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Interaction of retinal electrophysiology and novel orthokeratology lens use on myopia control efficacy in children

Kai Yip Choi [1], Gigi Tsz King Wong,[1] Sonia Seen Hang Chan [1], Thomas Chuen Lam [1,2,3] Henry Ho-lung Chan [1,2,3]

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[1]School of Optometry, The Hong Kong Polytechnic University, Hong Kong SAR, Hong Kong
[2]Research Centre for SHARP Vision, The Hong Kong Polytechnic University, Hong Kong SAR, Hong Kong
[3]Centre for Eye and Vision Research, 17W Hong Kong Science Park, Hong Kong SAR, Hong Kong

Correspondence to
Prof Henry Ho-lung Chan; henryhl.chan@polyu.edu.hk and Dr Thomas Chuen Lam; thomas.c.lam@polyu.edu.hk

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ABSTRACT

Aims The relationship between retinal electrophysiological function and myopia progression was evaluated in school-aged children wearing Breath-O-Correct Orthokeratology (OK) lenses compared with those wearing single vision (SV) lenses over 24 months.

Methods In this randomised, single-blind, parallel controlled trial, children aged 8–12 years with −1.00 to −4.00 D of myopia were recruited. Retinal function was evaluated using global-flash multifocal electroretinography at baseline before OK or SV treatment. Axial length was evaluated at 6-month intervals up to 24 months. The main outcome measures were axial elongation (AE) between groups and the interactive effect of baseline retinal function.

Results A total of 70 children (43 OK, 9.8±1.3 years; 27 SV, 9.5±1.4 years) completed the 2-year study and were included in the analysis. The 2-year normalised AE was 0.37±0.37 mm in the OK group and 0.60±0.41 mm in the SV group, respectively. For children in the SV group, the amplitude of the central inner retinal response was negatively correlated with axial length elongation (p=0.03). In contrast, this relationship between retinal electrophysiology and AE was not observed in OK group, indicating that they were independent of each other in children treated with OK (p=0.33).

Conclusion A weak retinal electrophysiological response was a risk factor for rapid AE in SV controls. However, OK treatment can lower this risk factor and significantly reduce AE in school-aged children.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Myopia has become a significant public health concern. There are many risk factors identified for myopia progression, and myopia control interventions have been adopted to retard its progression.

WHAT THIS STUDY ADDS

⇒ A sub-clinically weak retinal electrophysiology at the central retina was identified as a risk factor for rapid myopia progression. The use of orthokeratology (OK) can eliminate this risk factor.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We previously reported that children with weak retinal electrophysiology can be a good candidate for 0.01% atropine myopia control intervention. With the results of OK, the current study provided further evidence for determining whether myopia control interventions are likely to be useful in a child.

INTRODUCTION

Myopia has increased dramatically in recent decades, affecting more than 1.5 billion of the global population.[1] If the condition progresses into high myopia, these myopes have a considerably higher likelihood of developing various serious ocular complications, including glaucoma, macular degeneration and retinal detachment, causing irreversible vision loss.[2–4] Therefore, it is critical to identify potential fast myopia progressors early and implement myopia control intervention to retard rapid progression, which can help relieve personal and socioeconomic burdens.[5–7]

Effective and commonly adopted myopia control interventions include low-dose atropine,[8–10] specialty spectacle lens[11 12] and orthokeratology (OK).[13–15] While the efficacy of low-dose atropine at 0.01% concentration is controversial,[9 10 16] optical myopia control regimens provide a more stable treatment effect.[12] Combined with other clinical factors, such as ocular health conditions and compliance, it is essential for eye care practitioners to determine a suitable myopia control intervention for their patients. However, the scientific evidence for these clinical decisions is still inadequate to assist practitioners in choosing the optimal treatment with good myopia control efficacy for individuals.

