Higher order aberrations and axial elongation in combined 0.01% atropine with orthokeratology for myopia control

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Abstract

Purpose: To compare the changes in higher order aberrations (HOA’s) for photopic and mesopic pupil diameters in children undergoing orthokeratology treatment (OK) or combined 0.01% atropine with orthokeratology treatment (AOK), and their association with axial elongation.

Methods: Children aged 6 to <11 years with 1.00–4.00 D of myopia were randomly assigned to each treatment group. Photopic and mesopic pupil diameters were quantified using automated pupillometry and HOA’s were measured with a Hartmann-Shack aberrometer and Badal system to control for accommodation. HOA’s were rescaled to photopic and mesopic pupil diameters and fitted with a 6th order Zernike polynomial expansion. Axial length was measured using an optical biometer under cycloplegia.

Results: Baseline and six-month data from 25 AOK and 28 OK participants were analysed. At the six-month visit, pupil diameter was larger in the AOK group under photopic conditions (3.70 ± 0.42 vs 3.12 ± 0.33 mm, p < 0.001), along with a range of HOA metrics [3rd to 6th order and higher order root mean square error values (HO RMS), all p ≤ 0.003] and individual Zernike terms (primary spherical aberration, and oblique quadrafoil, both p ≤ 0.03). Axial elongation was greater in the OK treatment group (0.05 ± 0.08 vs −0.01 ± 0.12 mm, p = 0.02). In the AOK group, axial elongation was correlated with the increase in photopic pupil diameter (r = −0.45, p = 0.02) and with several HOA metrics; however, these associations were not observed in the OK group. Conclusion: AOK treatment resulted in increased photopic pupil size and HOA’s, and significantly less axial elongation over a six-month period compared to OK treatment alone. The improved myopia control observed with combination 0.01% atropine and orthokeratology may be a result of an enhanced optical effect due to a larger photopic pupil size.

Introduction

Orthokeratology has the greatest efficacy of all optical interventions for the reduction of axial eye growth in childhood myopia, with a greater slowing of axial elongation only observed with various concentrations of topical atropine. However, the exact optical mechanism underlying the myopia control effect of orthokeratology remains unclear. Following overnight reshaping of the anterior corneal surface from a prolate to an oblate shape, the eye exhibits a significant decrease in spherical refractive error and an increase in corneal and total ocular higher order aberrations (HOA’s).
The most notable changes in the HOA profile are a positive shift in primary spherical aberration and variations in horizontal and vertical coma related to treatment zone centration, which result in an increase in higher order root mean square error values (HO RMS) that typically stabilises after one to four weeks of lens wear. Since HOA’s cannot be corrected with a conventional spherico-cylindrical refraction they may potentially influence eye growth through a vision-dependent mechanism by altering retinal image quality, or providing a directional cue through variations in optical vergence across the pupil.

Recent longitudinal studies have reported an association between axial elongation with inherent corneal or total ocular HOA’s in spectacle-wearing children, as well as the change in total ocular HOA’s in children treated with orthokeratology. These studies have utilised fixed pupil diameters across all participants (4–6 mm) with higher levels of individual Zernike terms, such as primary spherical aberration or coma (or greater HO RMS), associated with less axial eye growth. However, the natural pupil size of individuals may be an important factor in the regulation of eye growth with myopia control interventions, given that greater treatment efficacy has been reported for orthokeratology in children with larger pupil diameters.

Despite the moderate level of myopia control efficacy with orthokeratology (a 32%–55% average reduction in axial eye growth compared to controls), treatments combining orthokeratology with low concentration atropine are now emerging. Preliminary retrospective and prospective analyses suggest the potential for enhanced myopia control efficacy for combined orthokeratology and atropine therapy compared to orthokeratology alone up to one year of treatment. While it is now established that the myopia control effect of atropine is concentration dependent (even for low concentrations), the mechanism of action of the drug is still under debate. Atropine may enhance the optical effect of orthokeratology by increasing the pupil diameter or reducing accommodation, or through an independent non-optical mechanism directly influencing ocular tissues involved in eye growth regulation (i.e., the retina, choroid or sclera).

The primary aim of this study was to compare the changes in the total HOA profile of the eye over photopic and mesopic pupil diameters in children undergoing orthokeratology alone or combined low concentration 0.01% atropine with orthokeratology, and their association with axial elongation over a six-month period, as part of a randomised clinical trial.

