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Myopia Control during Orthokeratology Lens Wear in Children Using a Novel Study Design

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Purpose: To investigate the effect of overnight orthokeratology (OK) contact lens wear on axial length growth in East Asian children with progressive myopia.

Design: A prospective, randomized, contralateral-eye crossover study conducted over a 1-year period.

Participants: We enrolled 26 myopic children (age range, 10.8–17.0 years) of East Asian ethnicity.

Methods: Subjects were fitted with overnight OK in 1 eye, chosen at random, and conventional rigid gas-permeable (GP) lenses for daytime wear in the contralateral eye. Lenses were worn for 6 months. After a 2-week recovery period without lens wear, lens–eye combinations were reversed and lens wear was continued for a further 6 months, followed by another 2-week recovery period without lens wear. Axial eye length was monitored at baseline and every 3 months using an IOLMaster biometer. Corneal topography (Medmont E300) and objective refraction (Shin-Nippon NVision-K 5001 autorefractor) were also measured to confirm that OK lens wear was efficacious in correcting myopia.

Main Outcome Measurements: Axial length elongation and myopia progression with OK were compared with conventional daytime rigid contact lens wear.

Results: After 6 months of lens wear, axial length had increased by 0.04±0.06 mm (mean ± standard deviation) in the GP eye ($P = 0.011$) but showed no change (−0.02±0.05 mm) in the OK eye ($P = 0.888$). During the second 6-month phase of lens wear, in the OK eye there was no change from baseline in axial length at 12 months (−0.04±0.08 mm; $P = 0.218$). However, in the GP eye, the 12-month increase in axial length was significant (0.09±0.09 mm; $P < 0.001$). The GP lens-wearing eye showed progressive axial length growth throughout the study.

Conclusions: These results provide evidence that, at least in the initial months of lens wear, overnight OK inhibits axial eye growth and myopia progression compared with conventional GP lenses. Apparent shortening of axial length early in OK lens wear may reflect the contribution of OK-induced central corneal thinning, combined with choroidal thickening or recovery due to a reduction or neutralization of the myopiogenic stimulus to eye growth in these myopic children. *Ophthalmology 2015;122:620-630 © 2015 by the American Academy of Ophthalmology.*

Myopia is among the most common refractive errors that affect children. It is usually caused by excessive axial length of the eye, which causes light rays from distant objects to focus in front of the retina, giving rise to blurred distance vision. In children, myopia is typically progressive in early to middle childhood.[1] Early onset of myopia is frequently associated with the development of high myopia,[1] which can be associated with serious ocular complications, such as glaucoma, macular degeneration, and various pathologic retinal changes.[1,2] Thus, there are important benefits of interventions that might slow or arrest the development of myopia in children.

Myopia prevalence rates have been increasing worldwide. For example, in the United States the prevalence of myopia in the 12- to 54-year-old population increased from 25% in 1971 and 1972 to 41.6% in 1999 through 2004.[3] In Australia, increasing myopia prevalence has also been reported; the Sydney Adolescent Vascular and Eye Study (SAVES) followed a group of children over 5 to 6 years.[4] They reported an increase in myopia prevalence in 12-year-olds from 1.4% to 14.4%, and from 13% to 29.6% in 17-year-olds, over the study period.

However, the highest myopia prevalence rates have consistently been reported from East Asian countries. Epidemic levels of myopia prevalence have recently been reported from South Korea and China; 96.5% of 19-year-old South Korean males[5] and 95.5% of Chinese university students were found to have myopia.[6]

There has been growing clinical and research interest in developing strategies to control myopia progression, including both optical and pharmaceutical approaches.[7] To date, the most effective means for slowing myopia progression is the use of atropine drops.[7,8] Recent research using low concentrations of atropine (as low as 0.01%) seem to avoid many of the problems of 1% atropine, such as loss of accommodation and pupil dilation, without significant sacrifice of efficacy.[9]

Optical approaches have included the use of bifocal and progressive addition lenses. Although these approaches do

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have a small, statistically significant effect, their clinical effect is minimal, even when subgroups that show enhanced efficacy are considered.[10] More recently, spectacle lenses and contact lenses designed to manipulate the peripheral retinal image have been investigated.[11–13] These approaches are based on the hypothesis developed by Smith et al[14] that manipulation of the peripheral retinal image to maintain myopic rather than hyperopic defocus may act to inhibit axial eye growth. Results from clinical studies using such optical manipulations have been encouraging.

Orthokeratology (OK) is a well-established clinical technique that involves wearing specialized rigid contact lenses with a reverse geometry lens design overnight. For myopia correction, OK lenses flatten the central cornea to correct mild to moderate degrees of central or on-axis myopia after lens removal in the morning.[15] Over the last few years, a number of clinical studies have clearly demonstrated that overnight OK lens use in myopic children is effective in reducing the rate of myopia progression.[16–23] It is hypothesized that this effect results from the induction of myopic defocus on to the peripheral retina as a result of the effects of the OK lenses on mid peripheral and peripheral corneal topography.[24]

Previous studies of myopia control in OK have relied on conventional study designs that have typically involved separate study and control groups of children wearing lenses over 2-year study periods. Such clinical studies are cumbersome and expensive to conduct, require large sample sizes and carefully matched subject groups, and suffer from difficulties with maintaining subject matching over the lengthy study period. Significant dropouts have been noted in some of these studies, ranging from 13% to 46% overall and up to 54% in the OK treatment group,[16–23] confounding the conclusions that can safely be drawn, particularly when reasons for dropout differ between control and treatment groups.[25]

In the study reported herein, we used a novel contralateral eye crossover study design to avoid many of the problems associated with previous conventional clinical trials. Using this efficient strategy, a relatively short-term study with minimal subject numbers was used to test the hypothesis that overnight OK lens wear inhibits axial elongation and myopia progression compared with conventional daytime rigid contact lens wear. The contralateral eye study design allowed paired analysis to minimize subject numbers without sacrificing statistical power, and it limited the risks of attrition bias from study dropouts. The crossover study design provided efficient confirmation of study outcomes over 2 consecutive 6-month lens-wearing periods.

Methods

This 12-month study used a prospective, randomized, contralateral eye crossover study design. The research conducted in this study conformed to the tenets of the Declaration of Helsinki (2008), and the research protocol and documentation received approval from the University of New South Wales Human Research Ethics Committee before study commencement. All subjects and their parents or guardians gave written consent to study participation after the nature of the study and risks and benefits of participation in the research had been fully explained. Separate consent forms using appropriate language were prepared for subjects <10 years of age, >10 years of age, and for parents or guardians.

