
	Low contrast	X	X	X
Photo-biomicroscopy	Ocular health	X	X	X
	Lens assessment		X	X
Topography	Pre-fitting	X		
	Post-fitting		X	X
Corneal thickness	Pre-cycloplegic	X		X
Pupillary response		X		X
Axial length	Post-cycloplegic	X		X

2.3.6.3 Objective refraction

The Shin-Nippon Open field 5500K autorefractor (Ajinomoto trading Inc., Japan) was used to measure distance objective refraction at all visits. Three average readings, each from a set of three measurements of difference within 0.25D in sphere and cylinder, were recorded for analysis.

2.3.6.4 Subjective refraction

Subjective refraction was measured in an examination room with lighting of 400 lux. The same room was used throughout the study. The maximum plus maximum visual acuity was taken as the end point of refraction.

2.3.6.5 Visual acuity

The Early Treatment Diabetic Retinopathy Study (ETDRS) charts series 2000 (Precision Vision, IL, US) were used to measure the high (>90%) and low (10%) contrast visual acuity. Three high contrast and one low contrast charts were used. Both habitual visual acuity and BCVA were measured, with the high contrast chart first, followed by the low contrast chart.

The subject was first asked to read the middle letter of the line with the largest letters and to continue down the chart to the smallest letter that could be read correctly. When the subject reached the line where the subject could not read the middle letter, the subject was asked to go back and read the letters on the previous line. If

the subject correctly read all the letters in this line, the subject was encouraged to attempt the next line down. If the subject read any of the letters incorrectly, s/he was asked to go back and attempt reading these letters again and the VA was then noted. Each correctly read letter in this line was scored 0.02 and subtracted from the logMAR visual acuity of the previous line. The visual acuity for the right eye was always assessed first, then the left eye, and finally both eyes together.

2.3.6.6 Slit-lamp examination

A Topcon TRC-NW6S with Topcon IMAGEnet (Topcon Corporation, Japan) was used to examine the anterior segment of the eyes of all subjects and to evaluate the lens fitting for subjects in the partial reduction ortho-k group. Photodocumentation was made for all corneal signs which were graded using the Efron grading scale (Efron 1998) where appropriate.

2.3.6.7 Axial length

Axial length was performed with the Zeiss IOLMaster (Carl Zeiss Meditec, Inc., USA) by masked examiners after cycloplegia at baseline and at every 6-month visit. Five axial length measurements, seeking a between-measurement difference not more than 0.02mm (Carkeet et al. 2004; Chan et al. 2006), were recorded and averaged for analysis.

2.3.6.8 Corneal topography

Corneal topography was performed using the Medmont E300 (Medmont International Pty Ltd, Australia) at baseline and at every 6-month visit for all subjects. At each visit, for each eye, four corneal profiles, each of a score not less than 98 (as recommended by the manufacturer), were saved for evaluation and monitoring purposes. This procedure was also performed on partial reduction ortho-k subjects at the 1-overnight, 1-week, and 1-month visits.

2.4 Treatment of data

Since this was a pilot study with a small sample size, non-parametric tests were used to analyze the results except for corneal thickness, axial length, flat K and steep K which were normally distributed. The significance level was set at 0.05, with a Bonferroni correction where multiple tests were performed. Only the data from the right eyes are presented. Medians and ranges were reported for data showing non-Gaussian distributions (age, pre-cycloplegic subjective myopia, post-cycloplegic subjective myopia and visual acuity) and mean±SD for data which were normally distributed (axial length, corneal thickness, flat K and steep K).

Chapter 3. Preliminary Results and Clinical Performance of Lenses

3.1 Introduction

The safety and effectiveness of overnight ortho-k in reducing and controlling myopia is well documented (Sections 1.4 and 1.7) in low to moderate myopia and astigmatism. For children with higher myopia, full reduction may not be possible and clinicians and researchers are cautious about the risks associated with the use of high targets (above 4.00D myopia). Currently, a special lens design for high myopes is not commercially-available and partial reduction ortho-k is a relatively more conservative and safer treatment for highly myopic children.

In this study, the lenses used for correcting low myopes (≤4.00D) are used to correct highly myopic children using a target of up to 4.00D. The children were required to wear spectacles to correct any residual refractive errors in the day time.

This chapter reports the preliminary results and clinical performance of the lenses used for partially correcting highly myopic children.

3.2 Results

A total of 79 subjects were screened and 52 eligible subjects were randomly assigned into the partial reduction ortho-k (n=26) and control (n=26) groups (Figure 3.1).

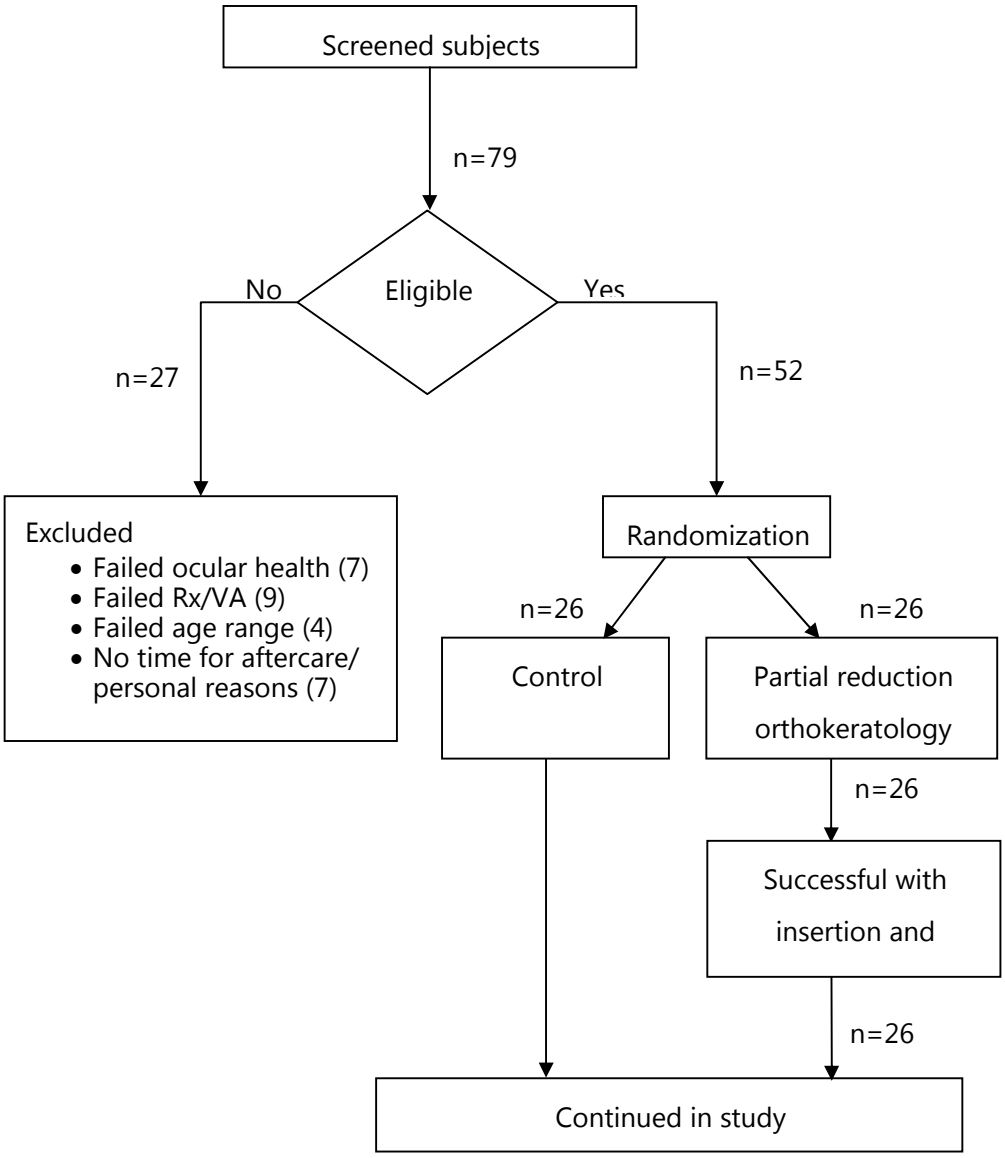


Figure 3.1 Flowchart showing recruitment of subjects in this study

3.2.1 Baseline data (n=26 per group)

Table 3.1 shows a summary of baseline data for the two groups of subjects.

The median (range) cycloplegic subjective myopia was 6.34D (5.00-8.00D) and 6.08D (5.00-8.00D) for the partial reduction ortho-k and control subjects respectively, and the mean±SD axial lengths were 26.02±0.57mm and 25.93±0.54mm respectively. No significant differences in age, baseline pre- and post-cycloplegic subjective myopia, high and low contrast BCVA, corneal thickness, steep and flat K were found between the two groups of subjects (Mann-Whitney tests, $0.19<p<0.83$). Ocular health were comparable between the two groups of subjects (Fisher's Exact Test, $0.669<p<1.000$). Corneal staining was found in six subjects (three in each group) but the severity of all staining was not more than Grade 1 (Efron 1998).

Table 3.1 Baseline data [median (range)] or mean±SD of subjects

	Partial reduction ortho-k (n=26)	Control (n=26)	p value
Age (years)	10 (8-11)	10 (8-11)	0.19*
High contrast BCVA (logMAR)	0.02 (–0.08-0.08)	0.04 (–0.10-0.16)	0.22*
Low (10%) contrast BCVA (logMAR)	0.25 (0.12-0.38)	0.22 (0.10-0.48)	0.83*
Pre-cycloplegic subjective Myopia (D)	6.41 (5.00-8.00)	6.22 (5.00-8.00)	0.25*
Post-cycloplegic subjective Myopia (D)	6.34 (5.00-8.00)	6.08 (5.00-8.00)	0.20*
Axial length (mm)	26.02±0.57	25.93±0.54	0.65#
Corneal thickness (μm)	573±46	573±37	0.94#
Flat K (mm)	7.78±0.17	7.87±0.16	0.23#
Steep K (mm)	7.55±0.18	7.60±0.18	0.42#

*Probability values for differences between groups using Mann-Whitney tests

#Probability values for differences between groups using Unpaired t tests

3.2.2 Lens performance in the first month (partial reduction orthokeratology group)

Of the 26 subjects, two subjects were terminated before the end of the first week of the study (see Section 3.2.3). For the remaining 24 subjects, lens performance was determined after at least one week of lens wear. Three subjects were fitted with toric lenses while the rest were fitted with sphiercal lenses. Optimum fit was achieved in 11 subjects (46%) with the first pair of lenses. Of the remaining 13 subjects, five (21%) and three (13%) subjects required two and three pairs of lenses respectively before achieving an optimum lens

fit. Five subjects (21%) did not manage to achieve a satisfactory fit even after three pairs of lenses. Only 19 subjects achieved lens stabilization and continued in the study after 1-month visit.

The median (range) in myopic reduction and residual myopia were 3.75D (2.25-5.00D) and 2.75D (1.50-5.25D) respectively at the 1-month visit. All subjects wore single vision spectacles to correct their residual refractive errors. No significant difference was found in high and low contrast BCVA among visits (ie. baseline, 1-overnight, 1-week and 1-month) (Friedman tests, High: $p=0.148$; Low: $p=0.192$). Changes in refractive components are shown in Figure 3.2.

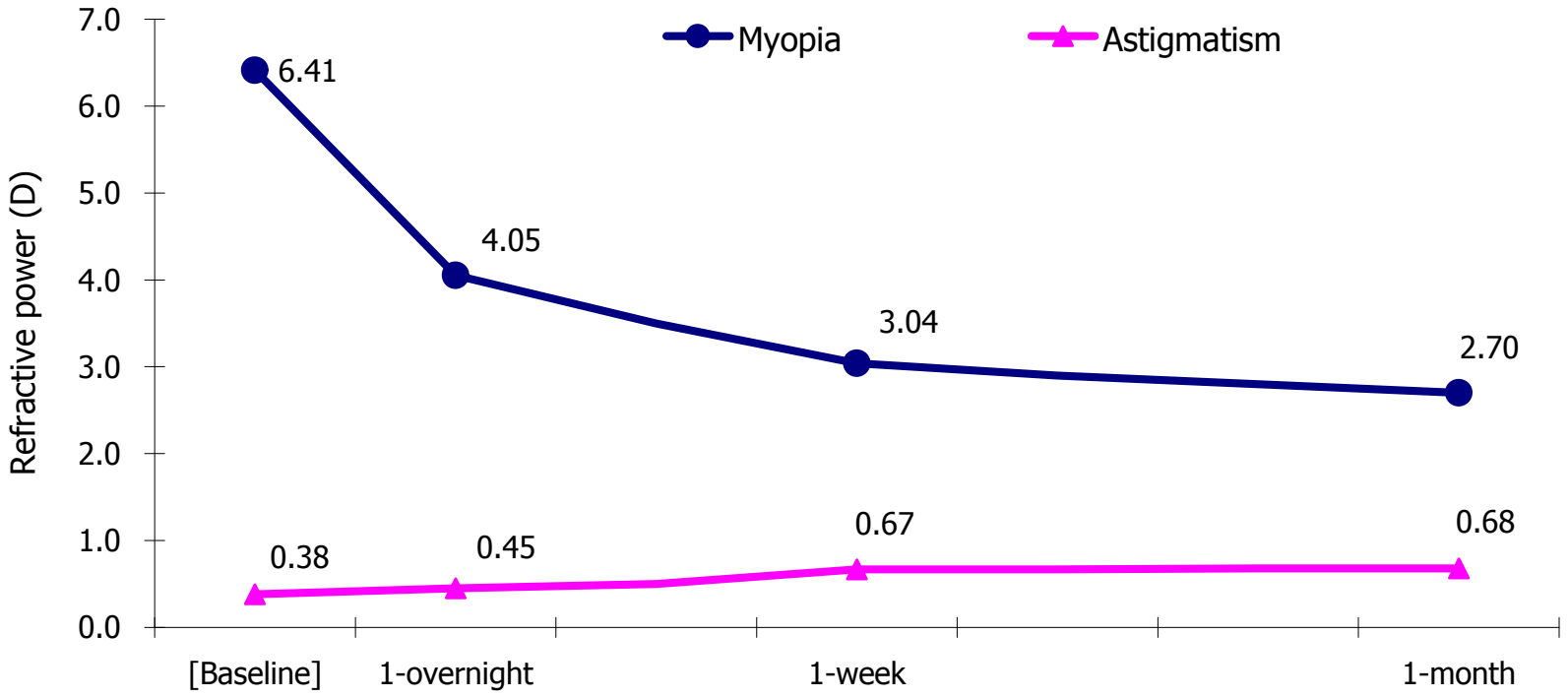


Figure 3.2 Baseline and changes in refractive components (median) during lens stabilization