Methods

This study is a registered clinical trial (ClinicalTrials.gov number, NCT02955927). The experimental design and participant inclusion/exclusion criteria have been described in detail previously and are briefly outlined below. Ethical approval was obtained from the Human Subject Ethics Subcommittee of the School of Optometry of The Hong Kong Polytechnic University and the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster. The certificate for the clinical trial/medicinal test was obtained from The Pharmacy and Poisons Board of Hong Kong. All children provided assent and parents provided informed consent prior to participation, and the study followed the tenets of the Declaration of Helsinki. A sample size of 24 participants in each treatment group was required to achieve 80% power to detect a significant difference in axial elongation (0.18 mm over two years) based on previously published data.

Following an initial screening examination and mastery of lens handling, children of Chinese ethnicity aged 6 to <11 years with 1.00–4.00 D of myopia were randomly assigned to the orthokeratology group (OK) or the combined atropine and orthokeratology (AOK) group. Children with anisometropia ≥1.00 D or astigmatism >2.50 D (for an axis within 180 ± 30 degrees) or >0.50 D (for other axes) were excluded. Other exclusion criteria included any contraindications to atropine (e.g., allergy, cardiovascular disease, epilepsy) or contact lens wear, history of prior myopia control treatment or any ocular or systemic conditions that might influence refractive development. Baseline measurements were obtained after randomisation, prior to commencing orthokeratology lens wear and the six-month visit was scheduled at the same time of day as the baseline visit for each participant.

Participants were fitted with reverse geometry orthokeratology lenses (KATT BE Free Lens, Precision Technology Services, www.ptsoptics.com) using web-based software. This is a 4-zone lens design with a 6 mm optic zone diameter and overall lens diameters from 10.2 to 11.2 mm. A toric lens design was used if the corneal sagittal height [measured with a videokeratoscope (E300, Medmont, www.medmont.com.au)] differed by more than 30 µm between the horizontal and vertical meridians over an 8 mm chord diameter. A compression factor of 0.75 D was used for all lenses. Complimentary contact lens solutions (Ophtecs, www.ophtecs.com) were provided to all participants including O2 Daily Care Solution Pure (rubbing), Cleawed saline (rinsing), Cleawed GP (disinfecting), and Tiare W artificial tears (prior to lens insertion to minimise bubble formation and prior to removal in cases of lens binding). All participants were required to wear orthokeratology lenses for at least 8 h each night, and the children in the AOK group had one drop of 0.01% preservative-free atropine (Aseptic Innovative Medicine Co., www.aimedine.com.tw) instilled in each eye, 10 min prior to lens insertion each night. The single-dose atropine vials were
returned to the investigators at the next visit to monitor compliance.

Examination procedures

Pupil diameter and accommodation
The pupil diameter was measured using the OPD-Scan III (Nidek Co. Ltd, www.nidek.co.jp) with the examination room lights off (room illuminance 2 lux), following 2 min of adaptation to the dark room\(^\text{20}\) (after 1 min of exposure to normal room illuminance of 56 lux). Participants fixated the internal instrument target, which was fogged to relax accommodation. Three measurements were obtained for each eye under mesopic (10–12 cd m\(^{-2}\)) and photopic (100–150 cd m\(^{-2}\)) conditions\(^\text{21}\) (based on internal light sources within the instrument) and later averaged. Monocular amplitudes of accommodation were measured three times using the Royal Air Force rule (www.good-lite.com) with optimal distance refractive correction. The average of three consecutive measurements was used for analysis.

