



Safety and efficacy following 10-years of overnight orthokeratology for myopia control

Takahiro Hiraoka¹ , Yasuo Sekine², Fumiki Okamoto¹, Toshifumi Mihashi¹ and Tetsuro Oshika¹

¹Faculty of Medicine, Department of Ophthalmology, University of Tsukuba, Ibaraki, and ²Kashiwa Eye Clinic, Chiba, Japan

Citation information: Hiraoka T, Sekine Y, Okamoto F, Mihashi T & Oshika T. Safety and efficacy following 10-years of overnight orthokeratology for myopia control. *Ophthalmic Physiol Opt* 2018; 38: 281–289. <https://doi.org/10.1111/opo.12460>

Keywords: long-term, myopia control, myopia progression, orthokeratology, schoolchildren, soft contact lens

Correspondence: Takahiro Hiraoka
E-mail address: thiraoka@md.tsukuba.ac.jp

Received: 17 October 2017; Accepted: 25 February 2018

Abstract

Purpose: To compare rates of myopia progression and adverse events between orthokeratology (OK) and soft contact lens (SCL) wearers over a 10-year period in schoolchildren.

Methods: Medical records of consecutive patients (≤ 16 years of age at baseline) who started OK for myopia correction and continued the treatment for 10 years were retrospectively reviewed. For the control group, patients who started using soft contact lenses (SCLs) for myopia correction and continued to use them for 10 years were also reviewed. Clinical data, including sex, age, manifest refraction, visual acuity, prescription lens power, and adverse events during the 10-year period, were recorded. Estimated myopia progression was calculated as the sum of ‘changes in prescription lens power during 10 years’ and ‘residual refractive errors at the 10-year visit,’ and was compared between groups. We also compared the incidence of adverse events between groups over the 10-year study period.

Results: A total of 104 eyes of 53 patients who underwent OK treatment and 78 eyes of 39 patients who wore SCLs fulfilled the criteria. The estimated myopia progression over the 10-year period found in the OK and SCL groups were -1.26 ± 0.98 and -1.79 ± 1.24 days, respectively; this difference was statistically significant ($p = 0.001$). Additionally, lower myopia progression was found in the OK in comparison to the SCL group at all baseline ages ($p = 0.003$ to $p = 0.049$) except at 16 years old ($p = 0.41$). No significant difference was found in the number of adverse events found between the OK (119) and SCL (103) groups ($p = 0.72$).

Conclusions: The results of this study supports the long-term efficacy and safety of OK lens wear in reducing myopia progression in schoolchildren.

Introduction

The prevalence of myopia in Western countries has been estimated to affect 20%–50% of the population,^{1–6} while that in Asian countries has been reported to be much higher^{4,7–9} (e.g., over 80% among schoolchildren in Taiwan).⁹ Of particular concern is the fact that the prevalence of myopia is rapidly increasing,^{9–13} and the condition is estimated to affect nearly 5 billion people worldwide by 2050.¹⁴

Myopia progression is associated with an increased risk of vision-threatening eye abnormalities, such as glaucoma, macular degeneration, retinal detachment, and chorioretinal degeneration.^{15–18} Additionally, patients diagnosed with

myopia at a younger age are more likely to develop severe visual impairment and blindness later in life than patients diagnosed with myopia at an older age.^{12,19,20} It should also be noted that myopia is associated with a considerable socioeconomic burden.^{21–23} Therefore, controlling myopia progression could have important implications in terms of reducing ocular-related morbidity and substantial health-care costs.

Thus far, various clinical interventions, including topical application of tropicamide,²⁴ atropine,^{25–28} pirenzepine,^{29–31} and ocular hypotensive agents^{32,33} have been used in an attempt for arresting or slowing the progression of myopia in children. However, a treatment method with optimal

efficacy, safety, economic feasibility, and mode of application has yet to be established. In a recent study, Cheung *et al.*³⁴ reported that parents who are concerned about myopia progression in their children tend to be proactive in searching for a treatment for myopia control and that orthokeratology (OK) is currently the most popular treatment option for young children in Hong Kong. Many studies have confirmed the effect of OK in slowing the progression of myopia over the last decade,^{35–41} and the results of recent meta-analyses and systematic reviews have confirmed the substantial efficacy of OK in controlling myopia progression in schoolchildren.^{42–45} Furthermore, OK lens wear has a relatively low rate of adverse events and discontinuations⁴⁶ and is well accepted by parents and children.⁴⁷ In fact, a recent systematic review of 170 publications concluded there is sufficient evidence to suggest OK is a safe option for myopia correction and retardation,⁴⁸ and the risk of microbial keratitis in overnight OK have been found to be similar to that of other modalities of overnight contact lens wear.⁴⁹ However, there have been very few studies that assessed the long-term safety and efficacy of OK lens wear in reducing myopia progression.^{50,51} Given that a substantial number of children wear OK lenses throughout childhood until early adulthood, it is crucial to elucidate the long-term efficacy and safety of OK lens wear for myopia control in children. Therefore, we assessed the long-term myopia control efficacy and safety of OK lens wear by comparing rates of myopia progression and adverse events between OK and SCL wearers over a 10-year period in schoolchildren.