Subjects

A total of 32 subjects who met the study entry criteria were recruited for participation in this research. Inclusion criteria specified age between 8 and 16 years at initial study enrollment and East Asian ethnicity (Chinese, Singaporean, Taiwanese, Malaysian-Chinese, and Vietnamese) based on parental reports of ethnic background. Refractive criteria included myopia between −1.00 and −4.00 diopters (D) spherical equivalent, evidence of progression of myopia in the previous 12 months (based on a reported increase in spectacle prescription), <1.50 D of corneal toricity, and <1.00 D difference in spherical equivalent refraction between the 2 eyes. For study entry, subjects also were required to demonstrate good binocular coordination (based on a range of standard optometric tests of binocularity, including measurement of stereoacuity using the Titmus Fly Stereotest), good ocular health, and no contraindications for rigid contact lens wear.

Contact Lenses

The rigid lenses used for overnight OK were of a reverse geometry design (BE or A-BE; Capricornia Contact Lens Pty Ltd, Brisbane, Qld, Australia) that is available commercially for use as an overnight OK lens. Overall diameter of these lenses was either 11.00 mm (BE) or 10.60 mm (A-BE), depending on the subject's horizontal visible iris diameter and palpebral aperture dimensions. Both BE and A-BE lenses have an optic zone diameter of 6.00 mm, and specifications of the optic zone, first reverse curve, and peripheral alignment curve are identical between designs. The difference in lens diameter is achieved by using a slightly steeper and narrower second reverse curve in the A-BE lens to maintain sagittal height equivalence between the 2 designs.

The conventional rigid gas-permeable (GP) lenses used were a standard alignment fitting design (J-Contour, Capricornia), a 4-curve lens with an overall diameter of 10.00 or 10.50 mm, and a spherical back optic zone with a diameter of 8.50 or 9.00 mm, respectively. To achieve an acceptable lens fit, the Modcon lens design (Capricornia) with an overall diameter of 10.00 mm, a spherical back optic zone of 7.90 mm in diameter, and a tangent periphery, was used for 5 subjects during study phase 1 (2 of whom discontinued) and 4 subjects during study phase 2 (1 of whom was refitted from a J-Contour to a Modcon lens). The choice of lens design to use for the GP lens-wearing eye was based on conventional rigid contact lens fitting considerations to encourage comfortable and safe daily GP lens wear.

Both lenses (OK and GP) were fabricated from the hyper-Dk Boston XO_2 material (hexafocon B, Dk 141 ISO/Fatt units; Bausch & Lomb Boston, Wilmington, MA). Nominal center thickness for the OK lenses was 0.23 mm, and 0.17 mm for the GP lenses, giving nominal central Dk/t of 61 and 83 Dk/t units, respectively. The OK lens was supplied with a purple handling tint, and the GP lens had a light blue handling tint.

Before the commencement of the study, OK lenses were fitted to both eyes according to the manufacturer's recommended procedure. Initial lens selection was based on corneal topographic variables including apical corneal radius and corneal sagittal height at a 9.35-mm chord (or 8.95 mm for A-BE lenses), as measured by the Medmont E-300 corneal topographer (Medmont Ltd, Melbourne, Victoria, Australia), horizontal visible iris diameter, and desired refractive change. An overnight lens-wearing trial using lenses indicated by the proprietary BE lens-fitting software algorithm was conducted, and outcomes from this overnight trial were

used to refine the lens parameters to determine the appropriate OK lenses to be ordered for use in the study.

Conventional GP lenses were fitted in both eyes based on standard contact lens fitting procedures, with initial lens selection based on central corneal curvature data from the Medmont topographer. Indicated trial lenses were inserted after application of 1 drop of topical anesthetic (Alcaine 0.5%; proxymetacaine hydrochloride; Alcon Laboratories, Frenchs Forest, NSW, Australia) to minimize reflex tearing. Slit-lamp assessment of lens centration and movement was conducted under white light, and sodium fluorescein dye under cobalt blue lighting was used to determine the lens-to-cornea fitting relationship. Lens parameters were adjusted until satisfactory dynamic lens performance and an alignment lens-to-cornea fitting relationship were obtained. Over-refraction was performed to determine the back vertex power of the required lenses to achieve $\geq$20/25 corrected vision in each eye.

Measurement Techniques

Axial Length. The IOLMaster ocular biometer (Zeiss, Jena, Germany) was used to measure axial length. This noncontact instrument is based on infrared interferometry principles and measures the distance in millimeters from the apex of the anterior corneal surface to the retinal pigment epithelium with a reported high repeatability (95% limits of agreement of -0.047 to 0.038 mm in Chinese children[26]). Five measurements of axial length were taken at each measurement session and averaged. As recommended by the manufacturer, for safety reasons no more than 20 repeated measures were taken in any eye on the same day.

Corneal Topography

The Medmont E-300 corneal videokeratoscope was used to capture images of the anterior corneal surface topography, which were analyzed using Medmont Studio version 5 software. Corneal topographic variables of interest included corneal apical radius of curvature (r_o; in millimeters), corneal asphericity (Q) over a 9.35-mm chord along the flat corneal meridian, and simulated keratometry readings (D) along the flat and steep meridians. On each measurement occasion, 3 topographic maps were captured for each eye and the mean values for the variables of interest were calculated.

Refractive Error

Distance objective refractive error was measured without cycloplegia in each eye using the Shin-Nippon NVision-K 5001 autorefractor (Shin-Nippon, Tokyo, Japan). Five measurements were automatically obtained from each eye and averaged on each measurement occasion.

Study Protocol

The study protocol is summarized in Figure 1. Before commencement of the study, a thorough optometric examination was performed to ensure that study entry criteria were met and that subjects were suitable for overnight OK lens wear. The OK and GP lenses to be ordered for wear in the study were then determined for each subject using the fitting procedures described above.

All subjects were then preadapted to binocular daily (open-eye) wear of the conventional GP lenses for 2 weeks to ensure that they were able to successfully wear these lenses during waking hours. A minimum daily wearing time of 8 hours was required before acceptance into the study. Once adaptation had been successfully demonstrated, subjects were required to cease lens wear for 2 weeks, and a series of baseline measurements (baseline 1 BL1) of axial length, corneal topographic variables, and refraction was then performed.

At study commencement, subjects were dispensed an OK lens for overnight wear only (with no lens wear during the day) in 1 eye chosen at random by coin toss (the "night" lens) and a conventional GP lens for the contralateral eye for daytime wear (the "day" lens). Subjects were required to wear the dispensed lenses as instructed for a 6-month period (study phase 1). Routine clinical aftercare examinations were conducted after 2 and 4 weeks, or on an unscheduled basis as indicated clinically, or if the subject or their parents had any concerns.