No significant differences were noted in ocular health (corneal staining and lens binding) between visits in the first month after the commencement of lens wear (Chi square tests, $p>0.068$), except for the formation of a pigmented arc (Chi square test, $p=0.001$). A brownish pigmented arc (Figure 3.3) was found in PR ortho-k subjects. The incidence of a pigmented arc at the 1-month visit was 32%. Although about 30% of the partial reduction ortho-k subjects reported lens binding at the beginning of the study, they were able to loosen their lenses in a safe manner as per instructions given (Appendix 6). There were no reports of damage or loss of lenses during the first month of lens wear.

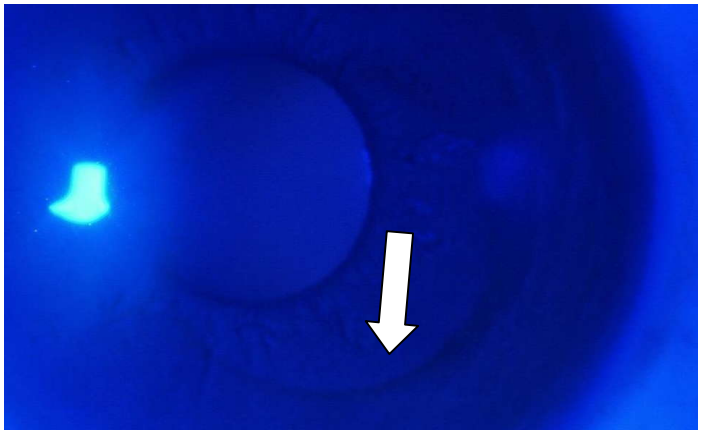


Figure 3.3 A pigmented arc

3.2.3 Dropouts within the first month

Seven subjects in the control group decided to end their participation in the study after the baseline examination, so there were 19 active subjects in the spectacle-wearing group.

One partial reduction ortho-k subject left the study after two days of lens wear due to discomfort, five left following poor lens fitting despite repeated (3) lens modifications, and another was terminated after one week of lens wear due to non-compliance with the aftercare schedule. Nineteen partial reduction ortho-k subjects continued in the study.

3.3 Discussion

The high myopia partial reduction using ortho-k (HM-PRO) study is a pilot study of myopic progression in high myopes using partial reduction ortho-k. It is a single-mask, randomized clinical trial. A double-mask study design is not possible as subjects would know whether or not they were wearing ortho-k lenses. Since the examiner would know from

the refraction and topography assessments whether or not a subject was wearing ortho-k lenses, the masked examiner was restricted in taking of axial length measurement only. In this study, the masked examiner was an independent examiner not involved in the study.

In the current study, 34% (n=27) of subjects screened were ineligible. All 27 ineligible subjects had no experience with contact lenses wear. Among them, 16 subjects were not suitable for spherical/toric ortho-k contact lens wear due to high astigmatism (>2.50D negative cyl) and poor ocular health (eg. Grade 3 corneal staining and trichiasis). Four subjects were out of the age range for this study and they sought ortho-k treatment in private practice. Five subjects were excluded because the parents were not able to comply with the required aftercare/data collection visits. Two subjects refused to join the study due to personal reasons – one was going overseas to study and the other was worried about lens handling.

For the eligible subjects, no significant differences were found in the pertinent baseline data between the control and partial reduction

ortho-k groups (Table 3.1). The first-fit success rate was about 46% (11 subjects) and five subjects (21%) were unable to achieve satisfactory fit even after three modifications. Since the lenses used in this study were actually designed for use on low myopes, the low first-fit success rate may be because these lenses were fitted on high myopic eyes. Further study is necessary to determine if this is in fact the case.

Most published ortho-k studies (Nichols et al. 2000; Potapova et al. 2004; Sorbara et al. 2005; Swarbrick 2006; Cheung et al. 2007; Chan et al. 2008a) recruited subjects with low spherical equivalent refractive errors (average myopia, 2.50D) and low astigmatism (<1.50 negative cyl).

As mentioned earlier in Section 1.10, corneal health may be compromised when higher target lenses were used. Hence, in this study, we only targeted for a 4.00D reduction for our high myopic subjects, and the median myopic reduction was about 3.75D at 1-month (Figure 3.2). The myopic reduction profile, in terms of a

percentage of reduction achieved with lens wear in this study, was similar to those reported in previous studies for low myopes (Swarbrick et al. 1998; Soni et al. 2003; Sridharan and Swarbrick 2003; Tahhan et al. 2003; Sorbara et al. 2005; Swarbrick 2006; Cheung et al. 2007; Chan et al. 2008a). About 65% of the target attempted (i.e. of 4.00D) was achieved after one night of lens wear, 90% after one week and about 99% after one month of lens wear. High and low contrasts BCVA were comparable between visits during lens stabilization in the partial reduction ortho-k subjects.

The most common ocular sign in the partial reduction ortho-k subjects was corneal staining (Table 3.2). Although the incidence of corneal staining tended to increase with duration of treatment, the severity of the staining was mild (Grade 1). Our results were in agreement with previous reports on low myopes. None of the staining episodes required any clinical intervention.

A pigmented arc was found in 32% of subjects after one month of lens wear, but there were no associated complications. The high incidence

of a pigmented arc found in this study may be because all subjects were targeted for a 4.00D reduction. Cho et al. (2003c) first reported the observation of pigmented arc in Chinese ortho-k children. They reported a pigmented arc in their subjects with high refractive errors after one week of lens wear. Cho et al. (2005b) reported that the incidence of corneal pigmented arc was 27% after three months of lens wear in their low myopic subjects. They reported that the incidence and the intensity of the arc was related to the baseline myopia, spherical equivalent refraction, the target myopia reduction, the amount of refractive myopia (and spherical equivalent refraction) reduction and changes in central corneal curvature. The formation of the pigmented arc is commonly accepted to be associated with an abrupt local discontinuity in corneal curvature which allows pooling of the tears in that area. Cho et al. (2005b) suggested the pigmented arc was formed in the mid-peripheral cornea because the area of the reverse curve of the lens coincides with the area of abrupt corneal curvature change where deep reservoirs of tears under the lens were induced. In the current study, all subjects were fitted with target 4.00D lenses. The 4.00D target lens created a deeper tear reservoir, compared to a low

target lens, at the reverse curve region, leading to substantial steepening of the midperipheral cornea, giving a more significant change in topography within a relatively shorter period of time. This may explain why an incidence of 32% was observed in the current study for pigmented arc after only one month of lens wear.

Table 3.2 Ocular signs (Efron's Grading scale) and symptoms reported during orthokeratology lens wear (n=19)

		Baseline (%)	1-overnight (%)	1-week (%)	1-month (%)	p-value*
Corneal staining (Grade 1)	Central	0	31.6	15.8	15.8	0.068
	Inferior	15.8	0	21.1	26.3	0.136
	Nasal	0	5.3	0	10.5	0.550
	Superior	0	5.3	10.5	5.3	0.282
	Temporal	0	10.5	0	0	0.104
Pigmented arc (Grade 1)	Inferior cornea	0	0	5.3	31.6	0.001#
Lens binding		0	31.6	21.1	15.8	0.073

*Probability values using Chi Square tests

#Significant differences between the two groups of subjects (Chi Square tests, p=0.001)

The combination of partial reduction ortho-k and spectacles offered stable vision for high myopic subjects. Although we did not conduct a formal survey, all children and parents indicated that they liked this mode of correction. The children appreciated the opportunity to wear thinner (weaker) lenses as well as the option of relatively clear vision even without glasses to correct their residual errors, which allowed them to enjoy outdoor activities, such as dancing, playing football and singing competitions.

The children in our study were required to handle their contact lenses on their own, including insertion, removal and cleaning, and all subjects were capable and diligent in this respect. No subjects reported lens damage or loss within the first month of lens wear.

3.4 Conclusion

This study showed that partial reduction ortho-k with spectacles for correcting residual refractive errors can be offered to high myopic children who wish to undergo ortho-k treatment for myopic control.

Chapter 4. Control of myopic progression

4.1 Introduction

The prevalence of myopia in East Asian countries, such as Hong Kong, China and Singapore is high (Section 1.1). To prevent myopia-related ocular diseases such as myopic degeneration, glaucoma and cataract, researchers have been investigating different methods to slow myopic progression in children for many years (Section 1.6). Researchers have been investigating myopic control using progressive lens/bifocals, soft contact lens and pharmaceutical agents. Results to date are not conclusive and all methods investigated have varying limitations (Section 1.6). Ortho-k has been shown to have a strong potential for myopic control (Section 1.7) although, to confirm the reported clinical results, a randomized, masked trial is needed (Section 1.11)

The majority of ortho-k lenses available commercially and used in published reports are for low to moderate myopes only (Section 1.7). For children with relatively high myopia (myopia above 4.00D), it may not be possible to achieve a full reduction even with high targets (above

4D) ortho-k lenses and clinicians and researchers are cautious about safety associated with the use of high targets. In a pilot study (unpublished data), significant corneal staining and lens decentration were observed in highly myopic children. This was in agreement with Cho et al. (2003a) that the severity of corneal staining increased when attempting to fully correct high myopes (Cho et al. 2002; 2003a). In view of these potential problems, and until lenses designed for high myopes are available, a more conservative approach for high myopes is to partially reduce myopia using a target of 4.00D and to use single vision spectacles to correct the residual refractive errors to obtain good visual acuity in the daytime (Chan et al. 2008a).

This chapter reports the control of myopic progression in high myopes using partial reduction overnight ortho-k with single vision spectacles in the daytime to correct the residual refractive errors after 2-year ortho-k treatment.

4.2 Results

4.2.1 Overview of the current study

As reported in Section 3.2, a total of 79 subjects were screened and 52 eligible subjects were randomly assigned to the partial reduction ortho-k (n=26) and control (n=26) groups at the baseline visit. After the first month of lens wear, only 19 subjects in each group continued in the study (Section 3.1).

In the control group, three subjects withdrew from the study after the 6-month visit because the parents wished to seek other myopic control methods. Hence, only 16 control subjects completed the 2-year study.

In the partial reduction ortho-k group, five subjects dropped out because of the demanding aftercare schedule (4) and asthma (1) after the 6-month visit. Grade 2 peripheral corneal staining was observed in both eyes in one subject at the 12-month visit and the parents decided to withdraw from the study. Another subject

presented with corneal opacities (Figure 4.1) in both eyes at the 18-month visit and was advised to cease lens wear and was referred to his ophthalmologist. The visual acuities and corneal curvatures of both subjects returned to baseline values within two months of ceasing lens wear (Section 4.3). Both of them were also withdrawn from the study. Hence only 12 subjects in partial reduction ortho-k group completed the study (Figure 4.2).

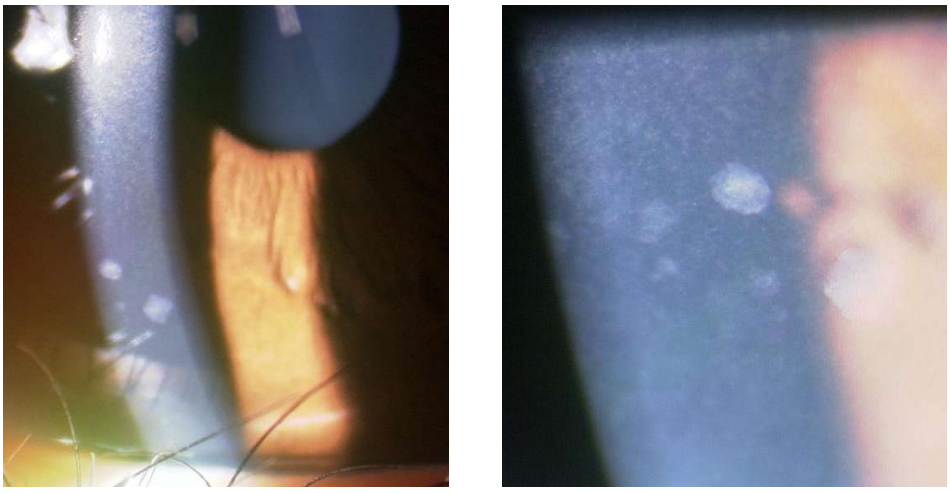


Figure 4.1 Corneal opacities (non orthokeratology related) observed in one subject after 18 months of lens wear

The baseline demographic and ocular characteristics between subjects who completed the study and subjects who did not complete the study were not significantly different (Mann-Whitney tests, $p>0.05$).