Methods

Medical records of consecutive patients (≤ 16 years of age at baseline) who started OK for myopia correction after January 2002 and continued the treatment for 10 years at Kashiwa Eye Clinic were retrospectively reviewed. The exclusion criteria were as follows: presence of ocular or systemic pathologies; history of ocular trauma, surgery, previous OK treatment, or use of contact lenses; myopia less than -7 dioptre (D); ≤ 1.25 D of cylinder; spectacle corrected visual acuity (VA) at baseline $\leq 20/20$ (equivalent to 6/6 metric Snellen, 1.0 decimal or 0.00 logMAR); and nonattendance for periodic examination for over a year. For the control group, patients who started using SCLs for myopia correction and continued to use them for 10 years were enrolled if they fulfilled the above inclusion and exclusion criteria. Clinical data, including sex, age, manifest refraction, visual acuity, prescription lens power, and adverse events during the 10-year period, were recorded. This study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of University of Tsukuba Hospital. At the time of the 10-year follow-up

visit, patients were given complete information about the study, and written informed consent was obtained.

All OK patients were fitted with five-zone reverse geometry OK lenses (α ORTHO-K[®]; ALPHA Corp., Nagoya, Japan; www.alphacl.co.jp) with a nominal Dk of 104×10^{-11} (cm²/s)(mL O₂/mL-mmHg), in accordance with the manufacturer's fitting instructions. After lens dispensing, patients were recommended to wear their OK lenses for at least seven consecutive hours every day. Upon stabilization of refractive error correction, they were instructed to wear their lenses for at least five nights per week. Refraction, visual acuity, corneal topography, and lens fitting were evaluated at every visit, and the treatment lenses were generally replaced if visual acuity was found to be less than 20/25 in two successive visits (equivalent to 6/7.5 metric Snellen, 0.8 decimal or 0.10 logMAR). Even if patients reported no changes in visual acuity, the lenses were replaced on a yearly basis. The procedures for fitting, prescription, and replacement of OK lenses were all performed by a single experienced specialist (Y.S.). Subjects were provided with O₂ Care Milpha[®] solution for daily lens cleaning and disinfection and Progent[®] intensive cleaner for lens cleaning once a month (Menicon Co., Ltd., Nagoya, Japan; www.menicon.co.jp).

Control subjects in this study were fitted with the following types of SCLs: 1-Day Acuvue[®], 1-Day Acuvue[®] Moist[®], 1-Day Acuvue[®] TruEye[®], Acuvue[®] 2[®], Acuvue[®] Advance[®], or Acuvue[®] Oasys[®] (Johnson & Johnson K.K., Tokyo, Japan) (www.jnj.co.jp); Medalist[®], Medalist[®] Plus, Medalist[®] Premier, Medalist[®] Premier Toric, or Medalist[®] FreshFit[®] (Bausch + Lomb Japan, Tokyo, Japan) (www.bausch.co.jp); Menicon 1Day, 2 Week Menicon Premio, or 2 Week Menicon Premio Toric (Menicon, Nagoya, Japan) (www.menicon.co.jp); or 2 Week Aquair[®] (CooperVision Japan, Tokyo, Japan) (www.coopervision.jp). All SCLs were daily disposable or frequent replacement single-vision lenses manufactured in either hydrogel or silicone hydrogel materials. None of the subjects received multifocal or other specially designed lenses. SCLs were selected and fitted at the practitioner's description depending on the patient's ocular surface condition. The patients then selected one of the recommended lenses. During the 10-years follow-up period, patients were allowed to change to different contact lens types if such change would not affect the successful clinical performance of the lens on the eye.

We compared myopia progression over 10 years between OK and SCL groups. Myopia progression was calculated as 'change in lens power' + 'residual refractive error' over a 10-year follow-up period. Changes in prescription lens power were calculated by subtracting the final from the baseline back optic zone radius (BOZR) power of the lenses, whereas residual refractive errors were calculated as over refraction lens power (subjective refraction with the

OK lens *in situ*) required for attaining spectacle corrected VA at the final study visit. For example, if baseline and final prescribed BOZR lens powers were -3.50 D and -4.25 D, respectively, and the residual refractive error for attaining spectacle corrected VA at the 10-year visit was -0.50 D, the estimated myopia progression over 10 years was calculated as follows:

$$\begin{aligned} & \text{[Estimated myopia progression]} \\ & = \text{[Changes in lens power]} + \text{[Residual refractive errors]} \\ & = [(-4.25 \text{ D}) - (-3.50 \text{ D})] + [-0.50 \text{ D}] \\ & = [-0.75 \text{ D}] + [-0.50 \text{ D}] \\ & = [-1.25 \text{ D}] \end{aligned}$$

All baseline demographic characteristics except sex distribution were compared between the OK and SCL groups using the unpaired *t*-test. Sex distribution was compared using the chi-square test. Changes over time in refraction and visual acuity were compared between groups using a general linear model with repeated measures. As right and left eye data of myopia progression were correlated (Pearson correlation coefficient = 0.75, $p < 0.001$), right/left eye was included as a factor in the model.⁵² If the results revealed significant differences, the Bonferroni *post-hoc* test for multiple comparisons was performed to identify the time points that exhibited significant differences. For the purpose of comparison, the incidence of adverse events was calculated as a percentage of eyes per annum.⁴⁶ Recurrences of the same adverse event in the same or fellow eye at any of the subsequent study visits were classified as separate events, and bilateral events were counted as two separate events. The difference in incidence of adverse events between groups was tested with Fisher exact test. All statistical analyses were performed using PASW Statistics 18 (SPSS Inc., www.spss.com.hk). $p < 0.05$ was considered significant.