Aberrometry
Monochromatic total ocular aberrations were measured under mesopic lighting conditions (for a wavelength of 555 nm) without cycloplegia using a COAS (Complete Ophthalmic Analysis System) version 1.44.12 Hartmann-Shack aberrometer (Wavefront Sciences, www.wavefrontsciences.com). Participants viewed the centre of an external Maltese cross target through a beam splitter and Badal lens, with the position of the target altered to correct the distance non-cycloplegic spherical equivalent refractive error and ensure a 0 D accommodative demand. The internal fixation target within the aberrometer was turned off. Following alignment to ensure the pupil was centred on the instrument measurement axis, five repeated measurements were captured following a blink (each consisting of 25 measurements captured within \(~\text{1–2 s}\) ), which provided 125 measurements of the total ocular aberrations. The data for each participant at each study visit were then exported and screened for outliers. Individual measurements with a pupil diameter more than \(\pm 0.50\) mm beyond the sample median or HOA RMS value more than \(\pm 0.10\) \(\mu\)m beyond the sample median were excluded, and the remaining measurements were fitted with a Zernike polynomial expansion up to the 6th radial order and averaged. This data was then rescaled to the natural photopic and mesopic pupil diameters measured with the OPD-Scan III for each participant, following the method described by Schwiegerling.\(^\text{22}\) This rescaling process involved data interpolation only for the photopic pupil diameters (i.e., the COAS pupil size was always greater than the OPD-Scan III pupil diameter measured under photopic conditions), but required data extrapolation for the natural mesopic pupil diameters. For the AOK group, 86% of measurements required extrapolation of the COAS pupil diameter by 18 \(\pm 11\)% on average, compared to 88% of measurements extrapolated by 17 \(\pm 10\)% in the OK group.

Axial length
Since changes in crystalline lens thickness with accommodation can affect axial length measurements,\(^\text{23}\) axial length was measured using an IOLMaster 500 (Carl Zeiss Meditec AG, www.zeiss.com/meditec-ag) at least 30 min after the instillation of a cycloplegic agent (2 drops of 1% cyclopentolate administered 5 min apart). The first five axial length measurements with a signal to noise ratio greater than five and with a maximum within-session difference of 0.02 mm were averaged and included in the analysis.

Statistical analyses
While both eyes were examined at each visit, only data from the right eye of each participant was included for statistical analyses, given the high degree of symmetry between the fellow eyes for various ocular biometrics, including axial length and total ocular aberrations.\(^\text{24}\) All statistical analyses were conducted using SPSS Statistics Version 26 (IBM, www.ibm.com). Normality of the data was confirmed using the Kolmogorov-Smirnov test. The baseline participant demographics between the two groups of subjects were compared using unpaired t-tests and the Chi square test of proportions. A series of repeated measures analysis of variance (RM ANOVA) were used to examine the changes in pupil diameter, amplitude of accommodation, axial elongation and various HOA metrics, with one within-subject factor of visit (baseline, six months) and one between-subject factor of treatment group (AOK, OK) and their interaction (visit by group). Bonferroni-corrected post-hoc comparisons were used to examine any significant main effects or interactions.

Since it is well established that orthokeratology significantly alters numerous corneal\(^\text{25,26}\) and total ocular aberrations,\(^\text{3,27}\) and slows axial eye growth over time relative to control groups,\(^\text{1}\) the primary focus of all RM ANOVA’s was the between-group comparisons at each visit (i.e., differences between the two groups at baseline and six months) and group by visit interactions (differences in the magnitude of change between the two groups over time) rather than the within-subject effect of changes over time averaged across the two groups. Unpaired t-tests were used to compare the number of days between visits (six-month visit minus baseline visit date) and the time-of-day HOA measurements were captured at the six-month visit between the two groups. Pearson’s correlation analyses were used to
examine the association between the magnitude of change in aberration metrics and the magnitude of axial elongation. \( p \)-values of \(<0.05\) were considered statistically significant. Data are presented as the mean or mean difference and the standard deviation.

Results

The mean duration between the baseline and six-month visit was 175 days (range 149–195 days). Six participants were excluded from the analysis due to missing aberration or pupil diameter data across the study period. Table 1 displays the participant demographics at the baseline visit. There were no significant differences between the AOK and OK groups (all comparisons \( p > 0.05\)).

Pupil diameter and amplitude of accommodation

A significant group by visit interaction was observed for both photopic and mesopic pupil diameters \( (p < 0.001) \) (Table 2). No significant differences in pupil diameter were observed between the two treatment groups at the baseline visit for either lighting condition; however for the photopic condition, the AOK group exhibited a significantly larger pupil diameter at the six-month visit \( (AOK \ 3.70 \pm 0.42 \text{ mm and OK } 3.12 \pm 0.33 \text{ mm, } p < 0.001) \). Under mesopic lighting conditions, the AOK group exhibited a larger change in pupil diameter between visits compared to the OK group; however, post-hoc pairwise comparisons revealed no significant difference in the mesopic pupil diameter at the six-month visit \( (p = 0.09) \). No statistically significant differences in the amplitude of accommodation were observed between the two groups at the baseline or six-month visit \( (Table 2) \). A significant effect of time was observed \( (F = 7.79, \ p = 0.007) \), with both groups exhibiting a decrease in monocular amplitude of accommodation over time; however this was primarily due to the decrease in the AOK group \((1.2 \pm 2.1 \text{ D reduction, } p = 0.01)\) compared to the OK group \((0.5 \pm 2.4 \text{ D reduction, } p = 0.21)\).