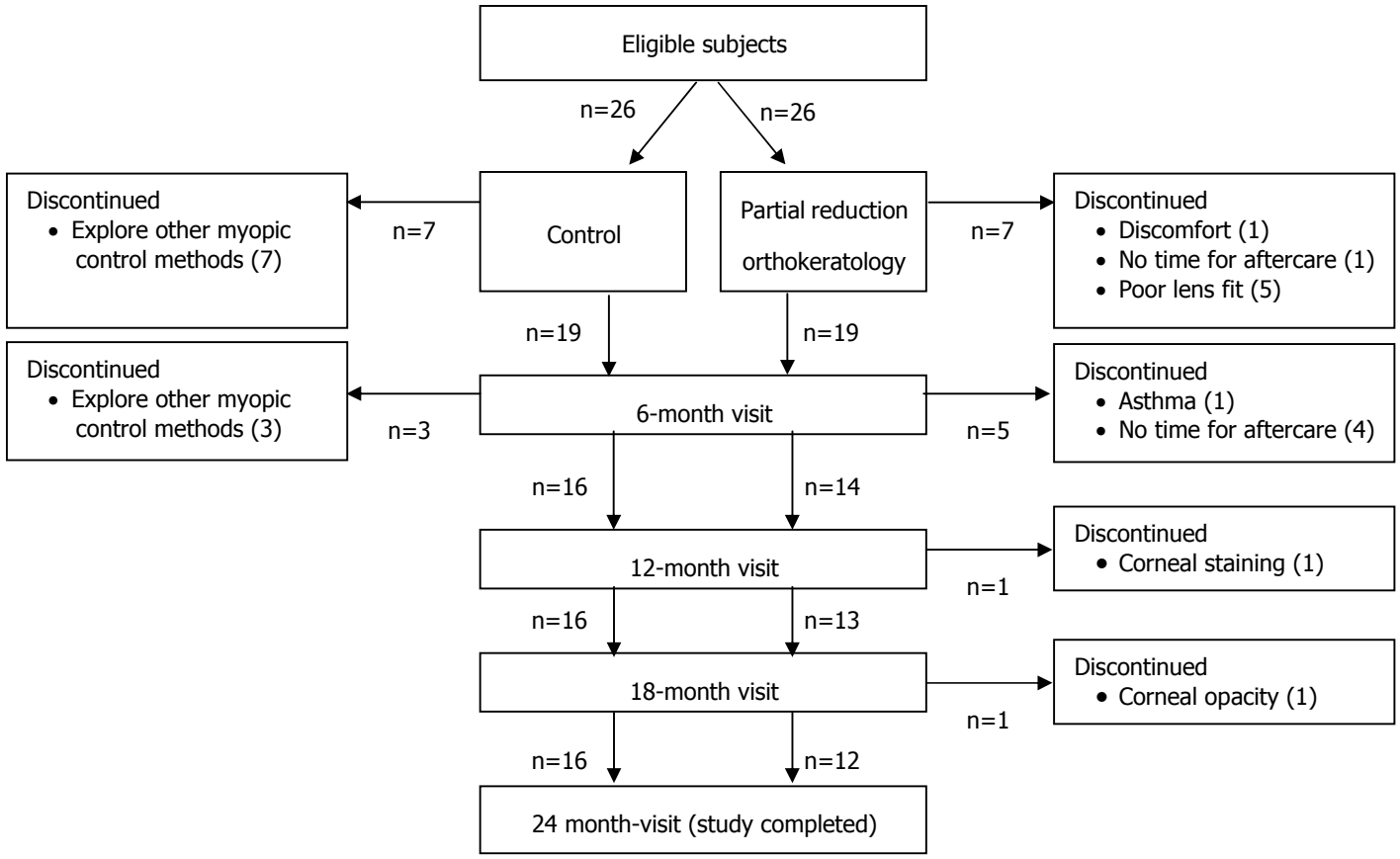


Figure 4.2 Flowchart showing the progress of the current study

4.2.2 Power of the study

Since the number of subjects completing the study was less than the estimated sample size, we performed power analysis using the results obtained and the power of HM-PRO was 85% (G*Power 3.0).

4.2.3 Baseline data (of completed cases)

Table 4.1 Baseline data [median (range)] or mean±SD of subjects who completed the study

	Partial reduction ortho-k (n=12)	**Control (n=16)**	**p value**
Age (years)	10 (9-11)	10 (8-11)	0.73 *
High contrast BCVA (logMAR)	−0.04 (−0.08-0.06)	−0.05 (−0.20-0.14)	0.22*
Low (10%) contrast BCVA (logMAR)	0.25 (0.12-0.38)	0.17 (0.10-0.48)	0.10*
Pre-cycloplegic subjective Myopia (D)	6.50 (6.00-8.30)	6.13 (5.00-8.30)	0.32*
Post-cycloplegic subjective Myopia (D)	6.38 (5.75-8.25)	6.00 (5.50-8.00)	0.36*
Post-cycloplegic subjective Astigmatism (D)	−0.63(−1.50-0.00)	−1.00 (−1.50-−1.00)	0.17*
Axial length (mm)	26.05±0.80	25.97±0.53	0.72#
Flat corneal curvature (mm)	7.78±0.30	7.84±0.13	0.49#
Steep corneal curvature (mm)	7.56±0.29	7.58±0.15	0.86#
Central corneal thickness (μm)	573±56	581±34	0.65#

BCVA: best corrected visual acuity, PR ortho-k: partial reduction orthokeratology *Probability values for differences between groups using Mann-Whitney tests

#Probability values for differences between groups using Unpaired t tests

Table 4.1 shows a summary of the baseline data of the two groups of subjects who completed the study. The median (range) age of the subjects was 10 (8-11) years and 10 (9-11) years in partial reduction ortho-k and control groups respectively. No significant differences in axial length, flat and steep corneal curvatures, and central corneal thickness were found between the two groups of subjects (unpaired t tests, $0.49<p<0.86$). Also, no significant between-group differences in age, pre-cycloplegic subjective myopia and post-cycloplegic subjective myopia and astigmatism, high and low contrast BCVA were found (Mann-Whitney tests, $0.10<p<0.73$).

Ocular health presentation was comparable between the two groups (Table 4.2) (Fisher's Exact Test, $0.583<p<1.000$). Corneal staining was found in four subjects (two in each group) but the severity was at most Grade 1.

Table 4.2 Ocular signs (incidence (%)) observed at the baseline visit (Efron's Grading scale) for subjects who completed the study

Ocular sign		Baseline	
		Partial reduction orthokeratology (n=12)	Control (n=16)
Corneal staining (Grade 1)	Central	0	0
	Inferior	16.7	12.5
	Nasal	0	6.3
	Superior	0	0
	Temporal	0	0
Papillae (grade 1)	Tarsal plate	25	16.7
Pigmented arc	Inferior	0	0

No significant differences between the two groups of subjects (Fisher's Exact Test, $0.583<p<1.000$)

4.2.4 Refractive and visual acuity changes over two years

Changes in myopia and astigmatism over the two years of monitoring are shown in Table 4.3 and Figure 4.3. In the control group, five subjects were required to change their spectacles once during the study period (two at the 6-month visit, two at the 12-month visit and one at the 18-month visit). In the partial reduction ortho-k group, no change in lens target was necessary during the study period.

Table 4.3 Changes [median (range)] in post-cycloplegic subjective myopia and astigmatism (D) in the two groups of subjects during the study period (negative value indicates increase, positive value indicates reduction)

Change in myopia	6-month	12-month	18-month	24-month
Partial reduction orthokeratology (n=12)	3.75 (3.00-5.00)	3.75 (3.00-4.75)	4.00 (2.50-4.75)	4.50 (2.75-6.25)
Control (n=16)	−0.25 (−1.25-0. 38)	−0.25 (−1.50-0.25)	−0.63 (−2.00-0.25)	−1.00 (−2.50-0.50)
p-value*	0.000	0.000	0.000	0.000

Change in astigmatism	6-month	12-month	18-month	24-month
Partial reduction orthokeratology (n=12)	−0.25 (−1.00-0.50)	−0.25 (−1.00-0.75)	−0.25 (−1.00-1.00)	−0.50 (−1.50-0.50)
Control (n=16)	0.00 (−0.50-1.00)	0.00 (−0.75-0.75)	0.00 (−0.50-0.75)	0.00 (−0.75-0.75)
p-value*	0.041	0.165	0.290	0.153

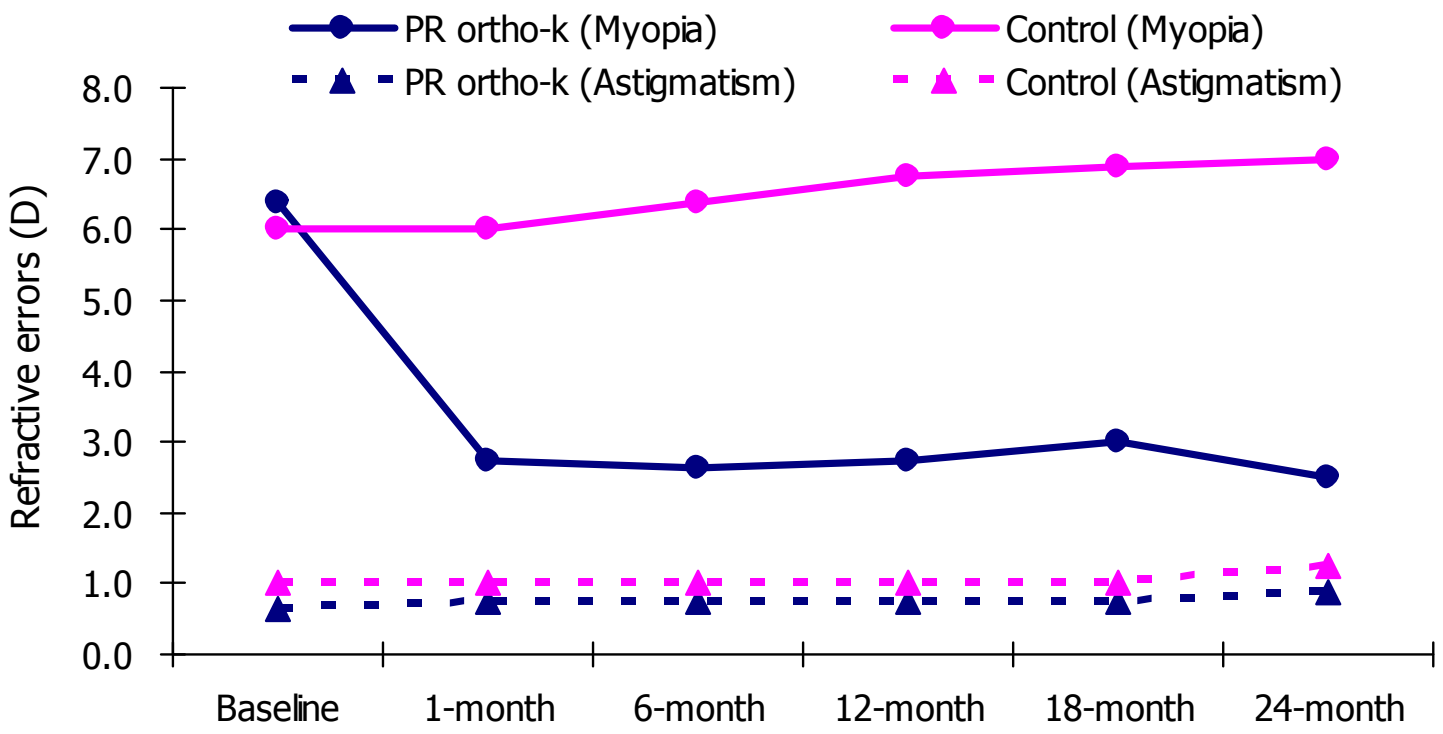
*Probability values for differences between groups using Mann-Whitney tests

For both groups of subjects, the myopia in the control group and the reduction of myopia in the partial reduction orthokeratology group significantly increased over time (Friedman tests: $p<0.001$). At the end of the study period, the median increase in myopia in the control group was −1.00D (−2.50-0.50D) and the median reduction in myopia was 4.50D (2.75-6.25D) in the partial reduction ortho-k group.

Compared to the residual refractive errors at the 1-month visit (lens stabilization), the median change in residual non-cycloplegic myopia at the 24-month visit was –0.13D (–0.75D-1.00D).

No significant increase in astigmatism in either group of subjects was observed over the two years of monitoring (Mann-Whitney tests with Bonferroni correction, $0.041<p<0.290$).

High and low contrast BCVA were not significantly different over time within-group (Friedman tests, $0.099<p<0.585$) or between groups at each visit (Mann-Whitney tests, $0.093<p<0.586$).