Results

A total of 104 eyes of 53 patients undergoing OK treatment (male, 24; female, 29) and 78 eyes of 39 patients who used SCLs (male, 15; female, 24) fulfilled the inclusion criteria

and were included for analysis in this study. The demographic details are summarised in *Table 1*. There were no significant differences in sex distribution, SER, UCVA, or spectacle corrected VA between the OK and control groups, although a significant intergroup difference was observed in patient age ($p < 0.001$) (*Table 1*).

In the OK group, lens power changed an average of 2.4 ± 1.1 times (range, 0–5 times) during the 10-year period. A statistically significant difference was found in average lens power between the initial (-2.47 ± 1.21 D, range: -5.25 to -0.75 D) and final prescription (-3.43 ± 1.29 D, range: -6.00 to -1.00 D) ($p < 0.001$). The average difference in lens power between the initial and final prescription was -0.95 ± 0.82 D (range, -3.00 to 0.00 D). In addition, the mean residual refractive error at the 10-year visit was -0.30 ± 0.47 D (range, -1.63 to 0.50 D). Thus, in the OK group, average myopia progression over 10 years was estimated to be -1.26 ± 0.98 D (range, -4.50 to 0.00 D). In contrast, average myopia progression in the SCL group was -1.79 ± 1.24 D (range, -6.00 to 0.25 D), which indicated a significant intergroup difference in myopia progression ($p = 0.001$).

Myopic refractive error was significantly reduced following OK treatment, and remained constant thereafter; significant differences were found at all time points in comparison to baseline ($p < 0.001$) (*Figure 1*). In contrast, in the SCL group, myopia increased over the first 5 years of lens wear and remained relatively constant thereafter ($p < 0.05$) (*Figure 1*). The changes in manifest refraction over time were statistically different between the OK and SCL groups ($p < 0.001$).

The UCVA improved significantly ($p < 0.001$) after the start of OK treatment and remained constant over the subsequent time points (*Figure 2*). Similarly, visual acuity improved significantly after initial SCL wear ($p < 0.001$), and remained constant thereafter (*Figure 2*). There was no statistically significant difference in visual acuity over time between the two correction methods ($p = 0.28$).

No statistically significant changes were found in spectacle corrected VA over the 10-year period in either the OK

Table 1. Baseline demographics for the OK and SCL groups

	OK mean \pm S.D. (range)	SCL mean \pm S.D. (range)	<i>p</i> -Value
Age (years)	11.5 \pm 2.1 (8 to 16)	13.4 \pm 2.3 (8 to 16)	<0.001*
Sex (male:female)	24:29	15:24	0.36
SER (D)	-2.63 ± 1.22 (-6.00 to -0.75)	-2.85 ± 1.68 (-6.875 to -0.50)	0.31
UCVA (logMAR)	0.80 ± 0.28 (0.15 to 1.30)	0.89 ± 0.39 (0.22 to 1.70)	0.07
Spectacle corrected VA (logMAR)	-0.12 ± 0.05 (-0.18 to 0.00)	-0.11 ± 0.06 (-0.18 to 0.00)	0.21

*Significant difference between groups by the unpaired *t*-test.

OK, orthokeratology; SCL, soft contact lens; S.D., standard deviation; SER, spherical equivalent refraction; D, dioptre; UCVA, uncorrected visual acuity; VA, visual acuity; logMAR, logarithm of the minimum angle of resolution.

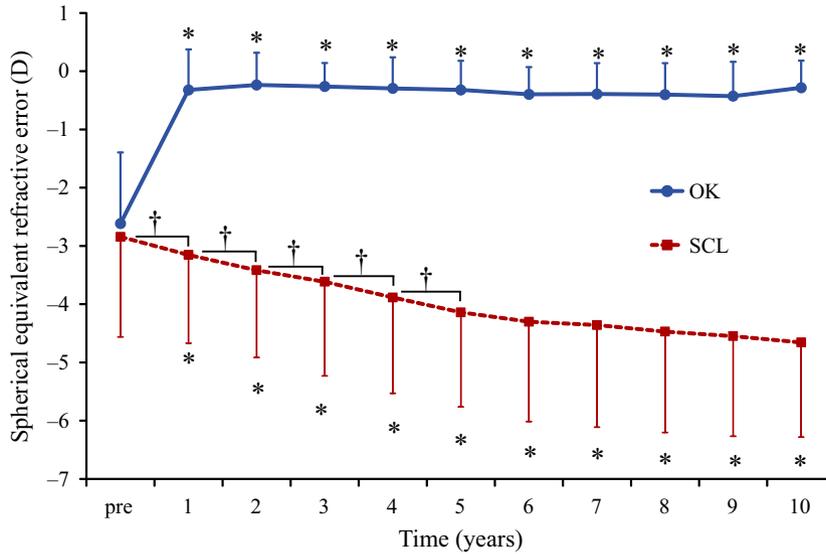


Figure 1. Changes over time in manifest refraction for the OK and SCL groups. OK, orthokeratology; SCL, soft contact lens. *Statistically significant differences compared to the baseline value by the Bonferroni *post-hoc* test. †Statistically significant differences between successive years by the Bonferroni *post-hoc* test.