Higher order aberrations

No significant differences were observed between the two treatment groups for any HOA terms or RMS values at the baseline visit for either the photopic or mesopic pupil diameter \((p > 0.05)\). At the six-month visit HOA measurements were captured at approximately the same time of day for both treatment groups, on average

Table 1. Participant demographics and clinical baseline data \( (AOK - 0.01\% \text{ atropine with orthokeratology; OK - orthokeratology}) \)

|                     | AOK \((n = 25)\) | OK \((n = 28)\) | \( p\)-value |
|---------------------|------------------|----------------|-------------|
| Sex (F:M)           | 16:9             | 16:12          | 0.61        |
| Age (years)         | \(8.9 \pm 1.2\)  | \(9.1 \pm 1.1\) | 0.65        |
| Cycloplegic spherical refraction (D) | \(-2.38 \pm 0.81\) | \(-2.58 \pm 0.91\) | 0.40 |
| Cycloplegic cylindrical refraction (D) | \(-0.38 \pm 0.36\) | \(-0.51 \pm 0.45\) | 0.26 |
| Amplitude of accommodation (D) | \(13.5 \pm 2.1\) | \(12.8 \pm 2.4\) | 0.27 |
| Axial length (mm)   | \(24.38 \pm 0.62\) | \(24.44 \pm 0.84\) | 0.77 |

Data is the mean and standard deviation, \( p\)-value for an independent t-test (except Chi-square test for sex comparison).

Table 2. Photopic and mesopic pupil diameters \( (\text{mean \pm standard deviation, mm}) \), amplitude of accommodation \( (D) \), and cycloplegic subjective refraction data for the 0.01% atropine with orthokeratology \( (AOK) \) and orthokeratology \( (OK) \) groups and the mean difference \( (95\% \text{ confidence interval}) \) between treatment groups at the six-month visit

| Group                  | Mean \( \pm SD \)   | Mean difference \( (95\% \text{ CI}) \) | Group x visit interaction \( (F, p) \) | Six-month between-group comparison \( (p) \) |
|------------------------|---------------------|-----------------------------------------|----------------------------------------|-----------------------------------------------|
|                        | Baseline 6 months   | AOK minus OK 6 months                   |                                        |                                              |
| Photopic pupil (mm)    |                     |                                         |                                        |                                              |
| AOK                    | \(3.24 \pm 0.28\)   | \(3.70 \pm 0.42\)                      | 0.58 \((0.37, 0.79)\)                   | 30.6, <0.001                                 | <0.001 |
| OK                     | \(3.17 \pm 0.30\)   | \(3.12 \pm 0.33\)                      |                                        |                                              |        |
| Mesopic pupil (mm)     |                     |                                         |                                        |                                              |        |
| AOK                    | \(6.34 \pm 0.76\)   | \(7.00 \pm 0.61\)                      | 0.36 \((-0.05, 0.77)\)                 | 24.75, <0.001                               | 0.09   |
| OK                     | \(6.55 \pm 0.90\)   | \(6.64 \pm 0.84\)                      |                                        |                                              |        |
| Amplitude of accommodation (D) |     |                                         |                                        |                                              |        |
| AOK                    | \(13.5 \pm 2.1\)    | \(12.3 \pm 1.6\)                       | 0.1 \((-0.8, 0.9)\)                    | 1.09, 0.30                                 | 0.89   |
| OK                     | \(12.8 \pm 2.4\)    | \(12.3 \pm 1.5\)                       |                                        |                                              |        |
| Cycloplegic spherical refraction (D) |     |                                         |                                        |                                              |        |
| AOK                    | \(-2.38 \pm 0.81\)  | \(0.64 \pm 0.63\)                      | 0.29 \((-0.03, 0.61)\)                 | 0.11, 0.74                                 | 0.07   |
| OK                     | \(-2.58 \pm 0.91\)  | \(0.35 \pm 0.52\)                      |                                        |                                              |        |
| Cycloplegic cylindrical refraction (D) |     |                                         |                                        |                                              |        |
| AOK                    | \(-0.38 \pm 0.36\)  | \(-0.53 \pm 0.45\)                     | \(-0.11 \((-0.33, 0.11)\)\)           | 2.48, 0.12                                 | 0.32   |
| OK                     | \(-0.51 \pm 0.45\)  | \(-0.42 \pm 0.35\)                     |                                        |                                              |        |
17:13 ± 2:51 h for the AOK group and 17:08 ± 3:00 h for the OK group (p = 0.91). No significant differences were observed between the two groups for ocular aberration measurements for the mesopic pupil diameter, consistent with the similar pupil diameters displayed in Table 2. Table 3 displays the RMS and individual higher order Zernike terms that were significantly different between the two treatment groups at the six-month visit. All RMS metrics (3rd to 6th order and HO RMS) and individual Zernike coefficients C(4,0) (primary spherical aberration) and C(4,−4) (oblique quadrafoil) were of greater magnitude in the AOK group compared to the OK group (all p ≤ 0.03). Figure 1 displays the mean objective refraction map28 for each treatment group, derived from higher order aberrations (radial orders 3 to 6 inclusive) for the group mean photopic pupil diameter, and highlights the difference in the optics across the pupil at the six-month visit (i.e., a noticeable increase in positive power towards the edge of the pupil, positive primary spherical aberration, in the AOK group).