Study variables were measured after 3 and 6 months of lens wear, at a morning visit within 2 hours of awakening, and at an afternoon visit approximately 8 to 10 hours after awakening. Subjects were then requested to cease lens wear for a 2- to 3-week period to allow corneal topographic recovery from the effects of overnight OK lens use. Corneal topography was monitored periodically during this time. After washout of the OK effect had been achieved (baseline $r_o \pm 0.05$ mm), measurements of study variables were repeated. These measurements are noted in the Results as both regression (Reg1) measurements, and also as baseline 2 (BL2) measurements for the commencement of study phase 2. Lens wear was then recommenced, but with lens–eye combinations reversed. The eye that had been wearing an overnight OK lens for the first 6 months now wore a daily wear GP lens, whereas the previous GP lens-wearing eye now wore an OK lens for overnight wear only.

During this second phase (study phase 2), routine clinical aftercare examinations were conducted after 2 and 4 weeks of lens wear or on an unscheduled basis as indicated. Study variables were measured after a further 3 and 6 months of lens wear (at 9 and 12 months into the study), at a morning visit within 2 hours of awakening, and at an afternoon visit approximately 8 to 10 hours after awakening.

After the completion of the full 12 months of lens wear, subjects were again requested to discontinue lens wear for a 2- to 3-week period to allow recovery from the effects of OK lens wear. A final set of study measurements was then obtained (noted as regression measurements Reg2 in the Results), including axial length, corneal topography, and objective refraction.

Clinical Management of Subjects

Before dispensing any contact lenses in this study, subjects and their parents received detailed education on lens handling, insertion and removal, and lens care. Intensive hands-on instruction, a booklet containing detailed instructions, and a DVD showing lens insertion and removal techniques were provided. Lenses were not dispensed until subject competence in their own lens handling had been demonstrated to the satisfaction of clinical study personnel.

Subjects were provided with a contact lens storage case and solutions for contact lens care and storage, including Boston Simplus Multi-Action solution for lens disinfection and storage, Boston Advance Cleaner for surfactant lens cleaning after removal, Sensitive Eyes Saline solution for lens rinsing before storage, and Boston Rewetting Drops for in-eye lubrication as required (all Bausch & Lomb Inc, Rochester, NY). Solutions were supplied by Bausch & Lomb (Australia) Pty Ltd (Frenchs Forest, NSW, Australia). Subjects were instructed to store the OK lens during the day in Simplus solution after surfactant cleaning and saline rinsing and to store the GP lens overnight after similar lens care steps. The open (unused) well of the lens case was to be rinsed with Simplus solution followed by saline solution, then left open to air dry when not in use. Replacement lens cases were supplied every 3 months.

A 24-hour contact telephone number was provided in case of emergencies or queries. Subjects and their parents were instructed to cease lens wear in the event of any unusual blurred vision, discomfort, or ocular redness and to contact the research team

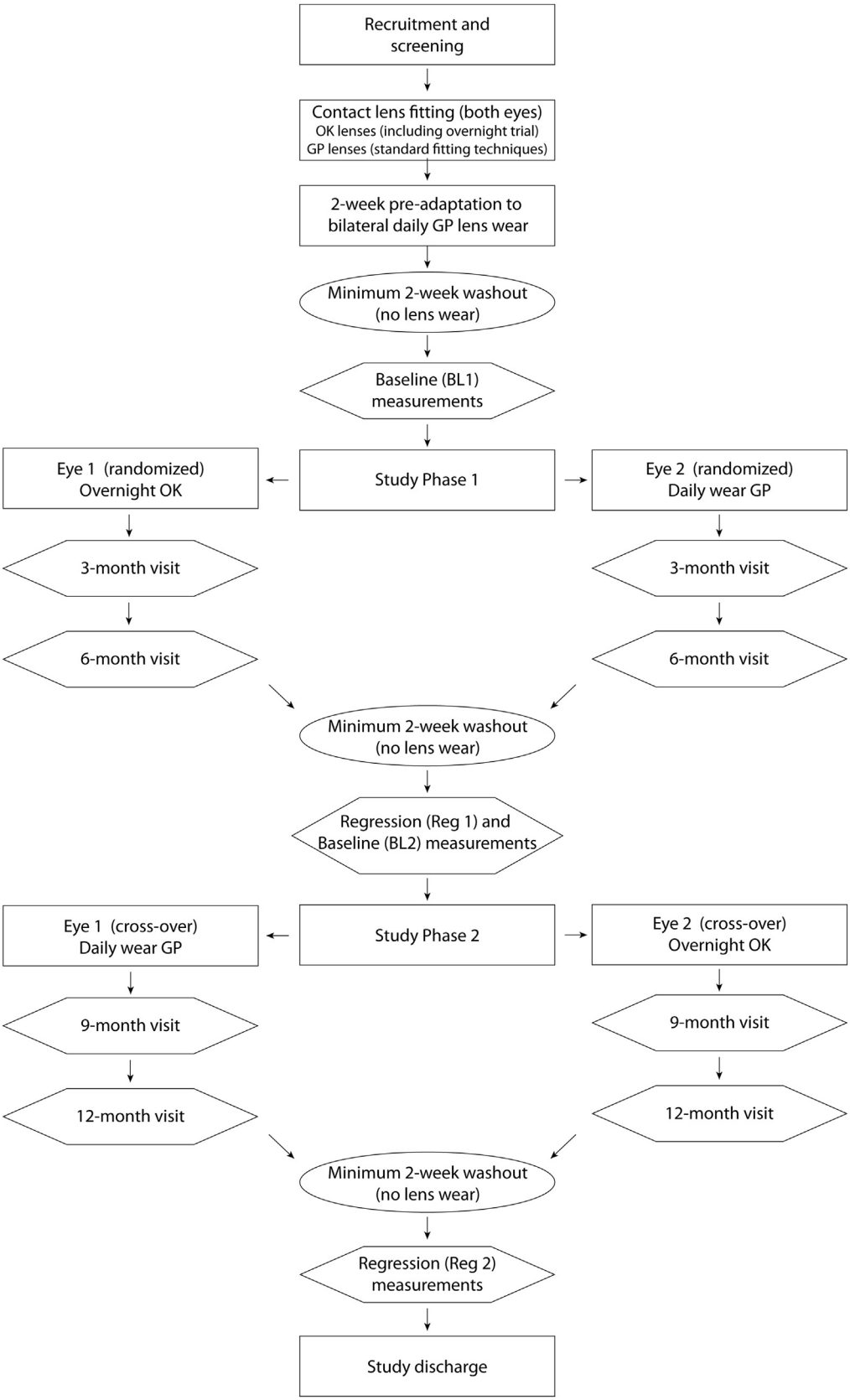

Figure 1. Study protocol. Items in hexagons indicate study data collection visits, items in ovals indicate periods of washout (no lens wear), and items in rectangles relate to study protocol stages including those conducted before the commencement of data collection visits. GP = gas-permeable; OK = orthokeratology.

immediately. Lens wear was also discouraged during ill health, when swimming, or in the event of travel for holidays or school trips, particularly overseas. Subjects were required to maintain a daily diary of lens insertion and removal times, occasions of no lens wear, or any other events related to contact lens wear to allow subsequent monitoring of lens-wearing schedules.