PR ortho-k: partial reduction orthokeratology

Figure 4.3 Changes (median) in the refractive components of the two groups of subjects during the study period

4.2.5 Ocular health

Corneal staining was observed in some subjects in both groups at each visit but the frequency was generally higher in the partial reduction ortho-k treated subjects (Table 4.4). However, all staining was not clinically significant (less than Grade 2) between the two groups of subjects during the 2-year study (Fisher's Exact Test, $0.175<p<1.000$) (Tables 4.4). No other adverse events were reported in either group of subjects who completed the study.

The incidence of a pigmented arc among the partial reduction ortho-k treated subjects at the 6-month visit was 92%. After one year of lens wear, the pigmented arc was found in all partial reduction ortho-k treated subjects. The intensity of the pigmented arc increased with lens wear during the monitoring period.

Table 4.4 Ocular signs (incidence (%)) observed in the two groups of subjects (Efron's Grading scale)

Ocular sign (Incidence)		6-month		12-month		18-month		24-month	
		PR ortho-k	control	PR ortho-k	control	PR ortho-k	control	PR ortho-k	control
Corneal staining (Grade 1)	Central	16.7	0	16.7	16.7	8.3	0	8.3	0
	Inferior	8.3	18.8	25	25	16.7	25	8.3	25
	Nasal	8.3	0	8.3	8.3	16.7	6.3	8.3	12.5
	Superior	8.3	0	0	0	0	0	8.3	18.8
	Temporal	8.3	0	0	0	0	0	8.3	6.3
Papillae (grade 1)	Tarsal plate	16.7	25	33.3	33.3	33.3	6.3	25	25
Pigmented arc	Inferior	92	0	100	0	100	0	100	0

PR ortho-k: partial reduction orthokeratology

No significant differences between the two groups of subjects (Fisher's Exact Test, $0.175<p<1.000$)

Significant differences were found in the central corneal thickness between baseline and subsequent visits for the partial reduction ortho-k group ($p=0.006$), but such differences were found in the control group ($p>0.05$).

Significant differences in the changes in central corneal thickness were found between the two groups at the 6-month, 18-month and 24-month visits (Mann-Whitney tests, $p=0.011$, 0.026 and 0.026 respectively) (Table 4.5). No significant differences were found within each group at different visits during the study period (Friedman tests: $p=0.359$ in ortho-k group and $p=0.474$ in control group).

No significant differences were found in the changes in mid-peripheral corneal thickness between the two groups of subjects at any visit (Table 4.5). However, a significant difference between 6-month and 24-month visits was noted in the partial reduction ortho-k group (Friedman tests: $p=0.000$; Wilcoxon Signed Ranks test, 6-month and 24-month, $p=0.012$). The mid-peripheral cornea was

significantly thicker at the 24-month (median: 9.6μm) visit compared to the 6-month visit (median: 2.6μm), though the difference was 7μm which was clinically insignificant.

The changes in central and mid-peripheral corneal thicknesses during the study for the partial reduction ortho-k and control groups are shown in Figure 4.4.

Table 4.5 Changes [median (range)] in corneal thickness in the two groups of subjects (negative value indicates thinning; positive value indicates thickening)

Visits	Groups	Central corneal thicknesses (μm) Median(range)	P value	Mid-peripheral corneal thicknesses (μm) Median(range)	P value
6-month	PR ortho-k	−11.7 (−27.6-12.7)	0.011*	2.6 (−15.7-20.3)	0.236
	Control	0.7 (−15.7-14.3)		0.2 (−18.3-15.7)	
12-month	PR ortho-k	−3.7 (−39.6-34.3)	0.064	7.5 (−8.7-47.3)	0.132
	Control	−1.3 (−14.0-7.3)		−0.5 (−19.0-12.0)	
18-month	PR ortho-k	−8.4 (−35.9-10.8)	0.026*	6.5 (−12.3-28.0)	0.318
	Control	2.3 (−16.3-30.0)		0.3 (−18.0-36.0)	
24-month	PR ortho-k	−4.6 (−34.6-5.3)	0.026*	9.6 (0.7-25.7)	0.099
	Control	3.5 (−13.0-28.5)		2.2 (−14.3-30.2)	

PR ortho-k: partial reduction orthokeratology

*Probability values for differences between groups using Mann-Whitney tests ($p<0.05$)

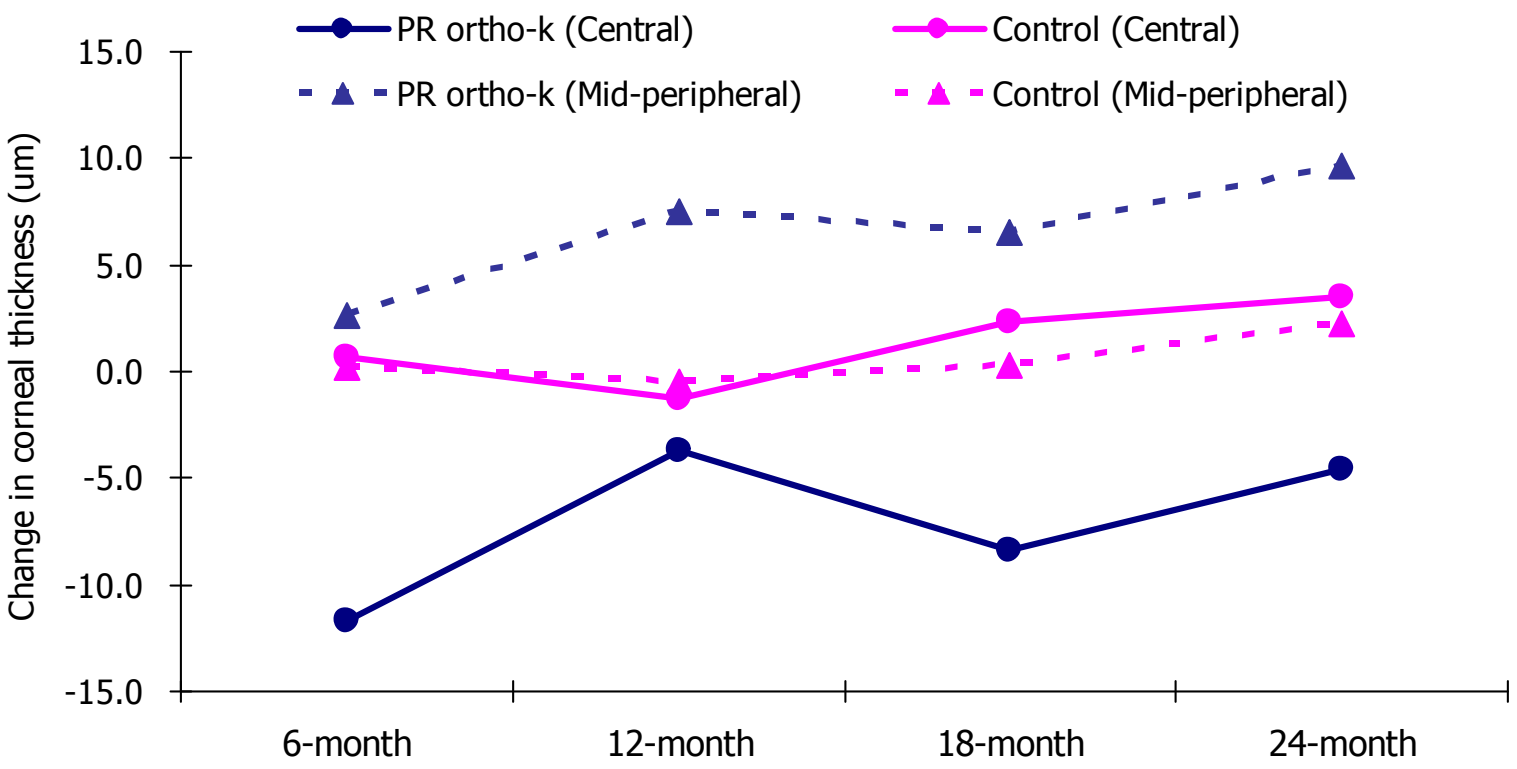


Figure 4.4 Changes (median) in corneal thickness at central and mid-peripheral in the two groups of subjects during the study period

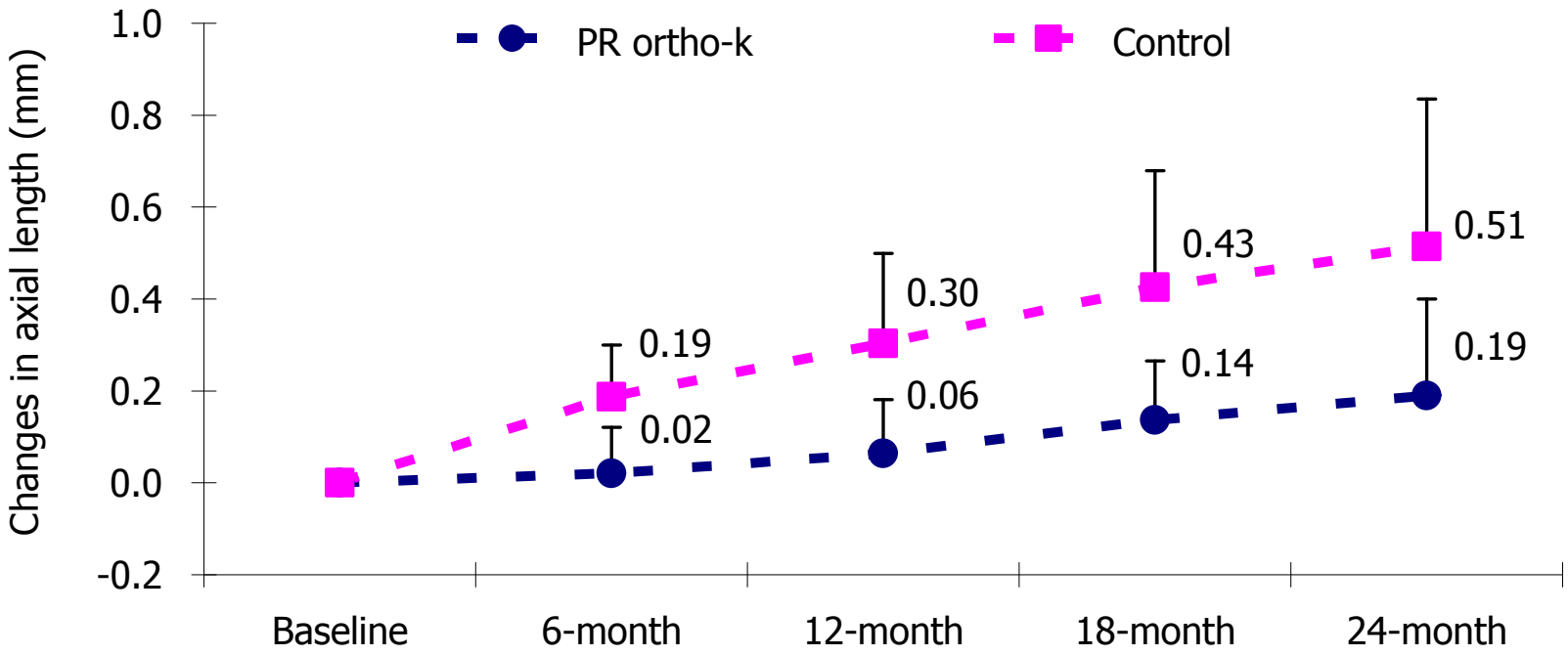
4.2.6 Len binding and lens replacements

None of the partial reduction ortho-k treated subjects reported lens binding at and after the 6-month visit. All subjects had a lens replacement at the 12-month visit except for one subject who reported lens damage at the 6-month visit. Since a pair of spare lenses was ordered for each subject after the stabilization of treatment, this subject had an extra lens replacement (no change in lens parameters) during the study period without ceasing lens wear.

4.2.7 Axial length changes

Both groups of subjects showed increases in axial length over the 2-year monitoring period but at different rates (Figure 4.5). Increases in axial length were significantly slower (by 63%) in the partial reduction ortho-k group compared to the control subjects ($p=0.005$). At the end of the 2-year monitoring period, the mean±SD increases in axial length were 0.19±0.21mm for the partial reduction ortho-k group and 0.51±0.32mm for the control group.

Figures 4.6a and 4.6b show the the relationship between the change in myopia and the change in axial length at the 24-month visit. There was a moderate relationship between two parameters in the control group (R^2=0.77, p<0.001)) but no relationship was found in the partial reduction ortho-k group (R^2=0.02, p=0.69).