### Axial elongation

RM ANOVA revealed a significant group by visit interaction (F = 6.34, p = 0.02), indicating that the axial elongation over the six-month period was significantly greater in the OK group (0.05 ± 0.08 mm) compared to the AOK group (−0.01 ± 0.12 mm). The magnitude of axial elongation was associated with the magnitude of change in photopic pupil diameter between the baseline and six-month visits in the AOK group (r = −0.45, p = 0.02), but not in the OK group (r = −0.04, p = 0.84). Correlation analyses were also conducted for the photopic pupil diameter aberration metrics, which displayed a significant between-group difference at the six-month visit (Table 3).

Table 4 shows the correlation between the change in various ocular aberrations and metrics for a photopic pupil diameter and the magnitude of axial elongation for all participants considered together, and the AOK and OK treatment groups. For all participants considered together, several significant correlations were observed, with an increase in RMS values and primary spherical aberration and oblique quadrafoil associated with less axial elongation. These trends were also observed in the AOK group (although the strength of the association varied due to differences in the sample size), but were not consistently observed in the OK group. For the OK group, none of the HOA metrics (RMS 3rd to 6th order) or individual Zernike coefficients were associated with the magnitude of axial elongation.

### Discussion

The key findings from this study were that combined atropine and orthokeratology resulted in a significantly larger photopic pupil size, elevated total ocular HOA’s, and less axial eye growth compared to orthokeratology alone. On average, eye growth in the AOK group was −0.01 ± 0.12 mm compared to 0.05 ± 0.08 mm in the OK group over six months. This is a similar trend to the one-month data from the same study (AOK −0.05 ± 0.05 mm; OK −0.02 ± 0.03 mm),16 although the data cannot be directly compared since the sample size

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**Table 3.** Summary (mean ± standard deviation, and mean difference with 95% confidence interval) of the higher order aberration analysis for photopic pupil diameters [AOK - 0.01% atropine with orthokeratology; OK – orthokeratology; C(4,0) – primary spherical aberration; C(4,−4) oblique quadrafoil]