At each aftercare visit (scheduled or unscheduled) and at data collection visits, a detailed examination, including visual acuity measurement and slit-lamp biomicroscopic assessment of the cornea and adnexa, was performed. Fluorescein dye was instilled to examine corneal integrity. Temporary discontinuation of lens wear was mandated by study protocol in the event of any clinically significant adverse effects of contact lens wear.

Binocular vision assessment was conducted with the GP lens in 1 eye (and OK-induced reshaping correction in the fellow eye) at each aftercare visit to ensure that good binocularity was maintained during the study. Relative axial length changes in the 2 eyes were also inspected to estimate the induction of any significant anisometropia. Study protocol mandated early termination of lens wear in the event of an apparent induced refractive difference between the 2 eyes of >1.00 D.

At discharge, all subjects were provided with a complimentary pair of lenses (either OK or GP as preferred), a supply of contact lens solutions, and referral to a contact lens practitioner of their choice for continuing contact lens care.

Data Analysis

Sample size calculations conducted during study planning were based on a number of variables that were measured in this study but are not reported herein. This led to the calculation of a minimum sample size that was substantially larger than required to achieve statistical power for the outcome variables (axial length, spherical equivalent refraction, and corneal topographic variables) that are reported herein. Post hoc power analysis with an alpha level of 5% indicated that, for the primary outcome variable (axial length), a statistical power of 81.9% was achieved at the end of study phase 1 and 98.0% at the end of study phase 2.

Data obtained at the morning visits only are reported in this article. Normality of data was assessed using the Shapiro-Wilk test before conducting parametric tests (SPSS version 21; IBM, Chicago, IL). Paired *t* tests were conducted on baseline (BL1) data. The effects of OK and GP lenses on axial length, refraction, and corneal topography changes or progression were assessed initially using linear mixed model analysis. The linear mixed model analysis was chosen to account for sporadic missing clinical data. If significant differences between lens types were identified with this analysis, post hoc *t* tests with Bonferroni correction were then used to compare effects between visits in eyes wearing OK and GP lenses. $P = 0.05$ was used to denote significance.

Results

Subject Demographics and Study Discontinuations

Of the 32 subjects who were initially recruited to participate in this research, a total of 26 subjects (12 female, 14 male; mean age, 13.4±1.9 years; age range, 10.8−17.0 years) completed the first 6 months of lens wear, and 24 subjects successfully completed 12 months of the study. There were no significant differences in demographic or study variables at baseline for the 26 subjects who completed 6 months of the study and the 24 subjects who completed the full 12 months of lens wear.

Five subjects were discontinued from the study before the 6-month time point. Two of these subjects discontinued because of persistent difficulty adapting to open-eye GP lens wear, associated with noncompliance with daily GP lens wear in the control eye, and 2 subjects withdrew because of the inconvenience of travelling long distances to the research facility for frequent aftercare and data collection. One subject was discontinued because of persistent severe daytime lens adherence to the eye, accompanied by peripheral staining and erosion in the GP lens-wearing eye.

Two subjects withdrew at the 6-month time point because of time constraints and long distances of travel to the research facility. Finally, data for 1 subject were discarded after scrutiny of corneal topographic maps indicated noncompliance with the study protocol, with lenses being swapped randomly between the 2 eyes.

Baseline biometric data for OK and GP lens-wearing eyes obtained immediately before commencement of lens wear in study phase 1 are presented in Tables 1 to 4. There were no significant differences in any baseline parameters between eyes assigned for OK and GP lens wear.

Axial Length

Axial lengths in the GP and OK lens-wearing eyes in the two 6-month phases of the study are presented in Figure 2. For the first 6-month period of lens wear, the baseline measurement (BL1) was obtained after the preadaption phase of the study. For the second 6-month period of lens wear, the baseline (BL2) refers to axial length measured after the midstudy washout period of no lens wear. Changes in axial length from BL1 (study phase 1) and BL2 (study phase 2) are shown in Figure 3 and Table 1.

Study Phase 1. In the first 6-month period of lens wear, a significant overall difference in change in axial length from baseline was found between the OK and GP eyes ($F = 23.927$; $P < 0.001$). In the OK eye, axial length was significantly shorter at 3 months compared with BL1 ($P = 0.021$) and Reg1 ($P = 0.004$). There were no differences in axial length change between BL1 and Reg1 ($P > 0.99$) or between the 3- and 6-month visits ($P = 0.751$). In the GP eye, there was no change in axial length during the first 3 months ($P = 0.458$). However, axial length became significantly longer at 6 months ($P = 0.011$) and at the Reg1 ($P = 0.001$) visit compared with BL1.

Study Phase 2. After reversal of lens−eye combinations in the second 6-month lens-wearing period, a significant difference in change in axial length from baseline was found between the OK and GP eyes ($F = 40.981$; $P < 0.001$). In the OK eye, there were no differences in axial length change measured at the different study visits ($P > 0.05$). In the GP eye, there was an increase in axial length from BL2, which became significant at 12 months

Table 1. Changes in Axial Length from Baseline (BL) (Phase 1, and BL2; Phase 2) in Eyes Assigned to Orthokeratology (OK) and Gas-permeable (GP) Lens Wear

Study Phase	OK Eye	GP Eye
1		
3 months	−0.04±0.08*	0.02±0.06
6 months	−0.02±0.09	0.04±0.08*
Reg1	0.01±0.08	0.05±0.09*
2		
9 months	−0.05±0.07	0.04±0.09
12 months	−0.05±0.11	0.09±0.12*
Reg2	0.00±0.11	0.10±0.12*

Reg = regression.
Values are presented as mean ± standard deviation (mm).
*$P < 0.05$ versus baseline (protected post hoc paired *t* test).