Risk factors have been determined for a rapid myopia progression, including baseline refraction, age of myopia onset, parental myopia and environmental exposure.[17 18] In recent studies, the relationship between retinal electrophysiology and myopia progression in school-aged children has been identified.[16 19 20] It was revealed that a weakened central inner retinal electrophysiological response at baseline was a potential risk factor for subsequent rapid myopia progression after controlling for various confounders. Thus, the likelihood of myopia progression in children can be predicted by evaluating central inner retinal function.

This group has recently conducted a randomised placebo-controlled clinical trial evaluating the myopia control efficacy of 0.01% atropine over 18 months, and its interaction with retinal electrophysiology.[16] Although the intervention did not significant differences in myopia progression for the overall group, 0.01% atropine was found to be effective in children with a weak baseline central inner retinal function, suggesting a significant interaction between the pharmacological intervention and retinal electrophysiology. However, whether this interaction would also exist in patients undergoing OK remains unclear. The Myopia Control Efficacy and Long-term Safety of a Novel Orthokeratology lens (MESOK) study aimed to evaluate the interaction of baseline retinal electrophysiological function in children treated with OK.

METHODS

The MESOK study design has been recently described for reports on clinical and proteomic parameters.[14] In brief, it was a single-blind, randomised, spectacle-controlled study, which enrolled normal-sighted children aged 8–12 years with −1.00 to −4.00 D of spherical equivalent refraction (SER). Participants in the intervention group received Breath-O-Correct OK lens (SEED Co, Tokyo, Japan), while the participants in the control group were prescribed with single vision (SV) spectacles lenses (Stellify, Hoya Vision, Tokyo, Japan) after randomisation. Information regarding the study is available online (https://clinicaltrials.gov/ct2/show/NCT03919396).

The recruitment period was between April 2019 and April 2020, with data collection completion in April 2022. All clinical procedures were conducted in the Optometry Research Clinic of The Hong Kong Polytechnic University. Axial length (AL) was measured five times by IOLMaster 500 (Carl Zeiss, Dublin, CA) and evaluated at 6-month intervals up to 24 months. SER was measured 30 min after instillation of two drops of 1% cyclopentolate using an open-field autorefractor (NVision K5001, Shin-Nippon, Japan) on five occasions. Due to the COVID-19 lockdown, some scheduled visits were delayed, which was accounted for by normalising the axial elongation (AE) by dividing the total AE by the number of months between baseline and follow-up visit, then multiplying by 12 and 24 for the 12- and 24-month analyses, respectively.

Retinal electrophysiology

The retinal function was measured at baseline by global flash multifocal electroretinography (MOFO mfERG) (VERIS Science 6.0.6d19, Electro-Diagnostic Imaging, Milpitas, CA). The measurement was only conducted when mydriasis achieved a minimum pupil diameter of 7 mm. A Dawson-Trick-Litzkow thread was used as the active electrode, which was placed between the cornea and palpebral conjunctiva. For the reference and ground electrodes, gold-cup surface electrodes, placed 2 cm temporally to the outer canthi and on the forehead, respectively, were used. The stimulus pattern was displayed on a 23.6-inch monitor with a 60 Hz refresh rate (S24E650PL, Samsung, South Korea) at 40 cm, with a viewing distance-adjusted spherocylindrical correction based on the cycloplegic refraction. The stimulus pattern consisted of 61 scaled hexagons and subtended 44° and 40° of horizontal and vertical visual fields, respectively (figure 1).

The MOFO mfERG is a specialised paradigm to better isolate the inner retinal response.[21] The paradigm started with a multifocal frame (M), followed by a dark frame (O), then a global flash frame (F) and finally a second dark frame (O). This sequence was repeated for 2^{12}–1 times to acquire spatial localisation of the retinal responses. The entire measurement lasted for approximately 4 min, which was divided into 16 segments. Subjects were given rest between segments to improve fixation stability. The luminance for the bright and dark hexagons and background were 140, 48 and 94 cd/m^2, respectively, to achieve 49% contrast. The bandpass filter was set at 10–200 Hz