| Metric         | Group     | Mean ± SD (µm) | Mean difference (95% CI) (µm) (AOK minus OK) | Group x visit interaction (F, p) | 6-month between-group comparison (p) |
|----------------|-----------|----------------|---------------------------------------------|---------------------------------|-------------------------------------|
|                |           | Baseline 6 months | 6 months |                                   |                                    |                                     |
| RMS 3rd order  | AOK       | 0.040 ± 0.016    | 0.138 ± 0.075 | 0.055 (0.020, 0.090) | 8.30, 0.06 | 0.003                     |
|                | OK        | 0.036 ± 0.016    | 0.083 ± 0.050 |                                    |                                    |                                     |
| RMS 4th order  | AOK       | 0.019 ± 0.010    | 0.083 ± 0.072 | 0.040 (0.011, 0.069) | 5.72, 0.02 | 0.009                     |
|                | OK        | 0.015 ± 0.006    | 0.043 ± 0.026 |                                    |                                    |                                     |
| RMS 5th order  | AOK       | 0.002 ± 0.001    | 0.017 ± 0.013 | 0.009 (0.003, 0.015) | 8.18, 0.06 | 0.007                     |
|                | OK        | 0.002 ± 0.002    | 0.009 ± 0.009 |                                    |                                    |                                     |
| RMS 6th order  | AOK       | 0.001 ± 0.001    | 0.015 ± 0.015 | 0.009 (0.002, 0.015) | 8.08, 0.06 | 0.008                     |
|                | OK        | 0.001 ± 0.001    | 0.006 ± 0.007 |                                    |                                    |                                     |
| RMS HO         | AOK       | 0.046 ± 0.016    | 0.169 ± 0.095 | 0.071 (0.030, 0.112) | 9.98, 0.03 | 0.001                     |
|                | OK        | 0.040 ± 0.014    | 0.098 ± 0.050 |                                    |                                    |                                     |
| C(4,0)         | AOK       | 0.013 ± 0.011    | 0.060 ± 0.080 | 0.054 (0.021, 0.088) | 8.22, 0.006 | 0.002                     |
|                | OK        | 0.009 ± 0.009    | 0.006 ± 0.035 |                                    |                                    |                                     |
| C(4,−4)        | AOK       | 0.003 ± 0.006    | 0.008 ± 0.021 | 0.009 (0.001, 0.017) | 4.37, 0.04 | 0.03                      |
|                | OK        | 0.002 ± 0.004    | −0.001 ± 0.006 |                                    |                                    |                                     |
in the current study was slightly reduced due to missing HOA and pupil size data for some participants. This finding is also similar to data from Kinoshita et al,15 who reported significantly reduced eye growth (mean 0.10 mm less over one year) in Japanese children treated with orthokeratology and 0.01% atropine compared to orthokeratology alone. However, in contrast to the current study, their AOK group underwent three months of orthokeratology before commencing topical atropine. Chen et al14 also reported an additive effect of 0.01% atropine with orthokeratology on axial elongation in their retrospective analysis of fast progressing myopes. Children treated with orthokeratology for one year who displayed rapid axial elongation (mean ± SD: 0.46 ± 0.16 mm year⁻¹) were switched to combination treatment, which reduced eye growth to 0.14 ± 0.14 mm year⁻¹ in the following year. However, without a control group of rapid progressors, it is difficult to attribute this slowing of axial elongation to atropine alone, since some of the myopia control effect may be related to a natural slowing of progression with age. The data from the current study supports previous research, which suggests that combination therapy of 0.01% atropine and overnight orthokeratology provides a greater myopia control effect than orthokeratology alone; however, longer-term data are still required.

The observed changes in photopic pupil diameter at the six-month visit for the AOK group (on average 0.47 ± 0.39 mm or 14% larger than baseline) were also consistent with previous studies of low concentration atropine when considered as a percentage change to account for methodological differences in pupil size measurements (for example, a 0.69 mm or 11% increase19 and a 0.74 mm or 16% increase29). While a larger pupil diameter was observed in the AOK group under both photopic and mesopic conditions, this difference was only significant under photopic conditions (0.58 mm or 19% larger than the OK group). This larger photopic pupil diameter may be a potential factor contributing to the enhanced myopia control efficacy of AOK compared to OK alone, through an optical mechanism, given the exponential relationship between pupil size and increasing levels of HOA’s across all ages.30

After six months of orthokeratology, significant changes in the ocular HOA profile were observed in both treatment groups (Table 3), as anticipated, based on previous studies of corneal reshaping in children.10,31 No significant