Table 2. Objective Spherical Equivalent Refraction (mean ± SD) in Eyes Assigned to Orthokeratology (OK) and Gas-permeable (GP) Lens Wear

Study Phase	OK Eye	GP Eye
1		
BL1	−2.43±0.98	−2.39±0.93
3 months	−0.19±0.94*	−2.51±1.07
6 months	−0.11±0.91*	−2.58±1.14
Reg1	−2.22±1.07	−2.58±1.17
2		
BL2	−2.60±1.21	−2.22±1.10
9 months	−0.32±0.92*	−2.39±1.05*
12 months	−0.31±0.97*	−2.59±1.20*
Reg2	−2.36±1.15	−2.76±1.27*

BL = baseline; Reg = regression.
Values are presented as mean ± SD (D).
*$P < 0.05$ versus baseline (protected post hoc paired t test).

($P < 0.001$) and Reg2 ($P = 0.001$). Furthermore, axial length was greater at Reg2 compared with the 9-month visit ($P = 0.031$).

Refractive Error

Spherical equivalent refractive error (M) in the OK and GP lens-wearing eyes during the 2 phases of the study are presented in Table 2.

Study Phase 1. There was a significant hyperopic shift or correction of myopia after 3 ($P < 0.001$) and 6 months ($P < 0.001$) of OK lens wear. There was no difference in M between the 3- and 6-month visits in the eye assigned for OK lens wear ($P > 0.99$) or between BL1 and Reg1 visits ($P > 0.99$). There was no change in M in the GP lens-wearing eye during study phase 1 ($F = 2.019$; $P = 0.119$), although there seemed to be a trend suggesting some myopia progression.

Study Phase 2. Similar to study phase 1, there was a significant positive shift in M in the eye assigned for overnight OK lens wear at the 9- ($P < 0.001$) and 12-month visits ($P < 0.001$) compared with BL2. The M was similar after 9 and 12 months of OK lens wear ($P > 0.99$) and between BL2 and Reg2 visits ($P = 0.636$). In the eye assigned for daily GP lens wear, M was significantly more negative or more myopic compared with BL2 at the 9-month ($P = 0.010$), 12-month ($P < 0.001$), and Reg2 visits ($P < 0.001$). However, there were no differences in M between the 9-month, 12-month, and Reg2 visits ($P > 0.99$).

Changes in spherical equivalent refractive error from relevant baselines at completion of the two 6-month lens-wearing phases are presented in Figure 4. The data shown in this figure were obtained after a washout period from lens wear to allow for recovery from myopia correction in the OK lens-wearing eye. The period of no lens wear during washout averaged 21±15 days (range, 7−46 days) after the first 6 months and 16±4 days (range, 11−29 days) after the second 6 months of the study. The period during which subjects abstained from lens wear was determined partially by a requirement for recovery of corneal apical radius to baseline values ± 0.05 mm but also was extended in some circumstances for subject convenience (e.g., because of school vacation periods).

After both study phases, the GP lens-wearing eye demonstrated increased myopia relative to baseline, which reached statistical significance ($P < 0.001$) only in study phase 2 (Reg2). Conversely, the OK lens-wearing eye retained a slight hyperopic shift relative to baseline, which failed to attain significance ($P = 0.636$).

At baseline (BL1) before commencing the study, among the 24 subjects who completed the full 12 months of the study, there was no difference in spherical equivalent refraction between the 2 eyes (GP-OK, 0.03±0.46 D). After washout at the end of study phase 1 (Reg1), the eye that wore the GP lens was, on average, −0.38±0.41 D more myopic than the OK lens-wearing eye. After crossover of lens, types, and a further 6 months of lens wear and washout (Reg2), the eye that had switched to the GP lens was now on average −0.40±0.38 D more myopic than the eye that had switched to the OK lens. Thus, a small but clinically insignificant degree of anisometropia was induced in this study (i.e., <0.50 D more myopia in the eye that commenced with OK lens wear then switched to GP lens wear). Some of this residual anisometropia may have resulted from incomplete washout of the OK effect at the end of study phase 2 (as suggested by Fig 4), meaning that the OK lens-wearing eye retained slightly reduced manifest myopia at the Reg2 visit.

Table 3. Corneal Topography Parameters in Eyes Assigned to Orthokeratology (OK) and Gas-permeable (GP) Lens Wear during Study Phase 1

Group	r_o (mm)	Flat K (D)	Steep K (D)	Q
OK				
BL1	7.77±0.19	43.11±1.09	44.38±1.18	−0.39±0.12
3 months	8.21±0.26*	41.22±1.27*	42.49±1.25*	−0.05±0.14*
6 months	8.18±0.30*	41.34±1.09*	42.62±1.24*	0.02±0.24*
Reg1	7.80±0.21	42.89±1.07	44.28±1.23	−0.38±0.14
GP				
BL1	7.76±0.21	43.09±1.12	44.30±1.26	−0.40±0.12
3 months	7.81±0.20*	42.88±1.09	44.11±1.17	−0.37±0.12
6 months	7.79±0.21	42.94±1.16*	44.30±1.23	−0.37±0.14
Reg1	7.75±0.22	43.10±1.18	44.57±1.32*	−0.43±0.14

BL = baseline; Q = corneal asphericity; Reg = regression; r_o = apical radius of curvature.
Values are presented as mean ± standard deviation.
*$P < 0.05$ versus baseline (protected post hoc paired t test).

Corneal Topography

Tables 3 and 4 summarize the topographic variables of interest every 3 months during study phases 1 and 2 in the OK and GP eyes.

Study Phase 1. After 3 and 6 months of OK lens wear, there was a significant increase in r_o or flattening of the corneal apex and a significant decrease or flattening of flat and steep keratometry (K) (all $P < 0.001$) compared with BL1. A significant positive shift in Q value (toward oblate) was also measured after 3 and 6 months (both $P < 0.001$). No differences in r_o, flat or steep K (in diopters) or Q value were found between BL1 and Reg1 ($P > 0.648$) or between the 3- and 6-month visits ($P > 0.656$).

In the GP eye, r_o measured at 3 months was slightly but significantly increased compared with BL1 ($P = 0.032$). At Reg1, r_o had significantly decreased compared with both the 3- and 6-month visits ($P < 0.009$). Flat K was significantly reduced at 6 months compared with BL1 ($P = 0.014$) but increased significantly at Reg1 ($P = 0.006$). Steep K was significantly increased at Reg1 compared with all other visits ($P < 0.05$). The Q values were significantly more negative at Reg1 compared with the 3- and 6-month visits ($P < 0.003$). Otherwise, r_o, flat and steep K, and Q values were similar between all other visits ($P > 0.05$).