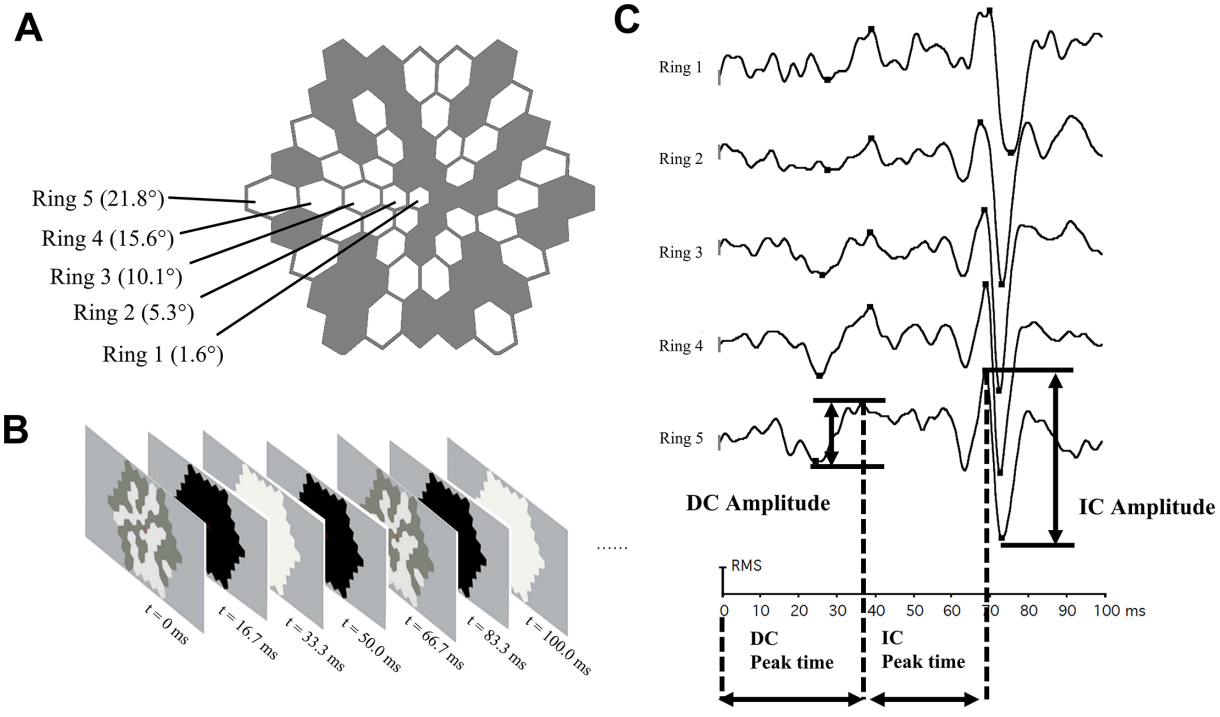

Figure 1 Global flash multifocal electroretinography. (A) Stimulus pattern. (B) Temporal sequence. (C) Measurement of direct component (DC) and induced component (IC).