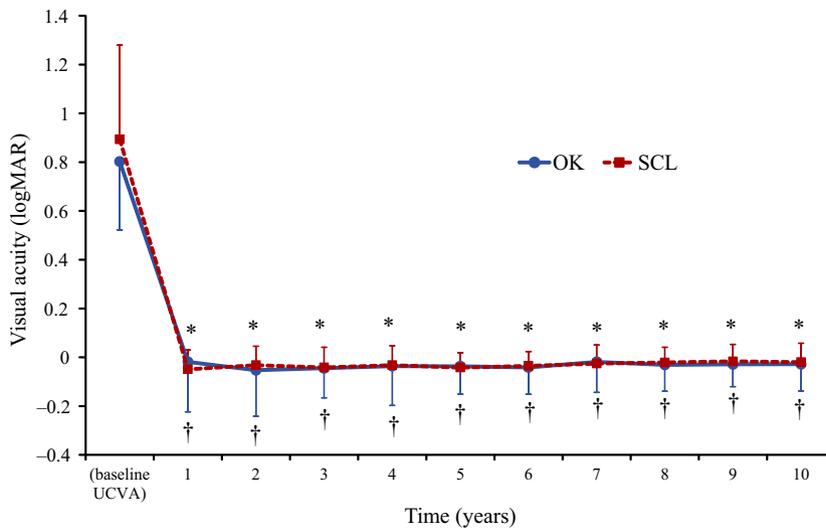


Figure 2. Time course of change in visual acuity with each correction method. OK, orthokeratology; SCL, soft contact lens; UCVA, uncorrected visual acuity. *Statistically significant differences compared to baseline in the OK group using the Bonferroni *post-hoc* test. †Statistically significant differences compared to baseline in the SCL group using the Bonferroni *post-hoc* test.

group ($p = 0.09$) or SCL group ($p = 1.00$). Additionally, no significant differences were found in spectacle corrected VA between groups ($p = 0.27$) (Figure 3).

Analysis of myopia progression over the entire 10-year period according to baseline age revealed higher levels of myopia progression in younger in compared to older children (Figure 4). Additionally, smaller amounts of myopia progression were found in the OK in comparison to the SCL group for all baseline ages ($p = 0.003$ to

$p = 0.049$) except for a baseline age of 16 years ($p = 0.41$) (Figure 4).

No significant differences were found in the number of adverse events found over the 10-year period of lens wear between the OK and SCL groups ($p = 0.72$) (Table 2). In the OK group, a total of 119 adverse events were observed in 53 eyes (51%); no adverse events were found in the remaining 51 eyes (49%). In the SCL group, a total of 103 adverse events were recorded in 43 eyes (50%), while the

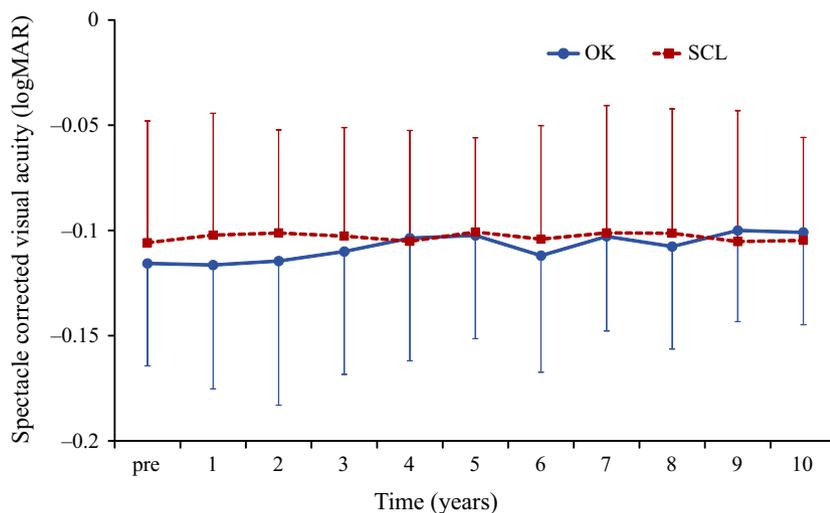


Figure 3. Time course of change in spectacle corrected visual acuity in both groups. OK, orthokeratology; SCL, soft contact lens.