Study Phase 2. Similar to phase 1, during study phase 2 there was a significant increase in r_o or flattening of the corneal apex, a significant decrease in flat and steep K, and a significant positive

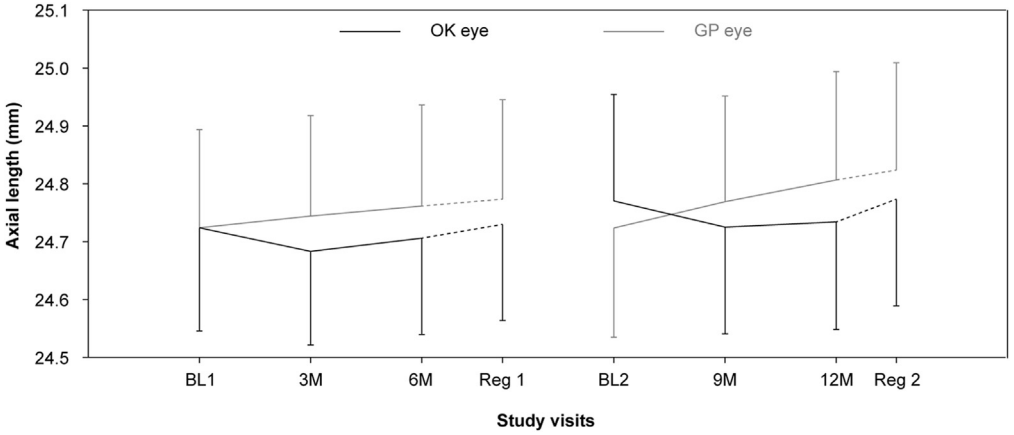

Figure 2. Axial length in gas-permeable (GP; grey) and orthokeratology (OK; black) eyes during study phases 1 and 2. Dashed lines indicate periods of no lens wear. Error bars represent standard error. BL = baseline; M = month; Reg = regression.

shift in Q values (all $P < 0.001$) after 3 and 6 months of OK lens wear (at the 9- and 12-month time points in the study) compared with BL2. No difference was found between BL2 and Reg2 visits ($P > 0.172$) or between the 9- and 12-month visits ($P > 0.99$) for r_o, steep K, and Q values. However, flat K values measured at Reg2 were slightly flatter compared with BL2 ($P = 0.046$).

In the GP eye, compared with BL2 there was a slight but significant steepening of r_o at 12 months ($P = 0.026$), which persisted at Reg2 ($P < 0.001$). This slight corneal steepening was also noted at Reg2 for steep K ($P = 0.008$) and was accompanied by a negative shift in Q values ($P = 0.014$). At all other visits, r_o, steep K, and Q values were similar ($P > 0.05$). There was no change in flat K in the GP eye in study phase 2 ($F = 2.059$; $P = 0.114$).

These data demonstrate clinically significant changes from baseline in apical corneal radius, flat and steep K values, and Q in the OK lens-wearing eyes only, confirming that an OK effect was achieved during overnight wear of the reverse geometry lenses during both study phases 1 and 2. In the eye assigned for GP lens wear, although sporadic statistically significant changes in corneal topography were found during both study phases, these were not clinically significant.

Table 4. Corneal Topography Parameters in Eyes Assigned to Orthokeratology (OK) and Gas-permeable (GP) Lens Wear during Study Phase 2

Group	r_o (mm)	Flat K (D)	Steep K (D)	Q
OK				
BL2	7.74±0.23	43.14±1.22	44.64±1.35	−0.43±0.14
9 months	8.13±0.24*	41.55±1.15*	42.93±1.34*	−0.09±0.15*
12 months	8.16±0.24*	41.37±1.07*	42.76±1.23*	−0.08±0.17*
Reg2	7.81±0.23	42.85±1.20*	44.31±1.32	−0.37±0.12
GP				
BL2	7.80±0.21	42.90±1.11	44.31±1.27	−0.38±0.14
9 months	7.78±0.21	43.01±1.19	44.43±1.37	−0.37±0.10
12 months	7.77±0.20*	43.00±1.16	44.33±1.24	−0.40±0.14
Reg2	7.75±0.21*	43.05±1.14	44.59±1.30*	−0.43±0.13*

BL = baseline; K = keratometric; Q = corneal asphericity; Reg = regression; r_o = apical radius of curvature.
Values are presented as mean ± standard deviation.
*$P < 0.05$ versus baseline (protected post hoc paired t test).

Clinical Observations

Clinical observations of interest during this study, such as transient and reversible unilateral ptosis in the conventional GP lens-wearing eye, and issues relevant to managing GP and OK lens wear in children, including analyses of lens replacements and breakages, unscheduled episodes of lens wear cessation, and lens-wearing diary entries, will be presented in detail elsewhere.

Discussion

By using a contralateral-eye crossover study design, this clinical study clearly demonstrated a slower rate of axial eye growth and myopia progression during overnight OK lens wear compared with daytime wear of conventional rigid GP contact lenses over 2 consecutive 6-month lens-wearing periods. Analysis of corneal topographic changes during the 12-month study confirmed the presence of a corneal reshaping effect in the OK lens-wearing eyes, and objective refraction also confirmed the myopia correction effects of the corneal reshaping induced by overnight OK lens wear. Changes in objective refraction after cessation of lens wear and regression of OK lens-induced corneal topographic effects were consistent with the different rates of axial length growth in the 2 eyes. The myopia control effects of OK lens wear were convincingly supported by the strong crossover effect when lens−eye combinations were reversed in the second 6-month phase of lens wear, resulting in complete crossover of axial growth rate differences between the study and control eyes.

There have been a number of previous reports demonstrating clinically and statistically significant myopia control effects with overnight OK lens wear.[16–23] All of these studies utilized the conventional clinical study protocol of comparing 1 group of subjects wearing OK lenses with a separate matched control group of subjects wearing spectacles[16,18–23] or conventional soft contact lenses.[17] Only recently have the results from truly randomized clinical trials been reported[20,22,23]—most early studies either used historical controls[16,17] or allowed subject self-selection into study or control groups. Typically, these previous studies have