PR ortho-k: partial reduction orthokeratology

Figure 4.5 Mean axial length elongations in the two groups of subjects (Error bar represents 1SD)

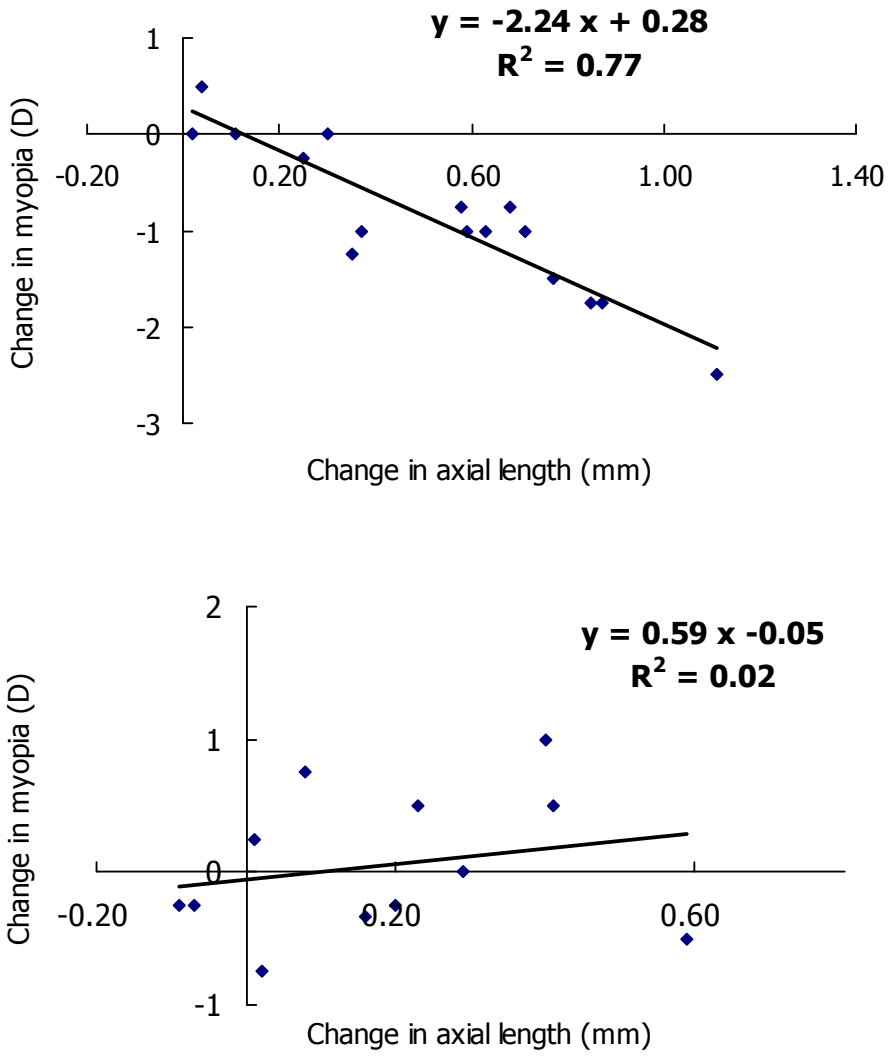


Figure 4.6 Changes in myopia against changes in axial length in (a) control group and (b) partial reduction orthokeratology group

4.3 Discussion

Compared to previous studies on low to moderate myopes (Cho et al. 2005a; Walline et al. 2009; Santodomingo-Rubido et al. 2011; Kakita et al. 2011; Cho 2012), the current study showed the highest myopic retardation rate (63%) (Figure 4.7).

Although the number of subjects in each of group was small, based on our sample sizes and axial length results, this study has a power of 85% at the 0.05% level of significance. To our knowledge, this study is the first randomized and single-blind study on the effectiveness of partial reduction ortho-k for myopic control in high myopic children. The high level of myopic control observed in this study may be due to a relatively high magnitude of myopic reduction in partial reduction ortho-k subjects. The median of myopic reduction in each of the partial reduction ortho-k treated subjects was about 4.00D throughout the study period (Figure 4.3).

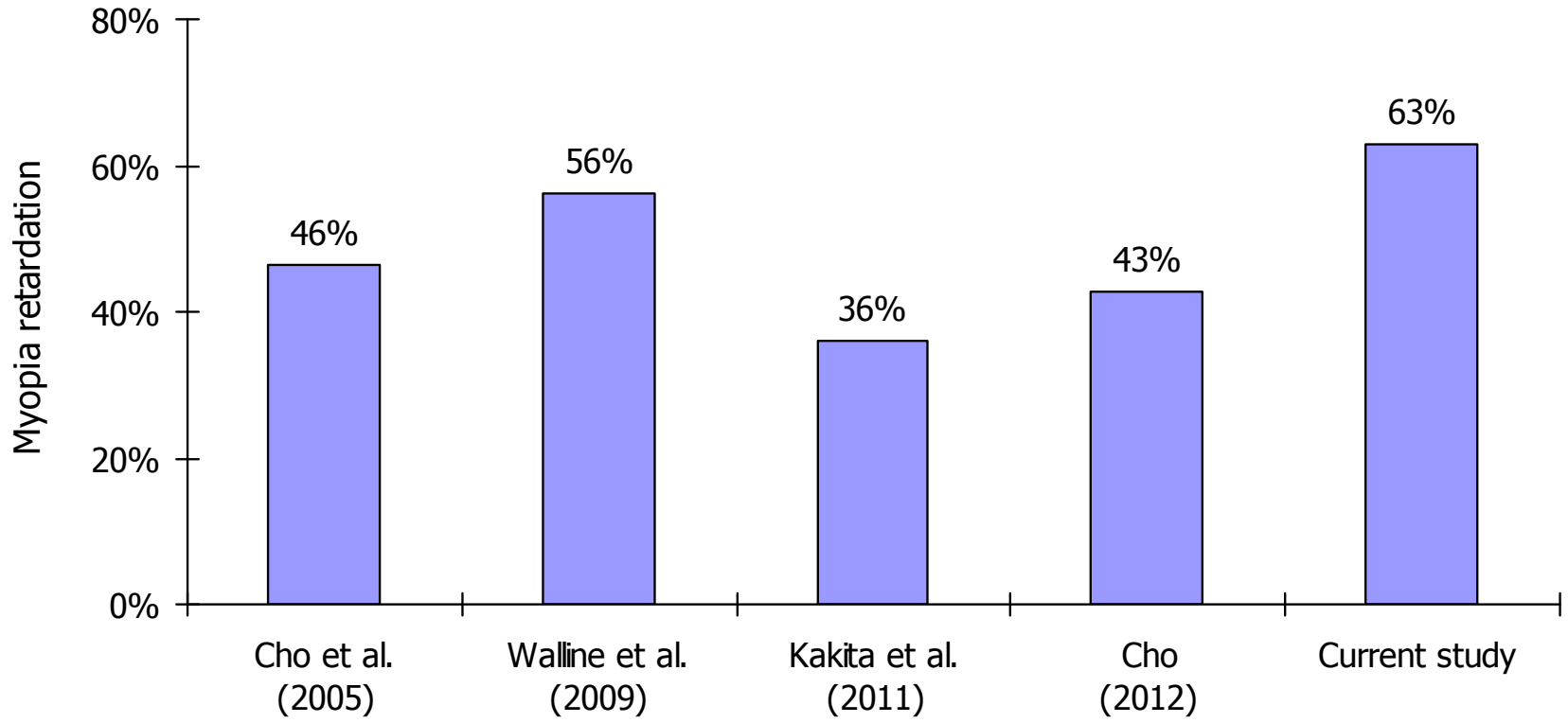


Figure 4.7 Myopic retardation in orthokeratology subjects, compared to control groups, in published myopic control studies and current study

It has been proposed that peripheral defocus in myopes may trigger axial elongation (Section 1.8). In ortho-k, there is a change in refractive status of the eye. The central cornea is flattened to reduce myopia while the mid-peripheral cornea is steepened to induce a ring of myopia. This combination may retard the visual feedback for eye elongation (Section 1.8). In the current study, all partial reduction ortho-k treated subjects wore ortho-k lenses of target 4.00D. Corneal changes in these subjects were therefore more significant compared to those using low targets, hence the increased peripheral myopia may have resulted in a better control of myopic progression. This may explain the higher level of myopic control compared to rates reported in previous studies on low to moderate myopes (Cho et al. 2005a; Walline et al. 2009). Further investigation in this area is warranted to confirm the role of peripheral refraction in myopic progression and in ortho-k.

The increase in axial length in the spectacles wearing control group over the 2-year monitoring period was relatively small compared to control subjects in previous studies on myopic control in Chinese children (Cho et al. 2005a; Walline et al. 2009; Kakita et al. 2011). This may be

because the subjects in the current study (mean age was 10 years old) were older than those in the other studies.

A moderate relationship was found between changes in myopia and changes in axial length in the control group (Figure 4.6a). This was in agreement with previous reports (Fulk et al. 2000; Gwiazda et al. 2003; Saw et al. 2005) that increases in myopia is related to increases in the axial length. However, after ortho-k lens wear, there was no such relationship (Figure 4.6b). When the corneal shape was altered, there may be other changes (eg. refractive index, crystalline lens thickness) that may affect the refractive status of the eye (Cheung and Cho 2012). Hence changes induced by ortho-k lens wear may disrupted the linear relationship between the change in axial length and the change in myopia.

In the LORIC study (Cho et al. 2005), a weak relationship was reported between baseline SER and increases in vitreous chamber depth. The more myopic ortho-k subjects showed greater slowing in the increase of vitreous chamber depth (R^2=0.30) while the more myopic

spectacle-wearing subjects showed faster progression in the increase of vitreous chamber depth (R^2=0.34) after two year of lens wear. In the current study, no relationship between the baseline SER and increases in axial length in control group (R^2=0.08) and partial reduction ortho-k (R^2=0.06) were observed. The amount of change in axial length cannot be predicted based on individual SER.

After 1-month visit, only 12 and 16 subjects in the partial reduction ortho-k and control groups, respectively, completed the study. The dropout rates were 37% and 16% in the partial reduction ortho-k and spectacles-wearing groups respectively. The dropout rate in the study group was higher than that reported in other studies (Cho et al. 2005a; Walline et al. 2009; Kakita et al. 2011). Cho et al. (2005a) reported that some form of complication (50%) was the main reason for dropouts while Walline et al. (2009) reported the loss of follow up contributed to 30% of the dropouts in the ortho-k group. Kakita et al. (2011) reported only three dropouts in their study on 45 subjects and the reason for the dropout was due to insufficient improvement in uncorrected visual acuity and loss to follow up in two subjects and one subject respectively. In

current study, the dropout was mainly due to the inability of the subjects (parents) to comply with the intensive follow-up/data collection schedule in the study group. Since a higher frequency of corneal staining was found in the partial reduction ortho-k group, a number of unscheduled visits had to be arranged for these subjects to ensure safe ortho-k lens wear, four subjects were withdrawn as they were not able to attend the follow-up visits. During the study period, two subjects in the partial reduction ortho-k group presented with undesired ocular signs and they were withdrawn before the completion of the study (Section 4.2.1). One subject had grade 2 (coverage) peripheral corneal staining at the 12-month visit. The staining was epithelial and the cornea recovered the next day. However, the parents were worried and decided to leave the study. Another subject was found to have corneal opacities in both eyes at the 18-month visit. He was referred for immediate medical consultation but his parents were too busy to take him until about two months later. His ophthalmologist confirmed that the opacities were probably due to allergy which was not ortho-k related. During the two months before he consulted the ophthalmologist, his ocular health was monitored and no changes were noted to the corneal opacities. Corneal

curvatures returned to baseline values within the two months and there were no associated complications. Although the ophthalmologist advised that the subject may resume ortho-k treatment, lens wear was discontinued for too long for the subject to be included in the study. Hence, he was withdrawn from the study.

Some studies have reported that the incidence of corneal staining tended to increase with lens wear in ortho-k for low-moderate myopes (Rah et al. 2002; Tahhan et al. 2003; Walline et al. 2004b; Mika et al. 2007), but the severity of the staining was mild (Grade 1). Our results were in agreement with these reports (Rah et al. 2002; Tahhan et al. 2003; Walline et al. 2004b; Mika et al. 2007) but only before lens stabilization. Contrary to these reports, we found no significant difference in the incidence of staining between ortho-k and control subjects in subsequent visits during the study period.

In this study, the pigmented arc was found in 32% of subjects at the 1-month visit (Chapter 3) and the incidence reached 92% and 100% after 6- and 12-month of lens wear respectively. As explained in Chapter

3, the high incidence of the pigmented arc found in this study was likely to be due to the 4.00D reduction for all subjects in the partial reduction ortho-k group.

In the current study, no significant differences were found in either high or low contrast BCVA between the two groups at any visit. Previous ortho-k studies (Swarbrick 2006; Cheung et al. 2007; Johnson et al. 2007) have reported that unaided visual acuity was significantly worse at low contrast level (Section 1.4.2). The current study did not aim to reduce the entire refractive error of subjects and all partial reduction ortho-k subjects had to wear spectacles to correct their residual refractive errors. Our results showed that both high and low contrast BCVA were stable and comparable between visits after lens stabilization in the partial reduction ortho-k treated subjects. All partial reduction ortho-k treated subjects had good vision for daily activities at different contrast levels.

Although significant differences in central corneal thickness between the two groups were obtained (Section 4.2.5), the magnitudes of these changes were less than the results from other studies (Section 1.4.3). In

the partial reduction ortho-k group, the median changes in central and mid-peripheral (4.0mm from central) corneal thickness were −4.6μm (−34.6-5.3μm) and 9.6μm (0.7-25.7μm) respectively at the 24-month visit (Figure 4.4). Similar to previous reports (Section 1.4.3), our results demonstrated central thinning and mid-peripheral thickening with ortho-k lens wear. The deviations in magnitudes between studies may be due to the use of different instruments in different studies (Swarbrick et al. 1998; Alharbi and Swarbrick 2003: Optical pachometry).