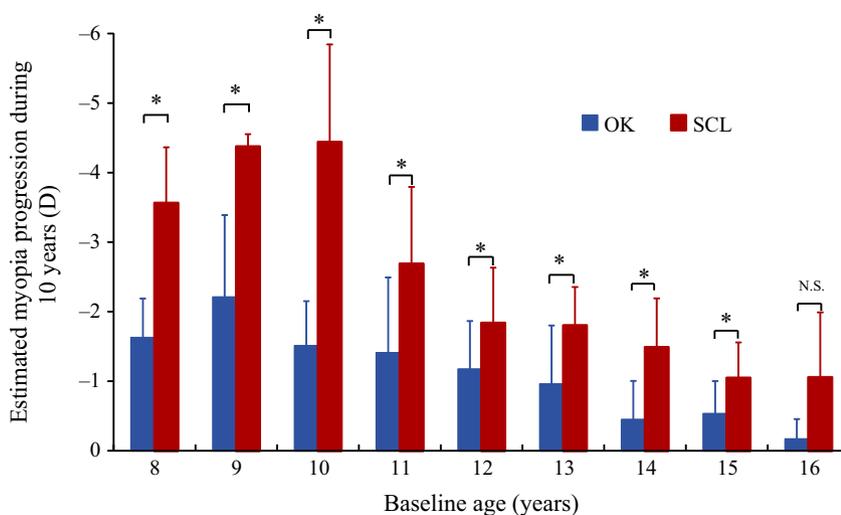


Figure 4. Estimated myopia progression over the entire 10-year lens wear period for the OK and SCL groups at each baseline age. OK, orthokeratology; SCL, soft contact lens. *Statistically significant differences between groups. n.s.: not significant.

remaining 43 eyes (50%) did not experience any adverse events. Conjunctival complications such as acute and allergic conjunctivitis and superficial punctate keratopathy were the most frequent adverse events found in both study groups. Relatively severe corneal complications such as corneal infiltration and keratitis were only observed in the OK group, showing a statistically significant higher incidence than that found in the SCL group ($p = 0.009$); however, no serious complications such as infectious keratitis were found throughout the study period. In contrast, eyelid complications such as blepharitis, hordeolum, and chalazion were only observed in the SCL group, showing a statistically significant higher incidence in comparison to that found in the OK group for hordeolum ($p = 0.001$) and chalazion ($p = 0.018$).

Discussion

To the best of our knowledge, this is the first retrospective study that has compared rates of myopia progression and adverse events between OK and SCL in schoolchildren over a period of time as long as 10 years. According to our results, the time course of change in visual acuity following OK lens wear was very similar to that observed following SCL wear. Additionally, there were no significant differences in spectacle corrected VA between the two groups throughout the 10-year study period. These findings indicate that patients wearing OK and SCL exhibited comparable vision over the study period. Myopia progression in the OK group (-1.26 ± 0.98 D) was 30% slower than that found in the SCL group (-1.79 ± 1.24 D) following

Table 2. Number and types of adverse events found over the 10-year period of lens wear for the OK and SCL groups

	OK group <i>n</i> (Incidence) ^a [95% CI]	SCL group <i>n</i> (Incidence) ^a [95% CI]	<i>p</i> -Value
Acute conjunctivitis	25 (2.4) [1.4 to 3.4]	23 (2.7) [1.5 to 3.8]	0.74
Allergic conjunctivitis	48 (4.6) [3.1 to 6.1]	29 (3.4) [1.5 to 5.2]	0.10
Phlyctenular conjunctivitis	2 (0.2) [0.0 to 0.5]	0 (0.0)	0.50
Superficial punctate keratopathy	32 (3.1) [1.9 to 4.3]	33 (3.8) [2.2 to 5.5]	0.29
Corneal erosion	1 (0.1) [0.0 to 0.29]	1 (0.1) [0.0 to 0.3]	1.00
Corneal infiltration and Keratitis	8 (0.8) [0.2 to 1.3]	0 (0.0)	0.009b
Blepharitis	0 (0.0)	3 (0.3) [0.0 to 0.7]	0.09
Hordeolum	0 (0.0)	8 (0.9) [0.2 to 1.7]	0.001b
Chalazion	0 (0.0)	5 (0.6) [0.0 to 1.2]	0.018b
Others	3 (0.3) [0.0 to 0.7]	1 (0.1) [0.0 to 0.3]	0.63
Total	119 (11.4) [8.2 to 14.6]	103 (12.0) [8.7 to 15.2]	0.72

OK, orthokeratology; SCL, soft contact lens; CI, confidence intervals.

^aIncidence of adverse events as a percentage of eyes per annum. Recurrences of the same adverse event in the same or fellow eye at any of the subsequent study visits were classified as separate events, and bilateral events were counted as two separate events.

^bSignificant difference between groups by the Fisher exact test.

10 years of lens wear, indicating that the inhibitory effect of OK lens wear on myopia progression is not limited to relatively short periods of lens wear. Two previous studies investigated the long-term efficacy of OK lens wear on myopia progression.^{50,51} A retrospective study conducted by Downie and Lowe in Australia reported OK lens wear to significantly stabilise manifest refractive errors for a treatment interval up to 8 years, although the mean duration of OK treatment was reported to be 4.90 ± 0.35 years. Furthermore, the study reported that a subpopulation of OK eyes ($n = 18$; 64%) demonstrated an apparent total arrest of manifest myopic refractive change.⁵⁰ Another study performed by Santodomingo-Rubido *et al.*⁵¹ in Spain found a reduction in the rate of axial elongation of 33% in the OK in comparison to the control group over a 7 years follow-up period; this reduction rate is very similar to that observed in the present 10-year study (30%).