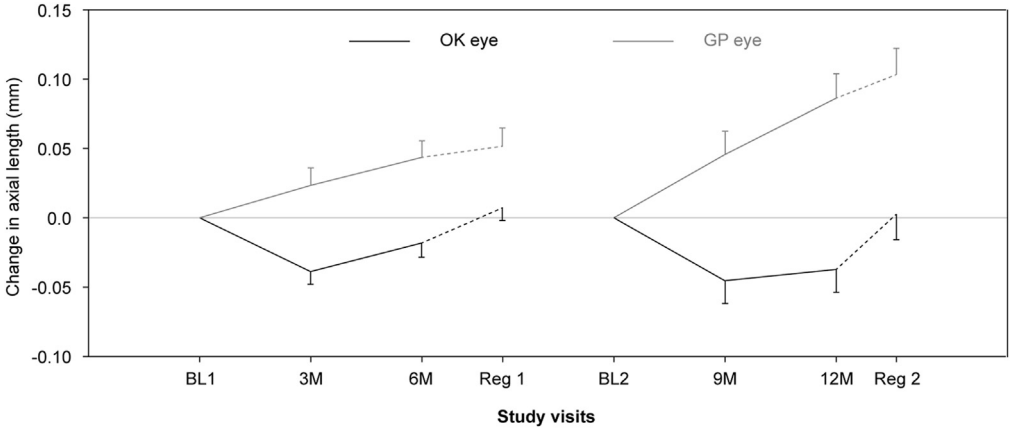

Figure 3. Changes in axial length from baseline (BL) 1 (phase 1, and BL2; phase 2) in gas-permeable (GP; grey) and orthokeratology (OK; black) eyes during study phases 1 and 2. Dashed lines indicate periods of no lens wear. Error bars represent standard error. M = month; Reg = regression.

been conducted over a 2-year period of lens wear, although an article reporting 5 years of OK lens wear has been recently published.[21] Although most studies have included only subjects with low to moderate myopia, 2 recent studies investigated the effects on myopia progression of astigmatic OK[22] and partial OK correction in high myopia.[23] The myopia control effects of OK reported by previous studies have ranged between 32% and 63% compared with controls.

The study design used in previous OK myopia control studies typically requires quite large numbers of subjects, and these studies are expensive and time-consuming to conduct. Difficulties can arise because of study dropouts, which may confound subject matching between study and control groups. More important, the risk of bias in study outcomes can be exacerbated if the reasons for dropout differ markedly between treatment and control groups.[25] For example, when subjects drop out of OK because of poor refractive outcomes, lens discomfort, or adverse events, this clearly has implications for the overall clinical efficacy of this treatment for myopia control.

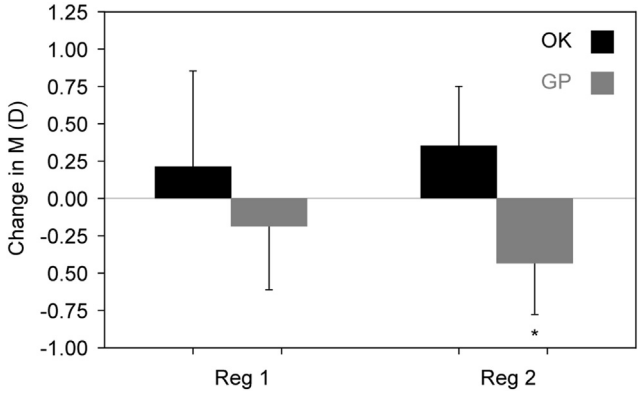

Figure 4. Change in objective spherical equivalent refraction (M) from baseline after a washout period of no lens wear at the end of study phases 1 (Reg1) and 2 (Reg2). Asterisk indicates statistically significant change from baseline. Error bars represent standard deviation. D = diopter; GP = gas-permeable; OK = orthokeratology.

The novel study design used in the current research avoids many of these difficulties by comparing the axial growth rate in the 2 eyes of the same subject simultaneously wearing 2 different lens types. Because of the use of the 2 eyes of the same subject for study and control conditions, paired statistics can be used to reduce significantly the required subject numbers while retaining statistical power, and dropouts from the study do not affect the within-subject matching of study and control conditions. We were also able to apply randomization in terms of which eye wore the OK lens and which wore the GP lens. A further advantage of our study was our ability to monitor crossover effects by repeating the 6-month lens-wearing period with lens-eye combinations reversed.

Although we recorded a moderate dropout rate of 25%, the risk of bias arising from these dropouts is minimized because of the reasons for attrition. Of the 8 subjects who discontinued after study enrollment, 4 withdrew because of inconvenience in attending study visits, 3 because of lens-related problems in the control eye (2 because of persistent discomfort and 1 owing to an adverse event), and data from 1 subject were excluded from analysis because of noncompliance. According to the Cochrane Handbook, these reasons for dropout carry a low risk of introducing attrition bias.[25] Furthermore, because of the contralateral eye study design, these dropouts were balanced between treatment and control eyes.

Nevertheless, the application of this novel study design was not without its challenges, requiring excellent cooperation from both subjects and parents to maintain compliance with the complex study protocol. This compliance was monitored through use of a daily lens-wearing diary and was reinforced by using different lens tints for the 2 different study lenses, by careful subject selection and education on study protocol, and through regular communication with subjects and parents. That these strategies worked in maintaining compliance with the protocol is clearly reflected in the outcome that data from only 1 subject had to be rejected from analysis because of noncompliance.

Previous studies of myopia control by OK lens wear have used either spectacles or soft contact lenses as the control condition. The use of soft contact lenses is justified based on previous research that has demonstrated no myopia control

effect with this lens-wearing modality.[27] In our study, we chose to use conventional rigid GP lenses for daytime wear as our control condition. This was based on the findings from previous research that such lenses do not provide a myopia control effect when fitted in corneal alignment.[28] The choice was also made for logistical reasons in terms of simplifying the lens care regimen and because rigid contact lens daily wear has been demonstrated to carry the least risk of complications such as microbial keratitis.[29]

The challenge of using this modality was the possible difficulty of subjects adapting to rigid lens wear in the open eye. Walline et al[30] previously reported that children show excellent adaptation to rigid lens wear, with almost 80% of children able to wear rigid lenses successfully for up to 40 hours per week. We addressed this issue by requiring potential subjects to preadapt to daily wear of bilateral rigid lenses before formal enrollment into the study to ensure that they would be able to wear these lenses comfortably during the study period. Despite this, 2 subjects who were enrolled dropped out subsequently because of persistent discomfort in the GP lens-wearing eye. Nevertheless, our experience has confirmed the earlier observations of Walline et al; we found that the child subjects in our study on the whole were satisfied with the comfort of the "day" lens. This may also have been influenced by the fact that lens wear was unilateral, which may have ameliorated discomfort. There were no reports of persistent discomfort with the OK lenses, which were worn only in the closed eye.

There have been previous reports of contralateral or sympathetic effects of lens wear in 1 eye modifying the effects seen in the fellow eye. Contralateral effects on the corneal edema response[31] and epithelial cell proliferation[32] have been reported, although others have found no contralateral effect on corneal thickness, oxygen uptake, or endothelial bleb response,[33] suggesting that such sympathetic effects are quite subtle. Although the contralateral eye study design used in this research provided many advantages, there is a possibility that contralateral effects may have confounded the data. If this were the case, it would be expected that this would reduce the difference in response between the 2 eyes rather than exaggerate the difference in response. Although we concede that the myopia control differences between the eyes may be underestimated because of this possible confounder, the fact that significant differences in axial growth rates were found suggests that contralateral effects were minimal in their influence on study outcomes.