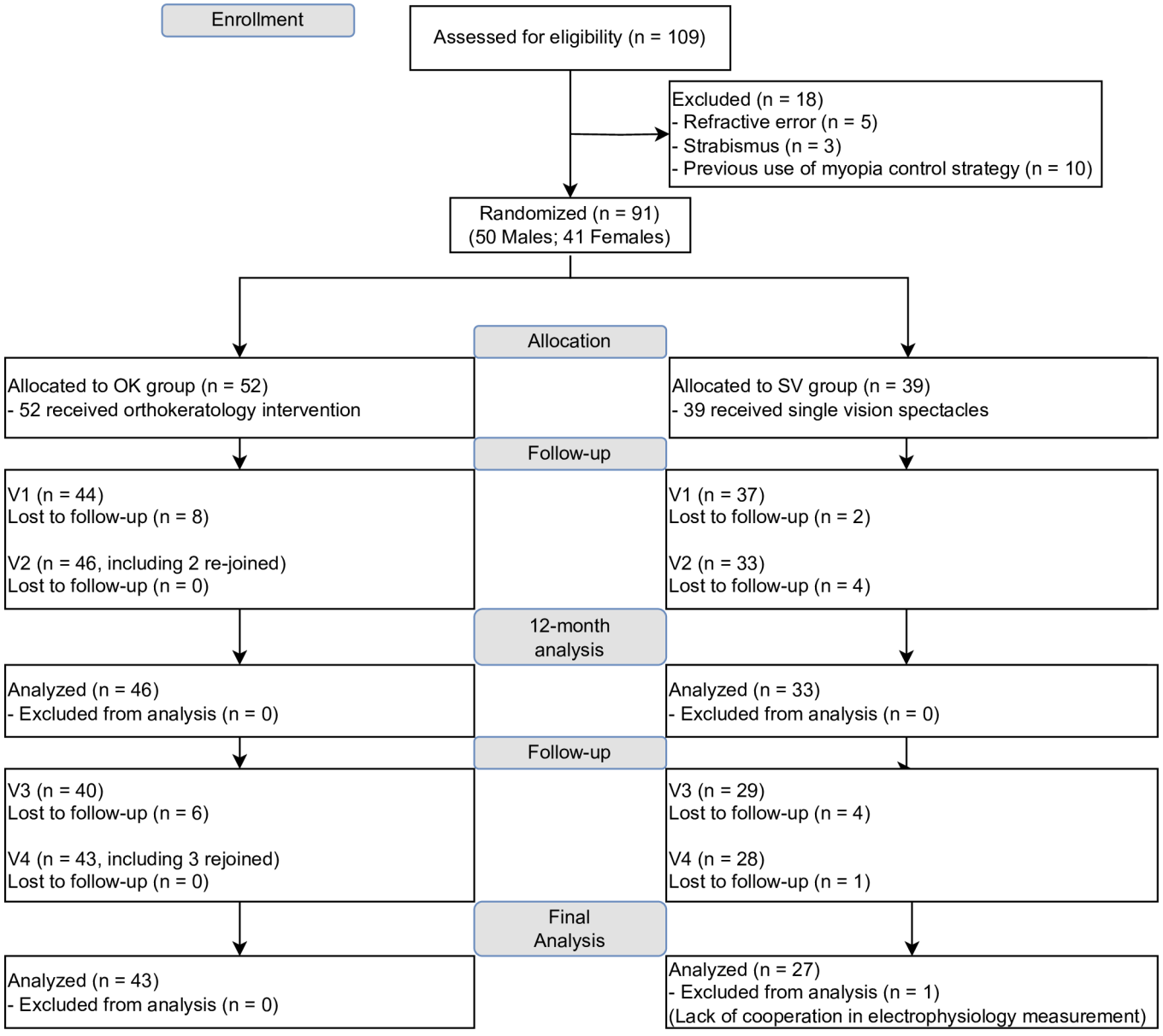

Figure 2 Consolidated Standards of Reporting Trials diagram. OK, orthokeratology; SV, single vision.

with signal gain of 100 k during the recording process. Post-acquisition analysis pooled localised retinal responses into five concentric regions: Rings 1–5 with increasing retinal eccentricity. In each waveform, the direct and induced components (DC and IC), reflecting outer and inner retinal functions, respectively, were determined, and the amplitudes and peak times were measured.[21]

Statistical analysis

As previously reported, the OK group had a significantly slower AE in both the 12- and 24-month analyses.[14] The current study focused on the effect of baseline retinal response on AE of the OK and SV groups. All statistical procedures for clinical data were performed using SPSS V.22.0 (IBM, Armonk, NY, USA). Owing to the strong correlation between right and left eyes ($r=0.89$, $p<0.001$), only clinical data from the right eyes were analysed. The age-controlled relationship between baseline retinal function and normalised AE was evaluated using general linear models and partial correlations. Additionally, the correlation coefficients regarding retinal function and AE of OK and SV groups were compared using Fisher's R-to-Z transformation test. Hochberg's adjustment was applied for multiple comparisons, with significance level set at $p\leq0.05$. The predictive value of retinal function on fast AE, that is, ≥0.36 mm for 12 months and ≥0.72 mm for 24 months,[13 22] was evaluated using receiver operating characteristics (ROC) analysis in both OK and SV groups.