Several studies have reported age to be a crucial factor influencing myopia progression.^{53–57} Furthermore, Hyman *et al.*⁵⁶ reported younger age at baseline to be the strongest independent factor correlated with faster myopia progression. We found less myopia progression in the OK in comparison to the SCL group for all baseline ages, except for the 16 years old. The insignificant intergroup difference in myopia progression among subjects with baseline age of 16 years may be attributed to the decreased rate of myopia progression with increasing age, thereby making it challenging to find significant differences in myopic progression between groups in older patients.^{53–57} Nevertheless, this finding is encouraging for children with myopia and their parents, who may be concerned about the future progression of myopia.

Cho and Cheung⁵⁸ reported the rate of axial elongation to increase when OK lens wear was discontinued following 2 years of lens wear before or at the age of 14 years,

suggesting that early termination of OK treatment might not be optimal for retaining the myopia control effect. The long-term effect of discontinuing OK treatment on axial elongation and myopia progression remains unknown. Several studies have reported the mean age at myopia stabilization to be 15–17 years.^{59–61} Thus, it is important to continue therapy until late in the second decade of life, when eye growth and myopia progression becomes stable. We believe that continuing treatment for prevention of myopia until crossing the age of myopia stabilization is beneficial. It is possible that the rebound phenomenon may be avoided or minimised even if a subject discontinues treatment after receiving OK for 10 years. Further studies should be conducted to clarify this point.

As for adverse events, the incidence of corneal complications such as corneal infiltration and keratitis was significantly higher in the OK group than in the SCL group, whereas the incidence of eyelid complications such as hordeolum and chalazion was significantly higher in the SCL group than in the OK group; however, no significant difference in the total incidence was observed. Additionally, there were no incidences of infectious keratitis during the study period. All complications resolved by discontinuing lens wear for a short period of time (i.e., ranging from a few days to 2 weeks) and/or by application of eye-drops (i.e., antibacterial and anti-inflammatory agents, sodium hyaluronate, artificial tears and steroids), and all affected patients resumed lens wear after resolution of complications, which indicates the acceptable safety of OK treatment over long periods of lens wear.

This study has several limitations. First, OK and SCL groups were not matched in terms of baseline age, which is likely to reflect on the normal characteristics of Japanese children wearing OK and SCL. Children wearing OK

normally handle their contact lenses at home, frequently under parental supervision, whereas children wearing SCLs normally handle contact lenses throughout the day by themselves. Consequently, it might not be uncommon for OK lens wearers to be slightly younger than SCL wearers. Second, axial length was not evaluated in this study. Nowadays, optical biometry using low-coherence interferometry technology allows precise and repeatable objective measurements of axial length,⁶² the key structural correlate of myopia progression and thus considered the gold standard to quantify changes in axial elongation associated to myopia progression in OK-treated eyes.⁶³ It cannot be denied that the lack of such key outcome variable in this study reduced the reliability of the results and conclusions. Third, even though only single vision SCLs were prescribed to the SCL cohort, differences in design between lens types can yield different peripheral refraction profiles, depending on the eccentricity, power, and the modulus of the lenses, which could ultimately affect the rate of myopia progression. Thus, the design and material of SCL should be uniformed in future studies. Fourth, the present study is limited by its retrospective design, which might have lead to inter- and intra-observer bias as well as selection bias. Ideally, prospective, randomised, long-term clinical trials involving axial-length measurements should be conducted to verify the findings of the present; however, it would be quite difficult to execute such a long-term prospective study over a 10-year period. For this reason, we believe that the present retrospective study provide valuable findings related to long-term safety and efficacy of OK lens wear in reducing myopia progression. Additionally, a major strength of this study is its relatively large sample size, which is the largest employed so far in studies of this kind.

In conclusion, the present findings showed that OK treatment was effective in slowing myopia progression over a 10-year treatment period and demonstrated a clinically acceptable safety profile among patients between the ages of 8 and 16 years. Patients undergoing OK treatment do not need to wear any vision-correction aids during daytime, which is advantageous and convenient for performing daily activities. Further studies are warranted to confirm the findings of this study.