Although on average the OK lens-wearing eye showed significantly less axial elongation in both phases of the study compared with the GP lens-wearing eye, there were significant individual differences in response. Some individual subjects showed no axial length growth, whereas others showed strong axial growth with OK lens wear, as indicated by the measures of variance presented in the Results. The reasons for this variability in response are currently unclear. Santodomingo-Rubido et al[34] suggested that myopia control with OK is influenced by a number of factors, including patient age and gender, age at onset, degree and progression rate of myopia, and various anatomic features, including corneal power and shape, anterior chamber depth, and iris and pupil diameter. Analysis of the influences of baseline characteristics on the efficacy of OK in our study is limited because of the small number of subjects, and the confounding effects of the contralateral eye study design.

There has been much speculation on the possible mechanisms underlying the demonstrated effect of OK lens wear on myopia control. The most strongly supported hypothesis is based on the animal work by Smith et al,[14] which demonstrated that the peripheral retina has a greater influence on axial eye growth in the developing eye than previously appreciated. Induction of hyperopic defocus on the peripheral retina in animal models induces axial eye growth and the development of myopia, whereas myopic defocus on the peripheral retina induces reductions in the rate of eye growth and hyperopia.[14,35] In humans, it has been demonstrated that myopes typically experience relative hyperopic defocus along the horizontal retinal meridian when wearing conventional myopic correction in the form of spectacles[36] or contact lenses.[37] However, corneal reshaping after OK lens wear has been shown to induce myopic defocus on the peripheral retina.[24] It is speculated that this may be the mechanism underlying the myopia control effects of OK lens wear.

Other optical effects such as spherical aberration, which is increased during myopic OK,[38] may also play a role in the myopia control effects of OK. Clearly, further research is needed to clarify the relative importance of these induced optical effects and other factors in myopic development, such as genetics and environment, in the progression of myopia in children.[2]

The results of our research give rise to some important questions. Axial length seemed to shorten in the first 3 months of OK lens wear, and this effect was apparent in both phases of the study. The amount of axial shortening averaged about 39 microns. Part of the explanation of this apparent axial shortening lies in the known effect of OK lenses on central corneal epithelial thickness. Alharbi and Swarbrick[39] reported an average of 19 microns of central corneal thinning after 3 months of overnight OK lens wear in young adult subjects who achieved an average refractive error correction of +2.63 D. Our cohort of child subjects achieved an average refractive correction of +2.25 D after 3 months of OK lens wear, which corresponds with approximately 16 microns of central corneal thinning. Thus, this well-established effect of OK lens wear explains about one half of the apparent axial shortening found in this study in the first 3 months of OK lens wear.

The explanation for the other component of axial shortening is more speculative. Read et al[40] recently demonstrated a rapid onset of choroidal thickening in humans exposed to myopic defocus in the short term. This is analogous to the choroidal thickening response that has been noted in many animal species during recovery from exposure to a myopiogenic stimulus such as defocus or form deprivation.[41] We speculate that some of the short-term axial shortening found in our study may represent choroidal thickening induced by a reduction in myopiogenic stimulus, which may result from OK lens wear. The IOLMaster biometer used in our study measures axial length from the apex of the cornea through to the front of the retinal pigment epithelium. Any choroidal thickening would move the retinal pigment epithelium forward, giving rise to an apparent shortening of the eye. We did not monitor choroidal

thickness in our study, so are not able to provide any evidence to support this hypothesis. Clearly, further research is needed to shed light on this possible mechanism.

Another interesting observation from our study was the apparent rapid progression of eye growth in the GP lens-wearing eye in study phase 2 compared with the rate of eye growth in the contralateral GP lens-wearing eye in study phase 1 (Fig 3). Axial length change in the GP lens-wearing eye during phase 2 was approximately double the change found during phase 1, and this difference reached statistical significance ($P = 0.043$). At the start of study phase 2, the GP lens-wearing eye had been wearing an OK lens for 6 months, and its axial growth had been inhibited. We speculate that the more rapid eye growth in phase 2 in this study may represent a "rebound" effect, such as that recently demonstrated in studies of atropine use for myopia control.[42] This may have important implications for the clinical use of OK for myopia control in children in terms of the period of OK lens wear required to achieve stability of refractive error. Clearly, our results indicate that a 6-month period of OK lens wear is insufficient for stable myopia control, but the question remains as to the necessary required period of OK lens wear, and other modalities of myopia control, to achieve stabilization and avoid rebound effects. Further research is required to answer this important clinical question.

In our study, OK lens wear was limited to 6 months, in 2 concurrent periods. Other studies have demonstrated myopia control effects over much longer periods. In our study, and in all other OK studies of myopia control, there seems to be continuing progression of myopia in OK lens-wearing eyes, as indicated by the upward trend in axial length at the 6-month time point in both phases of our study (Fig 2). Hiraoka et al[21] recently provided evidence that reduction in the rates of axial length growth in OK lens wear may only persist for $\leq$3 years, beyond which myopia may continue to progress at similar rates as eyes wearing spectacles, albeit from a lower base. Longer-term studies are clearly needed to determine whether there continues to be accrual of the effect of OK lens wear on myopia progression beyond 2 to 3 years of lens wear. This is an important clinical question that will underlie the acceptance of OK as an effective clinical modality for control of myopia progression into the future.

In conclusion, using a prospective, randomized, contralateral eye crossover study design, we demonstrated that overnight OK lens wear inhibits axial length growth in children with progressive myopia compared with daytime wear of conventional GP lenses. These results, obtained over two 6-month lens-wearing periods in a small cohort of myopic East Asian children, serve to confirm results from previously published longer-term studies of the effects of overnight OK lens wear on myopia progression that used separate groups of OK lens-wearing and control subjects.

The results of this study raise important questions for further research. What is the mechanism for inhibition of eye growth in overnight OK? Are changes in choroidal thickness implicated in the cascade of events that result in myopia control? How long must overnight OK (and other myopia control strategies) be continued to avoid rebound effects? How can the effects of overnight OK on axial elongation be optimized for all myopic children to improve the overall efficacy of this modality for myopia control?

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Abbreviations and Acronyms:
BL = baseline; **D** = diopters; **GP** = gas permeable; **M** = spherical equivalent refractive error; **OK** = orthokeratology; **Q** = corneal asphericity; r_o = apical radius of curvature; **Reg** = regression.

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