The combination of partial reduction ortho-k and spectacles offered stable vision for the high myopic subjects throughout the two years. Although we did not conduct a formal survey, all children and parents preferred to continue with this wearing mode at the end of the study. The parents appreciated the results of the study because they were not required to change the prescription of the ortho-k lenses and spectacles for two years, except for one subject who had to update his spectacle prescription at the 18-month visit (myopia increased by 0.75D). All the children in our study were required to handle the ortho-k lenses themselves, including insertion, removal and cleaning, and all subjects

were capable and diligent in these respects, although there was one report of lens damage. This subject was not required to cease lens wear as a spare pair of lenses was ordered for each subject after stabilization for such a purpose.

This study showed that partial reduction ortho-k with spectacles for correcting residual refractive errors can be offered to high myopic children who wish to undergo ortho-k treatment for myopic control. Partial reduction ortho-k was also found to retard myopic progression in high myopic children.

4.4 Conclusion

The results of this randomized, single masked study suggested that the combination of partial reduction ortho-k and spectacles is a safe and feasible option for myopic reduction and control for high myopic children. Elongation of axial length was slower by 63% over two years, when compared to subjects wearing spectacles.

Chapter 5. Conclusion

5.1 Conclusion of the study

The prevalence of myopia in Asia is high and there is a need for an effective method for controlling myopic progression. In recent years, ortho-k has been reported to have a potential for retarding myopic progression though the reports were on low to moderate myopes. There is a need for an ortho-k lens design that could be use for high myopes and until such a lens design is available, a conservative method is to partially reduce myopia in high myopes. This 2-year, single mask, randomized study aimed to evaluate clinical performance and myopic progression in high myopes.

In our study, eligible subjects were randomized into partial reduction ortho-k and control groups. The myopia of subjects in the ortho-k group was partially reduced using ortho-k lenses (DreamLite, Procornea Ltd, The Netherlands) of target 4.00D, and their residual refractive errors were corrected with spectacles. Subjects in the control group wore full correction spectacles. Cyclopedic measurements of refractive errors and

axial length were made every six months. Spectacles (both groups) were updated when the difference of refractive errors was more than 0.50D between two consecutive 6-month visits (Chapter 2). Ocular health, visual acuity and myopic progression of the subjects were monitored for two years.

The results on the right eyes were analysed in this study. There were no significant differences in age, ocular health presentation, baseline pre- and post-cycloplegic subjective myopia, high and low contrast BCVA, steep and flat K between the two groups of subjects (Chapter 3). The residual refractive errors in the partial reduction ortho-k group were stable after the first month of lens wear. Their high and low contrast BCVA were similar to their baseline data. The incidence of a pigmented arc at the 1-month visit (32%) in the partial reduction ortho-k group was high compared to ortho-k wearers in previous study (Cho et al. 2005b) but, other ocular health presentations were comparable between the two groups of subjects in the current study.

At the end of the 2-year monitoring period, 12 partial reduction ortho-k

and 16 control subjects completed the study (Chapter 4). Baseline demographic and ocular characteristics were not significantly different between the two groups of subjects who completed the study and between those who completed the study and subjects who did not complete the study (Section 4.2). During the study period, myopia/residual myopia significantly increased with time in both groups of subjects. The increase in axial length in the control group was about three times the increase in the partial reduction ortho-k group. Ocular health presentation (except the pigmented arc) and corneal thickness were comparable between the two groups. Pigmented arcs were found in all partial reduction ortho-k subjects at the 24-month visit (Chapter 4). Our results indicated that the combination of partial reduction ortho-k and spectacles can retard myopic progression in high myopes.

The drop-out rate in the current study was higher than those reported in other studies probably due to frequent unscheduled visits. However, the power of the study reached 85% even though only 12 partial reduction ortho-k and 16 control subjects completed the study. In the view of our findings, practitioners may offer this mode of correction to high myopic

children for myopic control.

5.2 Limitations of the study

As with most research studies, there are some limitations. Further studies are required to address some of these limitations.

As discussed in Section 1.6, axial length is the gold standard for monitoring progression of myopia in myopic control studies. The IOLMaster measures axial length from the anterior corneal surface to the retinal epithelium automatically along the visual axis. Since ortho-k exerts pressure on the cornea and alters the corneal shape, it may affect overall axial length. Although previous studies have shown that the anterior chamber depth did not show significant change after lens wear using A-scan (Cho et al. 2005a) and Pentacam (Tsukiyama et al. 2008), to investigate whether axial length is affected by ortho-k lens wear, axial length could be measured at the 1-month visit for both groups of subjects (one month to allow for lens stabilization in the ortho-k group), for comparison with the control group. However, in the current study,

axial length was only measured every six months. Although we did not measure axial length after lens stabilization, a recent study on myopic control on children (Cho 2012) has demonstrated no significant difference in axial length before and after stabilization of ortho-k.

Axial length has a diurnal variation (0.046±0.022mm) among young adults (Read et al. 2008). However, it is not feasible in Hong Kong to schedule all the visits in the morning because children are occupied by many school tasks and extra-curricular activities. According to Read et al. (2008), the variation of axial length was from −0.005mm to 0.01mm 10:00am to 4:00pm. Such variations, though small, may affect our results, though we assumed this would be minimal as both control and ortho-k groups were subjected to the same variations.

All partial reduction ortho-k subjects were reminded to wear the lenses every night for at least 8 hours. The subjects understood that their vision may be affected if the ortho-k lenses were not worn regularly. However, two partial reduction ortho-k subjects stopped lens wear for three and five days during the 2-year study because of corneal staining and

traveling respectively. The examiner reviewed the ocular health and refractive errors before they resumed lens wear. All subjects reported compliance with the lens wear protocol except these two cases. The period of no lens wear in these two cases was very short compared to the overall length of the study and so these two subjects were not excluded. However, such deviations may affect the findings on myopic progression in young children.

5.3 Suggestions for further investigation

Ortho-k lens wear has been shown to induce relative myopic defocus in the peripheral retina (Norton and Siegwart 1995; Smith et al. 2005; Charman et al. 2006; Mathur et al. 2009; Smith et al. 2009). The peripheral refraction in the two groups was not measured because it was beyond the scope of the study. In theory, in the partial reduction ortho-k group, the magnitude of defocus in the periphery would be reduced due to partial reduction in corneal changes. If the myopia of the subjects were fully reduced, the corneal shape may show larger changes, hence creating a greater magnitude of defocus in the peripheral retina. A follow

up study could be conducted to investigate peripheral refraction in partial and full correction ortho-k. Post-cycloplegic peripheral refraction can be measured using an open field auto-refractor such as Shin-Nippon Nvision-K5001 with fabricated external fixation targets at different eccentricities from on the optical center of the instrument.

On the other hand, if a new ortho-k lens design for high myopes is available, full correction using ortho-k is recommended because subjects will find it even more convenient if they do not have to wear spectacles in day time.

To aid subject recruitment, multiple advertisements may be necessary. In the current study, due to budget and time constraints, we only advertised once for subject recruitment.

Although run-in period and other incentives may be considered in future studies to minimise dropouts, they may not work as most of the subjects dropped out either because of adverse events (ortho-k group) or were seeking myopic control treatment for their children (control group).

For data collection, it might be a good idea to include a one month data collection for both groups of subjects and to compare subsequent changes in ocular parameters with the one month results rather than the baseline since ortho-k treatment needs about one month to stabilize.

Appendix 1. Information Sheet

Research Study Information Sheet

Title of Project:

Efficacy of overnight orthokeratology on high myopic children

(Alternate title: High Myopia – Partial Reduction Orthokeratology (HM-PRO))

Project Leader:

Dr Pauline Cho, SO (Tel: 2766 6100)

Project member:

Miss Jessie Charm, SO (Tel: 3400 3446)

Why is the study being performed?

This study aims at investigating the efficacy of overnight orthokeratology on high myopic children.

What do parents and volunteers for the study have to do?

1. If you would like to volunteer your child for the study, and your child is willing, you will be asked to sign an informed consent form on behalf of your child that you understand the information presented on this sheet.
2. Your child will be randomly assigned to spectacle group or orthokeratology group.
3. You or your representative will be required to come with your child to the Optometry Clinic at The Hong Kong Polytechnic University for a delivery visit, and every six months after the delivery visit for a period of two years.
4. Refraction, vision, noncontact tonometry, corneal topography, aberrometry, corneal health and axial length measurement will be performed at the delivery visit and six, 12, 18 and 24 months after commencement of the study. Topical

anesthetics, mydriatic and cycloplegic drugs will be applied to the eyes to assist the measurement of refraction and corneal health. The examination at each of these visits will take 3-4 hours.

5. If your child is assigned to wear orthokeratology lenses, in addition to the biannual visits, s/he will be required to come back regularly, accompanied by you or your representative, for the orthokeratology after-care visits:
   - Your child will be required to come in early in the morning (within two hours after awakening) for the orthokeratology after-care visits in which refraction, vision, corneal topography and corneal health will be assessed. Afternoon after-care visits may be arranged to check the regression of refraction.
   - Unless otherwise instructed, your child will wear the lenses every night, following the instruction given by the research personnel and use the solutions suggested in this study. You / your child will be required to fill in the ortho-k lens wear checklist everyday.
   - Your child will bring the used contact lens solutions and the checklist, which will be checked at each visit.
   - The orthokeratology after-care visits last for about 60-90 minutes.
6. If your child is assigned to the orthokeratology treatment group, you will be required to pay a cheque deposit of HK$5000 which will not be cashed as long as you remain in the study. You will be required to write a new cheque every six months. The last cheque will be returned to you upon receipt of the returned lenses on completion of or on withdrawal from this study.
7. You can keep the orthokeratology lenses after the completion of the study if you and your child wish to continue orthokeratology treatment, provided you agree to sign an agreement that your child will be followed up at our clinic as paid patients.
8. If your child is assigned to wear glasses, you are required to report to us immediately in case of lens damage.

Is there any benefit or risk if my child participates in the study?

Risk: Risks associated with overnight orthokeratology such as poor unaided vision, allergic reaction to contact lens solutions and possible corneal infection may resulted if the lenses were improperly used or stored. Complications can be minimized by careful patient selection, provision of high standard professional services (including clear oral and written instructions) to the patients.

Local anaesthetics, mydriatic and cycloplegia may produce stinging sensation and eye redness right after instillation, the effect is only transient and will not cause

any harm to the eyes. Some children may have allergic reaction to the eyedrops. Should any problem be detected, appropriate clinical action (e.g. medical referral) will be taken. Parents will be required to bear the medical expenses if referral is indicated. After-office contact number will be provided for emergency.

Benefit: Ortho-k subjects will be able to enrol in ortho-k treatment and be taken care of by an experienced optometrist. The treatment and service will be provided free of charge. S/he will be required to prescribe spectacles (frame and/or a pair of low powered spectacle lenses) as the treatment only gives partial correction, and contact lenses solutions. Regular eye examination will be provided with no charge and this includes both external and internal eye examinations.

Can a volunteer withdraw from the study?

Yes, you can stop your child from participating in the study at any time with no penalty or any prejudice to the orthokeratology treatment. The deposit will be refunded but the orthokeratology lenses, contact lens solutions and lens accessories must be returned to the research personnel.

Can I get more information on the study?

Yes, contact Dr Pauline Cho / Miss Jessie Charm and she will try to answer any questions you may have.

Confidentiality

Only members of this project are allowed to have access to the collected information. Results from the current study may be published but no personal information will be disclosed.

This study has been approved by the Departmental Research Committee of the School of Optometry of The Hong Kong Polytechnic University. If you have any complaints about the conduct of this research study, please do not hesitate to contact the Secretary of the Human Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University in person or in writing (c/o Human Resources Office of the University).

Drug Effects

The following drugs will be used in this study:

Drug name	**Alcaine 0.5%**	**Mydriacyl 1.0%**	**Cyclogyl 1.0%**
Drug effects	* Topical anesthetic – numb the corneal sensation temporarily	* Pupil dilation * Cycloplegia – paralysis of focusing muscles temporarily	* Cycloplegia – paralysis of focusing muscles temporarily * Pupil dilation
Indication	* Facilitate the measurement of the length of the eyeball	* Better examination of the retina, optic nerve and ocular blood vessels	* Help to yield more accurate assessment of the length of the eyeball, especially in far-sightedness, pseudo nearsightedness and squint
Recovery time	* 15-20 mins	* 4-6 hrs, maximum of 24 hrs	* 24 hrs
Possible side effects	* Blur vision * Mild eye pain * Swollen eyes	* Foggy vision * Eye pain	* Foggy vision, Eye pain * Incoherent speech * Hallucination * Imbalance
Cautions	* DO NOT rub eyes or put on contact lenses within 2 hours of eyedrop instillation, and avoid the windy and dusty conditions if possible.	* Blur vision at near within the first few hours of eyedrop instillation * Light sensitivity, sunglasses and a wide brimmed hat/cap may help to provide better comfort * AVOID outdoor activities in open daylight and vigorous activities which require the use of near vision within 12 hours of eyedrop instillation	

Appendix 2. Consent form

Title of Study

Efficacy of overnight orthokeratology on high myopic children

Informed Consent Form

Have you read the information sheet provided?	Yes / No
Have you had an opportunity to ask questions and discuss this study?	Yes / No
Have your received satisfactory answers to all of your questions?	Yes / No
Have you received enough information about the study?	Yes / No

Who provided the information / answered your questions

- Dr. Pauline Cho, SO, 2766 6100
- Miss Jessie Charm, SO, 3400 3446

Do you understand that participation is entirely voluntary?	Yes / No
Do you understand that your child is free to withdraw from the study	
• at any time	**Yes / No**
• without having to give a reason	**Yes / No**
• without affecting your future care	**Yes / No**
Do you agree to take part in this study	Yes / No

.....	.....
Signature of Child	**Signature of * Parent / Guardian**
.....	.....
Name of Child	**Name of * Parent / Guardian**
.....	.....
Date	**Date**

* Delete as appropriate

Appendix 3. Ethics approval letter

The Hong Kong
POLYTECHNIC UNIVERSITY
香港理工大學

MEMO

To : WONG Hie Hua, School of Optometry
From : YAP Keng Hung Maurice, Chairman, Departmental Research Committee, School of Optometry

Ethical Review of Research Project Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following research project for a period from 02/07/2008 to 01/06/2010:

Project Title : Efficacy of overnight orthokeratology on high myopic children

Department : School of Optometry

Principal Investigator : WONG Hie Hua

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the research personnel involved in the project. In the case the Co-PI has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee School of Optometry in advance of any changes in the research proposal or procedures which may affect the validity of this ethical approval.