Figure 1. Objective refraction maps derived from the total ocular wavefront (higher order Zernike coefficients from the 3rd to 6th radial order) for the photopic pupil diameter of each participant at each study visit (the mean group pupil diameter is listed in each panel). Note the significant difference in the distribution of refractive error across the pupil diameters between the treatment groups (AOK – 0.01% atropine with orthokeratology; OK – orthokeratology) at the six-month visit.
differences were observed between the two treatment groups with respect to HOA’s for mesopic pupil diameters. However, when aberration data was rescaled to the photopic pupil diameter for each participant, on average, the AOK group displayed elevated HOA metrics (3rd to 6th order RMS, and HO RMS) and greater levels of primary spherical aberration and oblique quadrafoil compared to the OK group. These between-group differences in the HOA’s could be due to either the increase in pupil diameter, or the partial paralysis of accommodation due to low concentration atropine (i.e., a relaxation of tonic accommodation) or the partial paralysis of accommodation due to low concentration atropine (i.e., a relaxation of tonic accommodation). To identify the cause of the greater level of HOA’s in the OK group, HOA data were also compared across fixed pupil diameters, to examine the effect of cycloplegia alone (i.e., controlling for pupil size between the two groups). When the HOA data were rescaled to a 3-mm fixed photopic pupil diameter, no significant differences in HOA terms or RMS error values were found between the two groups (all $p > 0.05$). This indicates that the observed differences in the HOA profile were due to the increased pupil diameter, rather than partial paralysis of accommodation.

A limitation of the current study was that the duration of time between lens removal and the measurement of HOA’s was not standardised across all participants at the six-month visit. Since the orthokeratology-induced changes in HOA’s regress over the course of the day, this would introduce some uncontrolled variability in the HOA data between each participant. However, because children were randomly allocated to each treatment group, this variation would likely be similar across both the AOK and OK groups. The timing of the HOA measurements at the six-month visit was not significantly different between the two groups, so any variability in HOA regression would be related to the time of lens removal. Stillitano et al. examined the stability of ocular HOA’s over the course of the day in adults treated with orthokeratology for six months. For a 6.5 mm pupil diameter, on average, a 0.042 μm reduction in C(4,0) was observed between 5 and 10 h after lens removal. Rescaling this data to the average photopic pupil diameters at the six-month visit in the current study suggests that the variability in C(4,0) due to a 5 h difference in the time of lens removal would be reasonably small; a variation of 0.002 μm and 0.004 μm for the for the OK and AOK group respectively.

Another limitation relates to the extrapolation of wavefront data obtained using the COAS to a larger natural mesopic pupil diameter measured by the OPD III scan, since the extrapolation of Zernike polynomials to a larger pupil diameter can result in inaccurate wavefront data. However, the extent of extrapolation was similar between the two treatment groups and no statistically significant differences were observed for all HOA metrics for the natural mesopic pupil size. It should also be noted that corneal flattening and thinning following orthokeratology will alter the main findings of the study.

In the AOK group, moderate statistically significant correlations were observed between the increased various photopic RMS error values with axial elongation over the six-month period (3rd, 5th, 6th and HO RMS), with greater increases in RMS values associated with less eye growth. Interestingly this was not observed in the OK group, despite significant increases in HOA’s with corneal

| Metric | All participants ($n = 53$) | AOK ($n = 25$) | OK ($n = 28$) |
|--------|-----------------------------|---------------|---------------|
|        | $r$ (95% CI) | $p$-value | $r$ (95% CI) | $p$-value | $r$ (95% CI) | $p$-value |
| RMS 3rd order | $-0.51\left(-0.69, -0.28\right)$ | <0.0001 | $-0.48\left(-0.74, -0.11\right)$ | 0.02 | $-0.37\left(-0.65, 0.00\right)$ | 0.05 |
| RMS 4th order | $-0.38\left(-0.59, -0.12\right)$ | 0.005 | $-0.37\left(-0.67, 0.03\right)$ | 0.07 | $-0.14\left(-0.49, 0.25\right)$ | 0.48 |
| RMS 5th order | $-0.36\left(-0.57, -0.10\right)$ | 0.008 | $-0.50\left(-0.75, -0.13\right)$ | 0.01 | $0.21\left(-0.18, 0.54\right)$ | 0.28 |
| RMS 6th order | $-0.35\left(-0.57, -0.09\right)$ | 0.01 | $-0.44\left(-0.71, -0.06\right)$ | 0.03 | $0.25\left(-0.14, 0.57\right)$ | 0.2 |
| RMS HO | $-0.54\left(-0.71, -0.32\right)$ | <0.0001 | $-0.52\left(-0.76, -0.16\right)$ | 0.01 | $-0.35\left(-0.64, 0.03\right)$ | 0.07 |
| C(4,0) | $-0.29\left(-0.52, -0.02\right)$ | 0.04 | $-0.22\left(-0.57, 0.19\right)$ | 0.29 | $-0.11\left(-0.46, 0.27\right)$ | 0.58 |
| C(4,−4) | $-0.45\left(-0.64, -0.21\right)$ | <0.001 | $-0.52\left(-0.76, -0.16\right)$ | 0.01 | $0.12\left(-0.26, 0.47\right)$ | 0.54 |