Disclosure

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Sveinsson K. The refraction of Icelanders. *Acta Ophthalmol (Copenh)* 1982; 60: 779–787.
2. Sperduto RD, Seigel D, Roberts J & Rowland M. Prevalence of myopia in the United States. *Arch Ophthalmol* 1983; 101: 405–407.
3. Wang Q, Klein BE, Klein R & Moss SE. Refractive status in the Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci* 1994; 35: 4344–4347.
4. Saw SM, Katz J, Schein OD, Chew SJ & Chan TK. Epidemiology of myopia. *Epidemiol Rev* 1996; 18: 175–187.
5. Katz J, Tielsch JM & Sommer A. Prevalence and risk factors for refractive errors in an adult inner city population. *Invest Ophthalmol Vis Sci* 1997; 38: 334–340.
6. Wu SY, Nemesure B & Leske MC. Refractive errors in a black adult population: the Barbados Eye Study. *Invest Ophthalmol Vis Sci* 1999; 40: 2179–2184.
7. Lin LL, Chen CJ, Hung PT & Ko LS. Nation-wide survey of myopia among schoolchildren in Taiwan, 1986. *Acta Ophthalmol* 1988; 185(suppl): 29–33.
8. Chow YC, Dhillon B, Chew PT & Chew SJ. Refractive errors in Singapore medical students. *Singapore Med J* 1990; 31: 472–473.
9. Lin LL, Shih YF, Tsai CB *et al.* Epidemiologic study of ocular refraction among schoolchildren in Taiwan in 1995. *Optom Vis Sci* 1999; 76: 275–281.
10. Hosaka A. The growth of the eye and its components. Japanese studies. *Acta Ophthalmol* 1988; 185(suppl): 65–68.
11. Mutti DO & Bullimore MA. Myopia: an epidemic of possibilities? *Optom Vis Sci* 1999; 76: 257–258.
12. Tan NW, Saw SM, Lam DS *et al.* Temporal variations in myopia progression in Singaporean children within an academic year. *Optom Vis Sci* 2000; 77: 465–472.
13. Vitale S, Sperduto RD & Ferris FL 3rd. Increased prevalence of myopia in the United States between 1971–1972 and 1999–2004. *Arch Ophthalmol* 2009; 127: 1632–1639.
14. Holden BA, Fricke TR, Wilson DA *et al.* Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology* 2016; 123: 1036–1042.
15. Goldschmidt E. Ocular morbidity in myopia. *Acta Ophthalmol* 1988; 185(suppl): 86–87.
16. The Eye Disease Case-Control Study Group. Risk factors for idiopathic rhegmatogenous retinal detachment. *Am J Epidemiol* 1993; 137: 749–757.
17. Mitchell P, Hourihan F, Sandbach J & Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology* 1999; 106: 2010–2015.
18. Saw SM, Gazzard G, Shih-Yen EC & Chua WH. Myopia and associated pathological complications. *Ophthalmic Physiol Opt* 2005; 25: 381–391.
19. Jensen H. Myopia in teenagers. An eight-year follow-up study on myopia progression and risk factors. *Acta Ophthalmol Scand* 1995; 73: 389–393.

20. Braun CI, Freidlin V, Sperduto RD, Milton RC & Strahman ER. The progression of myopia in school age children: data from the Columbia Medical Plan. *Ophthalmic Epidemiol* 1996; 3: 13–21.
21. Vitale S, Cotch MF, Sperduto R & Ellwein L. Costs of refractive correction of distance vision impairment in the United States, 1999–2002. *Ophthalmology* 2006; 113: 2163–2170.
22. Lim MC, Gazzard G, Sim EL, Tong L & Saw SM. Direct costs of myopia in Singapore. *Eye (London)* 2009; 23: 1086–1089.
23. Smith TS, Frick KD, Holden BA, Fricke TR & Naidoo KS. Potential lost productivity resulting from the global burden of uncorrected refractive error. *Bull World Health Organ* 2009; 87: 431–437.
24. Schwartz JT. Results of a monozygotic cotwin control study on a treatment for myopia. *Prog Clin Biol Res* 1981; 69: 249–258.
25. Shih YF, Chen CH, Chou AC et al. Effects of different concentrations of atropine on controlling myopia in myopic children. *J Ocul Pharmacol Ther* 1999; 15: 85–90.
26. Chua WH, Balakrishnan V, Chan YH et al. Atropine for the treatment of childhood myopia. *Ophthalmology* 2006; 113: 2285–2291.
27. Fan DS, Lam DS, Chan CK et al. Topical atropine in retarding myopic progression and axial length growth in children with moderate to severe myopia: a pilot study. *Jpn J Ophthalmol* 2007; 51: 27–33.
28. Tong L, Huang XL, Koh AL et al. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. *Ophthalmology* 2009; 116: 572–579.
29. Siatkowski RM, Cotter S, Miller JM et al. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. *Arch Ophthalmol* 2004; 122: 1667–1674.
30. Tan DT, Lam DS, Chua WH & Shu-Ping DF, Crockett RS; Asian Pirenzepine Study Group. One-year multicenter, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *Ophthalmology* 2005; 112: 84–91.
31. Siatkowski RM, Cotter SA, Crockett RS et al. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *J AAPOS* 2008; 12: 332–339.
32. Jensen H. Timolol maleate in the control of myopia. A preliminary report. *Acta Ophthalmol* 1988; 185(suppl): 128–129.
33. Wiener M. The use of epinephrine in progressive myopia. *Am J Ophthalmol* 1931; 14: 520–522.
34. Cheung SW, Lam C & Cho P. Parents' knowledge and perspective of optical methods for myopia control in children. *Optom Vis Sci* 2014; 91: 634–641.
35. Walline JJ, Jones LA & Sinnott LT. Corneal reshaping and myopia progression. *Br J Ophthalmol* 2009; 93: 1181–1185.
36. Kakita T, Hiraoka T & Oshika T. Influence of overnight orthokeratology on axial elongation in childhood myopia. *Invest Ophthalmol Vis Sci* 2011; 52: 2170–2174.
37. Cho P & Cheung SW. Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. *Invest Ophthalmol Vis Sci* 2012; 53: 7077–7085.
38. Charm J & Cho P. High myopia-partial reduction ortho-k: a 2-year randomized study. *Optom Vis Sci* 2013; 90: 530–539.
39. Chen C, Cheung SW & Cho P. Myopia control using toric orthokeratology (TO-SEE study). *Invest Ophthalmol Vis Sci* 2013; 54: 6510–6517.
40. Hiraoka T, Kakita T, Okamoto F, Takahashi H & Oshika T. Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: a 5-year follow-up study. *Invest Ophthalmol Vis Sci* 2012; 53: 3913–3919.
41. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortega R. Myopia control with orthokeratology contact lenses in Spain: refractive and biometric changes. *Invest Ophthalmol Vis Sci* 2012; 53: 5060–5065.
42. Si JK, Tang K, Bi HS, Guo DD, Guo JG & Wang XR. Orthokeratology for myopia control: a meta-analysis. *Optom Vis Sci* 2015; 2: 252–257.
43. Sun Y, Xu F, Zhang T et al. Orthokeratology to control myopia progression: a meta-analysis. *PLoS ONE* 2015; 10: e0124535.
44. Wen D, Huang J, Chen H et al. Efficacy and acceptability of orthokeratology for slowing myopic progression in children: a systematic review and meta-analysis. *J Ophthalmol* 2015; 2015: 360806.
45. Li SM, Kang MT, Wu SS et al. Efficacy, safety and acceptability of orthokeratology on slowing axial elongation in myopic children by meta-analysis. *Curr Eye Res* 2016; 41: 600–608.
46. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortega R. Orthokeratology vs. spectacles: adverse events and discontinuations. *Optom Vis Sci* 2012; 89: 1133–1139.
47. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortega R. Myopia control with orthokeratology contact lenses in Spain: a comparison of vision-related quality-of-life measures between orthokeratology contact lenses and single-vision spectacles. *Eye Contact Lens* 2013; 39: 153–157.
48. Liu YM & Xie P. The safety of orthokeratology – a systematic review. *Eye Contact Lens* 2016; 42: 35–42.
49. Bullimore MA, Sinnott LT & Jones-Jordan LA. The risk of microbial keratitis with overnight corneal reshaping lenses. *Optom Vis Sci* 2013; 90: 937–944.
50. Downie LE & Lowe R. Corneal reshaping influences myopic prescription stability (CRIMPS): an analysis of the effect of orthokeratology on childhood myopic refractive stability. *Eye Contact Lens* 2013; 39: 303–310.

51. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutiérrez-Ortega R & Sugimoto K. Long-term efficacy of orthokeratology contact lens wear in controlling the progression of childhood myopia. *Curr Eye Res* 2017; 42: 713–720.
52. Armstrong RA. Statistical guidelines for the analysis of data obtained from one or both eyes. *Ophthalmic Physiol Opt* 2013; 33: 7–14.
53. Saw SM, Nieto FJ, Katz J, Schein OD, Levy B & Chew SJ. Factors related to the progression of myopia in Singaporean children. *Optom Vis Sci* 2000; 77: 549–554.
54. Goss DA. Variables related to the rate of childhood myopia progression. *Optom Vis Sci* 1990; 67: 631–636.
55. Fan DS, Lam DS, Lam RF *et al.* Prevalence, incidence, and progression of myopia of school children in Hong Kong. *Invest Ophthalmol Vis Sci* 2004; 45: 1071–1075.
56. Hyman L, Gwiazda J, Hussein M *et al.* Relationship of age, sex, and ethnicity with myopia progression and axial elongation in the correction of myopia evaluation trial. *Arch Ophthalmol* 2005; 123: 977–987.
57. Cho P & Cheung SW. Protective role of orthokeratology in reducing risk of rapid axial elongation: a reanalysis of data from the ROMIO and TO-SEE studies. *Invest Ophthalmol Vis Sci* 2017; 58: 1411–1416.
58. Cho P & Cheung SW. Discontinuation of orthokeratology on eyeball elongation (DOEE). *Cont Lens Anterior Eye* 2017; 40: 82–87.
59. Goss DA & Winkler RL. Progression of myopia in youth: age of cessation. *Am J Optom Physiol Opt* 1983; 60: 651–658.
60. Thorn F, Gwiazda J & Held R. Myopia progression is specified by a double exponential growth function. *Optom Vis Sci* 2005; 82: 286–297.
61. COMET Group. Myopia stabilization and associated factors among participants in the Correction of Myopia Evaluation Trial (COMET). *Invest Ophthalmol Vis Sci* 2013; 54: 7871–7884.
62. Santodomingo-Rubido J, Mallen EA, Gilmartin B & Wolffsohn JS. A new non-contact optical device for ocular biometry. *Br J Ophthalmol* 2002; 86: 458–462.
63. Cheung SW & Cho P. Validity of axial length measurements for monitoring myopic progression in orthokeratology. *Invest Ophthalmol Vis Sci* 2013; 54: 1613–1615.