You will receive separate notification should you be required to obtain fresh approval.

YAP Keng Hung Maurice
Chairman
Departmental Research Committee
School of Optometry

Appendix 4. Procedures for lens cleaning

Daily Care of lenses

1. After cleaning and drying the hands thoroughly, unscrew the cap of the solution bottle with the palm and little finger and leave the cap on the nozzle
2. Remove the right lens. Place the lens concave up on the left palm. Add a few drops of daily cleaner on the lens. Using the index (or middle finger), gently rub lens to and forth (lens should move with the finger) for about 10 seconds to clean the front surface of the lens. Next, curve the palm of the hand so that the lens is nestled in the centre of the palm and does not move when you rub the inner lens surface for 10 seconds to clean this surface of the lens
3. Rinse the lens with multipurpose solution (MPS) thoroughly
4. Place the lens in the right lens well and fill the well with fresh MPS (2/3 full)
5. Ensure that the lens is immersed in the solution
6. Screw the lid on tightly
7. Repeat steps 2-4 for the left lens
8. Rinse the lenses with saline before insertion at night

Weekly Care of lenses

1. Place the lenses, after cleaning with daily cleaner, in the appropriate lens holders of the Menicon Progent container
2. Pour Progent A and B into the container and screw the lid on tightly
3. Soak for about 30 minutes. Do not exceed this duration
4. Pour away the solution
5. Rinse the lens holder and lens with saline thoroughly
6. Clean the lenses following the daily cleaning procedures above
7. Rinse the Progent container and lens holder with tap water and wipe off excessive water with a clean paper towel and leave to air dry with the items facing downwards and covered with a piece of clean tissue
8. After drying, cap the container and store in a cool dry place

Lens Replacement

Lenses should be replaced annually

Appendix 5. Procedures for lens case care

Daily Care (Flat lens case)

1. After removing the lenses, pour away the used solution in the lens case
2. Add 5-6 drops of MPS to each well and gently but thoroughly brush the inside and outside (paying particular attention to the ridges and the screw top) of the lens case using a soft-bristle toothbrush
3. Thorough rinse the items with MPS/water
4. Shake off the excessive fluid
5. Wipe the case dry with a piece of clean paper towel or tissue
6. Leave the case and lids to air dry face-down on a piece of clean dry tissue to avoid settling of particles and contaminants from the air in the wells of the case
7. The brush should be rinsed thoroughly, excess water shaken off and left to air dry with the case
8. Another piece of tissue may be used to cover these items as they are left to air dry
9. Always rinse the lens case with MPS before use

- Do not cap lens case when wet.
- Accessories should be stored or left to air dry in a cool, dry place, e.g. in bedroom. The bathroom, fridge, and kitchen are not appropriate places.

Weekly Care

1. Clean the lens case as per daily routine
2. Put the case, lids, and brush in a clean container, pour in boiling water, then cover the container and allow the items to SOAK (not boil) for 10 minutes
3. Air-dry after shaking off excessive water, wipe with tissue before air-dry
4. Rinse the accessories with MPS before use

Case Replacement

Lens cases and brushes used are recommended to be replaced monthly

Appendix 6. Procedures for loosening a bound lens in the morning

Procedures to loosen a bound lens

1. Wash hands with liquid soap. Rinse thoroughly with water and dry hands with a clean paper towel
2. Instill 1-2 drops of artificial tears into the eye and blink gently. Check if the lens is on the cornea and moving on blink by looking into a mirror
3. If the lens is not moving (bound to the cornea), blink (forcefully) 5 times to try to loosen the lens. You can feel the lens moving on your cornea if it is mobile. Check by looking into a mirror that the lens is still on the cornea and if it is moving on blink
4. If the lens is still bound to the cornea, look slightly upward. Gently but firmly press the lower eyelid margin against the inferior limbus three times without touching the lens
5. Then look slightly downward. Gently but firmly press the upper eyelid margin against the superior limbus three times without touching the lens
6. Blink forcefully 5 times to try to loosen the lens
7. If the lens is still not moving, instill 1-2 drops of artificial tears and repeat 4-6 until you can see/feel the lens moving before lens removal

References

- Alharbi A and Swarbrick HA (2003). The effects of overnight orthokeratology lens wear on corneal thickness. Invest. Ophthalmol. Vis. Sci. **44** (6): 2518-23.
- Anstice NS and Phillips JR (2011). Effect of Dual-Focus Soft Contact Lens Wear on Axial Myopia Progression in Children. Ophthalmology. 118:1152-61.
- Barr JT, Rah MJ, Jackson JM and Jones LA (2003). Orthokeratology and corneal refractive therapy: a review and recent findings. Eye Contact Lens. **29** (1 Suppl): S49-53; discussion S7-9, S192-4.
- Brand RJ, Polse KA and Schwalbe JS (1983). The Berkeley Orthokeratology Study, Part I: General conduct of the study. Am J Optom Physiol Opt. **60** (3): 175-86.
- Carkeet A, Saw SM, Gazzard G, Tang W and Tan DT (2004). Repeatability of IOLMaster biometry in children. Optom Vis Sci. **81** (11): 829-34.
- Caroline PJ (2001). Contemporary orthokeratology. Cont Lens Anterior Eye. **24** (1): 41-6.

- Chan B, Cho P and Cheung SW (2006). Repeatability and agreement of two A-scan ultrasonic biometers and IOLMaster in non-orthokeratology subjects and post-orthokeratology children. Clin Exp Optom. **89** (3): 160-8.
- Chan B, Cho P and Cheung SW (2008a). Orthokeratology practice in children in a university clinic in Hong Kong. Clin Exp Optom. **91** (5): 453-60.
- Chan B, Cho P and Mountford J (2008b). The validity of the Jessen formula in overnight orthokeratology: a retrospective study. Ophthalmic Physiol Opt. **28** (3): 265-8.
- Charman WN, Mountford J, Atchison DA and Markwell EL (2006). Peripheral refraction in orthokeratology patients. Optom Vis Sci. **83** (9): 641-8.
- Cheng D, Schmid KL and Woo GC (2007). Myopia prevalence in Chinese-Canadian children in an optometric practice. Optom Vis Sci. **84** (1): 21-32.
- Cheng D, Woo GC and Schmid KL (2010). Bifocal lens control of myopic progression in children. Clin Exp Optom. **94** (1): 24-32.

- Cheung SW, Cho P and Fan D (2004). Asymmetrical increase in axial length in the two eyes of a monocular orthokeratology patient. Optom Vis Sci. **81** (9): 653-6.
- Cheung SW, Cho P, Chui WS and Woo GC (2007). Refractive error and visual acuity changes in orthokeratology patients. Optom Vis Sci. **84** (5): 410-6.
- Cheung SW and Cho P (2012). Anterior segment length in orthokeratology. Presented at the 3rd Asia Orthokeratology and Specialty Lens Conference (AOSLC), Hangzhou, China.
- Cho P, Cheung SW and Edwards MH (2002). Practice of orthokeratology by a group of contact lens practitioners in Hong Kong--Part 1. General overview. Clin Exp Optom. **85** (6): 365-71.
- Cho P, Cheung SW and Edwards MH (2003a). Practice of orthokeratology by a group of contact lens practitioners in Hong Kong. Part 2: orthokeratology lenses. Clin Exp Optom. **86** (1): 42-6.
- Cho P, Cheung SW, Edwards MH and Fung J (2003b). An assessment of consecutively presenting orthokeratology patients

in a Hong Kong based private practice. Clin Exp Optom. **86** (5): 331-8.

- Cho P, Chui WS and Cheung SW (2003c). Reversibility of corneal pigmented arc associated with orthokeratology. Optom Vis Sci. **80** (12): 791-5.
- Cho P, Cheung SW and Edwards M (2005a). The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. Curr Eye Res. **30** (1): 71-80.
- Cho P, Cheung SW, Mountford J and Chui WS (2005b). Incidence of corneal pigmented arc and factors associated with its appearance in orthokeratology. Ophthalmic Physiol Opt. **25** (6): 478-84.
- Cho P, Cheung SW, Mountford J and White P (2008). Good clinical practice in orthokeratology. Cont Lens Anterior Eye. **31** (1): 17-28.
- Cho P (2012). Orthokeratology for myopic control for myopic and astigmatic children (ROMIO & TO-SEE studies). Presented at the 3rd Asia Orthokeratology and Specialty Lens Conference (AOSLC), Hangzhou, China.

- Choo JD, Holden BA, Papas EB and Willcox MD (2009). Adhesion of Pseudomonas aeruginosa to orthokeratology and alignment lenses. Optom Vis Sci. **86** (2): 93-7.
- Chua WH, Balakrishnan V, Chan YH, Tong L, Ling Y, Quah BL and Tan D (2006). Atropine for the treatment of childhood myopia. Ophthalmology. **113** (12): 2285-91.
- Coon LJ (1982). Orthokeratology: part I historical perspective. J Am Optom Assoc. **53** (3): 187-95.
- Coon LJ (1984). Orthokeratology. Part II: Evaluating the Tabb method. J Am Optom Assoc. **55** (6): 409-18.
- Curtin BJ and Karlin DB (1970). Axial length measurements and fundus changes of the myopic eye. I. The posterior fundus. Trans Am Ophthalmol Soc. **68**: 312-34.
- Dave T and Ruston D (1998). Current trends in modern orthokeratology. Ophthalmic Physiol Opt. **18** (2): 224-33.
- Edwards MH, Li RW, Lam CS, Lew JK and Yu BS (2002). The Hong Kong progressive lens myopia control study: study design and main findings. Invest. Ophthalmol. Vis. Sci. **43** (9): 2852-8.

- Efron N (1998). Grading scales for contact lens complications. Ophthalmic Physiol Opt. **18** (2): 182-6.
- Fan DS, Lam DS, Lam RF, Lau JT, Chong KS, Cheung EY, Lai RY and Chew SJ (2004). Prevalence, incidence, and progression of myopia of school children in Hong Kong. Invest. Ophthalmol. Vis. Sci. **45** (4): 1071-5.
- Fulk GW and Cyert LA (1996). Can bifocals slow myopia progression? J Am Optom Assoc. **67** (12): 749-54.
- Fulk GW, Cyert LA, Parker DE (2000). A randomized trial of the effect of single-vision vs. bifocal lenses on myopia progression in children with esophoria. Optom Vis Sci. **77**:395–401.
- Fulk GW, Cyert LA, Parker DE and West RW (2003). The effect of changing from glasses to soft contact lenses on myopia progression in adolescents. Ophthalmic Physiol Opt. **23** (1): 71-7.
- Gonzalez Blanco F, Sanz Fernandez JC and Munoz Sanz MA (2008). Axial length, corneal radius, and age of myopia onset. Optom Vis Sci. **85** (2): 89-96.

- Goss DA (1987). Linearity of refractive change with age in childhood myopia progression. Am J Optom Physiol Opt. **64** (10): 775-80.
- Grant SG and May CH (1970). Orthokeratology - a therapeutic approach to contact lens procedures. Contacto. **14**: 3-16.
- Grossniklaus HE and Green WR (1992). Pathologic findings in pathologic myopia. Retina **12** (2): 127-33.
- Grosvenor T (1987). A review and a suggested classification system for myopia on the basis of age-related prevalence and age of onset. Am J Optom Physiol Opt. **64** (7): 545-54.
- Grosvenor T, Perrigin DM, Perrigin J and Maslovitz B (1987). Houston Myopia Control Study: a randomized clinical trial. Part II. Final report by the patient care team. Am J Optom Physiol Opt. **64** (7): 482-98.
- Grosvenor T, Perrigin D, Perrigin J and Quintero S (1991). Rigid gas-permeable contact lenses for myopia control: effects of discontinuation of lens wear. Optom Vis Sci. **68** (5): 385-9.

- Guillon M and Sammons WA Contact lens design. In: Contact lens practice. Edited by Ruben M, Guillon M. London: Chapman and Hall**:** 87-112.
- Gwiazda J, Hyman L, Hussein M, Everett D, Norton TT, Kurtz D, Leske MC, Manny R, Marsh-Tootle W, Scheiman M (2003). A randomized clinical trial of progressive addition lenses versus single vision lenses on the progression of myopia in children. Invest Ophthalmol Vis Sci. **44**:1492–1500
- Haque S, Fonn D, Simpson T and Jones L (2007). Corneal refractive therapy with different lens materials, part 1: corneal, stromal, and epithelial thickness changes. Optom Vis Sci. **84** (4): 343-8.
- Harris DH and Stoyan N (1992). A new approach to orthokeratology. Contact Lens Spect. **7** (4): 37-9.
- Hasebe S, Ohtsuki H, Nonaka T, Nakatsuka C, Miyata M, Hamasaki I and Kimura S (2008). Effect of progressive addition lenses on myopia progression in Japanese children: a prospective, randomized, double-masked, crossover trial. Invest. Ophthalmol. Vis. Sci. **49** (7): 2781-9.