C(4,0) – primary spherical aberration, C(4, −4) oblique quadrafoil.
reshaping. Other authors have observed an association between the increase in 3rd order and HO RMS values with axial elongation in children treated with orthokeratology alone, and hypothesised that elevated aberrations (irrespective of the sign of the coefficient) may provide a visual signal that slows eye growth. Some authors have also reported a strong association between more positive primary spherical aberration and slower eye growth in both spectacle-wearing children and those treated with orthokeratology. While a significant difference in spherical aberration was observed between the two treatment groups after six months (mean 0.54 μm more positive primary spherical aberration in the AOK group), the magnitude of change in spherical aberration was not associated with the extent of eye growth (Table 4). With respect to analyses of HOA’s and eye growth in children treated with orthokeratology, this is the first study to examine the change in the optics of the eye using the natural pupil diameters rather than a fixed pupil size. Previous work has found that orthokeratology treatment has greater myopia control efficacy in children with larger pupil sizes, potentially related to changes in spherical aberration or peripheral myopic defocus. Therefore, when comparing optical changes or myopia control efficacy between treatments, it may be important to consider (or account for) the natural pupil size of participants. In the current study, natural pupil diameters were used to assess higher order aberrations during distance fixation, however future research examining the effects of combined atropine and orthokeratology during accommodation with natural pupil diameters may be of interest, given the association between near work and myopia.

The moderate correlations observed between the change in pupil size and HOA metrics with axial eye growth in the AOK group but not the OK group suggest that the combination treatment may provide greater regulation of eye growth through an optically-mediated mechanism. It cannot be ruled out that antimuscarinic agents may simply act directly on the ocular tissues involved in the regulation of eye growth (retina, choroid, sclera) without the involvement of an optical mechanism, and the observed changes in pupil diameter and HOA’s are simply a consequence of the treatment that does not influence myopia control efficacy. However, 0.01% atropine alone has minimal effect on the slowing of axial elongation in Chinese children during the first four to eight months of treatment; 0.03–0.04 mm (13%–19%) less eye growth compared to age-matched spectacle-wearing children. Additionally, improved myopia control efficacy in children with naturally larger scotopic pupils (without the use of pharmacological agents) reported previously does support the involvement of an optical pathway. In summary, nightly 0.01% atropine in combination with overnight orthokeratology resulted in significantly less axial eye growth compared to an age- and sex-matched control group of myopic children treated with orthokeratology alone over a six-month period. As anticipated, 0.01% atropine caused a small but significant increase in pupil diameter, which resulted in elevated levels of HOA’s (3rd to 6th order and HO RMS values, primary spherical aberration, and oblique quadrafoil) compared to the OK group for a photopic pupil size. The change in photopic pupil diameter and a number of HOA RMS metrics were moderately associated with the extent of axial eye growth in the AOK group, supporting the theory that the greater efficacy of myopia control observed in the combination treatment may be partly related to an enhanced optical effect.

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Author contribution

Stephen J Vincent: Conceptualization (equal); Data curation (equal); Formal analysis (lead); Methodology (supporting); Software (lead); Writing-original draft (lead); Writing-review & editing (lead). Qi Tan: Data curation (lead); Formal analysis (equal); Investigation (lead); Methodology (equal); Writing-review & editing (supporting). Alex Ng: Writing-review & editing (supporting). George Cheng: Conceptualization (equal); Funding acquisition (equal); Writing-review & editing (equal). Victor Woo: Funding acquisition (equal); Methodology (equal); Supervision (equal). Pauline Cho: Conceptualization (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Resources (lead); Supervision (lead); Writing-review & editing (supporting).

Conflict of interest

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

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