- Horner DG, Soni PS, Salmon TO and Swartz TS (1999). Myopia progression in adolescent wearers of soft contact lenses and spectacles. Optom Vis Sci. **76** (7): 474-9.
- Hsiao CH, Lin HC, Chen YF, Ma DH, Yeh LK, Tan HY, Huang SC and Lin KK (2005). Infectious keratitis related to overnight orthokeratology. Cornea. **24** (7): 783-8.
- Hsiao CH, Yeung L, Ma DH, Chen YF, Lin HC, Tan HY, Huang SC and Lin KK (2007). Pediatric microbial keratitis in Taiwanese children: a review of hospital cases. Arch Ophthalmol. **125** (5): 603-9.
- Hussin HM, Spry PG, Majid MA and Gouws P (2006). Reliability and validity of the partial coherence interferometry for measurement of ocular axial length in children. Eye. **20** (9): 1021-4.
- Jensen H (1991). Myopia progression in young school children. A prospective study of myopia progression and the effect of a trial with bifocal lenses and beta blocker eye drops. Acta Ophthalmol. (200): 1-79.
- Jesson GN (1962). Orthofocus technique. Contacto. **6**: 200-4.

- Johnson KL, Carney LG, Mountford JA, Collins MJ, Cluff S and Collins PK (2007). Visual performance after overnight orthokeratology. Cont Lens Anterior Eye. **30** (1): 29-36.
- Joslin CE, Wu SM, McMahon TT and Shahidi M (2003). Higher-order wavefront aberrations in corneal refractive therapy. Optom Vis Sci. **80** (12): 805-11.
- Kakita T, Hiraoka T and Oshika T (2011). Influence of overnight orthokeratology on axial length elongation in childhood myopia. Invest. Ophthalmol. Vis. Sci. **52** (5): 2170-4.
- Kang P and Swarbrick H (2011). Peripheral refraction in myopic children wearing orthokeratology and gas-permeable lenses. Optom Vis Sci. **88** (4): 476-82.
- Kleinstein RN, Mutti DO, Manny RE, Shin JA, Zadnik K (1999). Cycloplegia in African-American children. Optom Vis Sci. **76** (2):102-7.
- Lam CS and Goh WS (1991). The incidence of refractive errors among school children in Hong Kong and its relationship with the optical components. Clin. Exp. Optom. **74**: 97-103.

- Lam CS, Edwards M, Millodot M and Goh WS (1999). A 2-year longitudinal study of myopia progression and optical component changes among Hong Kong schoolchildren. Optom Vis Sci. **76** (6): 370-80.
- Lam DS, Houang E, Fan DS, Lyon D, Seal D and Wong E (2002). Incidence and risk factors for microbial keratitis in Hong Kong: comparison with Europe and North America. Eye . **16** (5): 608-18.
- Lam DS, Fan DS, Chan WM, Tam BS, Kwok AK, Leung AT and Parsons H (2005). Prevalence and characteristics of peripheral retinal degeneration in Chinese adults with high myopia: a cross-sectional prevalence survey. Optom Vis Sci. **82** (4) : 235-8.
- Leung JT and Brown B (1999). Progression of myopia in Hong Kong Chinese schoolchildren is slowed by wearing progressive lenses. Optom Vis Sci. **76** (6): 346-54.
- Lipson MJ, Sugar A and Musch DC (2005). Overnight corneal reshaping versus soft disposable contact lenses: vision-related quality-of-life differences from a randomized clinical trial. Optom Vis Sci. **82** (10): 886-91.

- Lum E and Swarbrick HA (2011). Lens Dk/t influences the clinical response in overnight orthokeratology. Optom Vis Sci. **88** (4): 469-75.
- Mathur A and Atchison DA (2009). Effect of orthokeratology on peripheral aberrations of the eye. Optom Vis Sci. **86** (5): E476-84.
- Mathur A, Atchison DA and Charman WN (2009). Effect of accommodation on peripheral ocular aberrations. Journal of vision. **9** (12): 20 1-11.
- McMonnies CW and Boneham GC (1997). Corneal topography validity and reliability for orthokeratology fitting. Clin Exp Optom. **80**: 69-73.
- Mika R, Morgan B, Cron M, Lotoczky J and Pole J (2007). Safety and efficacy of overnight orthokeratology in myopic children. Optometry. **78** (5): 225-31.
- Mitchell P, Hourihan F, Sandbach J and Wang JJ (1999). The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology. **106** (10): 2010-5.

- Mok KH and Chung ST (2011). Seven-year retrospective analysis of the myopic control, effect of orthokeratology in children: a pilot study. Clinical Optometry 2011:(3), 1-4. **3**: 1-4.
- Mountford J (1997). An analysis of the changes in corneal shape and refractive error induced by accelerated orthokeratology. Int Contact Lens Clin. **24**: 128-43.
- Mountford J, Ruston D and Dave T (2004). Orthokeratology: principles and practice. London: Philadelphia, Butterworth Heinemann.
- Mountford J, Cho P and Chui WS (2005). Is fluorescein pattern analysis a valid method of assessing the accuracy of reverse geometry lenses for orthokeratology? Clin Exp Optom. **88** (1): 33-8.
- Mountford JA (1998). Retention and regression of orthokeratology with time. Int Contact Lens Clin. **25**: 1-6.
- Nichols JJ, Marsich MM, Nguyen M, Barr JT and Bullimore MA (2000). Overnight orthokeratology. Optom Vis Sci. **77** (5): 252-9.

- Norton TT and Siegwart JT (1995). Animal models of emmetropization: matching axial length to the focal plane. J Am Optom Assoc. **66** (7): 405-14.
- Ogur A and Nishimura M (2003). Advanced Orthokeratology for Japanese Patients with High Myopia. Invest. Ophthalmol. Vis. Sci. **44** (E-Abstract 3290).
- Parsinnen O, Hemminki E and Klemetti A (1989). Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren. Br J Ophthalmol. **73**: 747-51.
- Potapova N, Wang G, Haji S and Asbell P (2004). Corneal topography in corneal refractive therapy (CRT): a 1-month follow-up. Eye Contact Lens. **30** (3): 166-8.
- Rah MJ, Jackson JM, Jones LA, Marsden HJ, Bailey MD and Barr JT (2002). Overnight orthokeratology: preliminary results of the Lenses and Overnight Orthokeratology (LOOK) study. Optom Vis Sci. **79** (9): 598-605.
- Ramachandran L, Sharma S, Sankaridurg PR, Vajdic CM, Chuck JA, Holden BA, Sweeney DF and Rao GN (1995). Examination of the

conjunctival microbiota after 8 hours of eye closure. CLAO J. **21** (3): 195-9.

- Read SA, Collins MJ and Iskander DR (2008). Diurnal variation of axial length, intraocular pressure, and anterior eye biometrics. Invest. Ophthalmol. Vis. Sci. **49** (7): 2911-8.
- Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutiérrez-Ortéga R (2011). Myopia control with orthokeratology contact lenses in Spain (MCOS): Refractive and biometric changes. Optom Vis Sci. 2011;88:E-abstract: 110916.
- Saw SM, Chua WH, Gazzard G, Koh D, Tan DT, Stone RA (2005). Eye growth changes in myopic children in Singapore. Br J Ophthalmol. **89** (11):1489-94.
- Saw SM, Nieto FJ, Katz J, Schein OD, Levy B and Chew SJ (2000). Factors related to the progression of myopia in Singaporean children. Optom Vis Sci. **77** (10): 549-54.
- Saw SM, Tong L, Chua WH, Koh D, Tan DTH and Katz J (2005). Incidence and progression of myopia in Singapore school children. Invest. Ophthalmol. Vis. Sci. **46** (1) : 51-7.

- Shih YF, Hsiao CK, Chen CJ, Chang CW, Hung PT and Lin LL (2001). An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. Acta Ophthalmol Scand. **79** (3): 233-6.
- Siatkowski RM, Cotter SA, Crockett RS, Miller JM, Novack GD and Zadnik K (2008). Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. J AAPOS. **12** (4): 332-9.
- Smith EL III, Kee CS, Ramamirtham R, Qiao-Grider Y and Hung LF (2005). Peripheral vision can influence eye growth and refractive development in infant monkeys. Invest. Ophthalmol. Vis. Sci. **46** (11): 3965-72.
- Smith EL III, Huang J, Hung LF, Blasdel TL, Humbird TL and Bockhorst KH (2009). Hemiretinal form deprivation: evidence for local control of eye growth and refractive development in infant monkeys. Invest. Ophthalmol. Vis. Sci. **50** (11): 5057-69.

- Song X, Xu L, Sun S, Zhao J and Xie L (2011). Pediatric microbial keratitis: a tertiary hospital study. Eur J Ophthalmol. **22** (2): 136-41.
- Soni PS, Nguyen TT and Bonanno JA (2003). Overnight orthokeratology: visual and corneal changes. Eye Contact Lens. **29** (3): 137-45.
- Soni PS and Nguyen TT (2006). Overnight orthokeratology experience with XO material. Eye Contact Lens. **32** (1): 39-45.
- Sorbara L, Fonn D, Simpson T, Lu F and Kort R (2005). Reduction of myopia from corneal refractive therapy. Optom Vis Sci. **82** (6): 512-8.
- Sridharan R and Swarbrick H (2003). Corneal response to short-term orthokeratology lens wear. Optom Vis Sci. **80** (3): 200-6.
- Sun X, Zhao H, Deng S, Zhang Y, Wang Z, Li R, Luo S and Jin X (2006). Infectious keratitis related to orthokeratology. Ophthalmic Physiol Opt. **26** (2): 133-6.
- Swarbrick HA, Wong G and O'Leary DJ (1998). Corneal response to orthokeratology. Optom Vis Sci. **75** (11): 791-9.

- Swarbrick HA (2006). Orthokeratology review and update. Clin Exp Optom. **89** (3): 124-43.
- Tahhan N, Du Toit R, Papas E, Chung H, La Hood D and Holden AB (2003). Comparison of reverse-geometry lens designs for overnight orthokeratology. Optom Vis Sci. **80** (12): 796-804.
- Tan DT, Lam DS, Chua WH, Shu-Ping DF and Crockett RS (2005). One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. Ophthalmology. **112** (1): 84-91.
- Tong L, Huang XL, Koh AL, Zhang X, Tan DT and Chua WH (2009). Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. Ophthalmology. **116** (3): 572-9.
- Tsukiyama J, Miyamoto Y, Higaki S, Fukuda M and Shimomura Y (2008). Changes in the anterior and posterior radii of the corneal curvature and anterior chamber depth by orthokeratology. Eye Contact Lens. **34** (1): 17-20.
- van der Worp E and Ruston D (2006). Orthokeratology: An Update. Optometry in Practice. **7**: 47-60.

- Van Meter WS, Musch DC, Jacobs DS, Kaufman SC, Reinhart WJ and Udell IJ (2008). Safety of overnight orthokeratology for myopia: a report by the American Academy of Ophthalmology. Ophthalmology. **115** (12): 2301-13 e1.
- Walline JJ (2004). Study design issues in a corneal reshaping contact lens myopia progression study. Eye Contact Lens. **30** (4): 227-9; discussion 30.
- Walline JJ, Jones LA, Mutti DO and Zadnik K (2004a). A randomized trial of the effects of rigid contact lenses on myopia progression. Arch Ophthalmol. **122** (12): 1760-6.
- Walline JJ, Rah MJ and Jones LA (2004b). The Children's Overnight Orthokeratology Investigation (COOKI) pilot study. Optom Vis Sci. **81** (6): 407-13.
- Walline JJ, Jones LA, Sinnott L, Manny RE, Gaume A, Rah MJ, Chitkara M and Lyons S (2008). A randomized trial of the effect of soft contact lenses on myopia progression in children. Invest. Ophthalmol. Vis. Sci. **49** (11): 4702-6.
- Walline JJ, Jones LA and Sinnott LT (2009). Corneal reshaping and myopia progression. Br J Ophthalmol. **93** (9): 1181-5.

- Watt K and Swarbrick HA (2005). Microbial keratitis in overnight orthokeratology: review of the first 50 cases. Eye Contact Lens. **31** (5): 201-8.
- Watt KG, Boneham GC and Swarbrick HA (2007). Microbial keratitis in orthokeratology: the Australian experience. Clin Exp Optom. **90** (3): 182-7.
- Watt KG and Swarbrick HA (2007). Trends in microbial keratitis associated with orthokeratology. Eye Contact Lens. **33** (6 Pt 2): 373-7; discussion 82.
- Wlodyga RJ and Bryla C (1989). Corneal molding: the easy way. Contact Lens Spectrum. **4** (8): 58-65.
- Yang Z, Lan W, Ge J, Liu W, Chen X, Chen L and Yu M (2009). The effectiveness of progressive addition lenses on the progression of myopia in Chinese children. Ophthalmic Physiol Opt. **29** (1): 41-8.