RESULTS

As reported previously, a total of 91 subjects completed the baseline measurement and were randomised into OK (n=52) and SV (n=39) groups. Of these, 46 from the OK and 33 from the SV groups completed the 12-month follow-up, and 43 from the OK (age 9.8±1.3 years) and 28 from the SV (age 9.5±1.4 years) groups completed the 24-month follow-up, respectively. The electroretinogram could not be measured in one subject from the SV group, due to a lack of cooperation, who was excluded from the current analysis (figure 2).

Table 1 Baseline global flash multifocal electroretinographic parameters (mean±SD)

	OK		SV	
Direct component (DC)	Amplitude (nV/deg^2)	Peak time (ms)	Amplitude (nV/deg^2)	Peak time (ms)
Ring 1 (1.6°)	22.80±7.92	37.95±3.54	24.36±10.24	37.82±3.41
Ring 2 (5.3°)	9.57±3.25	38.13±3.29	10.12±4.53	38.18±3.25
Ring 3 (10.1°)	5.94±1.79	39.98±3.47	5.77±2.72	39.24±2.79
Ring 4 (15.6°)	4.78±2.07	39.90±2.95	4.28±1.67	39.40±2.51
Ring 5 (21.8°)	3.87±1.41	40.05±3.62	3.52±1.54	39.61±3.10
Induced component (IC)				
Ring 1 (1.6°)	35.64±15.38	33.16±5.48	31.87±10.30	33.44±4.45
Ring 2 (5.3°)	16.53±7.21	31.93±5.26	16.98±5.25	31.81±4.13
Ring 3 (10.1°)	12.31±4.66	27.84±4.07	11.81±4.48	29.22±5.69
Ring 4 (15.6°)	8.90±3.35	28.91±3.77	8.64±2.95	29.07±3.19
Ring 5 (21.8°)	5.42±2.03	28.80±4.34	5.32±2.01	28.86±4.12

There was no significant difference in any of the electroretinographic parameters between the two groups by repeated-measures analysis of variance.
DC amplitude: ring×treatment F=0.38, p=0.82; peak time: ring×treatment F=0.89, p=0.87.
IC amplitude: ring×treatment F=1.38, p=0.24; peak time: ring×treatment F=1.09, p=0.36.
OK, orthokeratology; SV, single vision.

Descriptive results

The SV and OK groups had similar baseline SERs of −2.50±1.02 D and −2.67±1.08 D (independent t-test, p=0.45), and baseline AL of 24.42±0.69 mm and 24.62±0.94 mm (p=0.30), respectively. After 12 months, AE of the OK group was significantly slower (0.16±0.23 mm) than that of the SV group (0.34±0.26 mm) (general linear model, p=0.002). This significant difference in AE persisted at 24 months, with elongation in the OK group of 0.37±0.37 mm compared with 0.60±0.42 mm in the SV group (p=0.02). After 12 months, 13 subjects in SV group (40.6%) and 7 subjects in the OK group (15.2%) were classified as fast progressors, that is, having ≥0.36 mm AE, while after 24 months, 10 subjects in SV group (37.0%) and 6 subjects in OK group (14.0%) were classified as fast progressors, that is, having ≥0.72 mm AE. The distributions of fast AE were significantly different in the OK and SV groups at 12 months (χ^2=6.30, p=0.01) and 24 months (χ^2=5.46, p=0.02).

Table 1 summarises the MOFO mfERG results. Both the DC and IC amplitudes decreased with retinal eccentricity. At baseline, there was no difference between the SV and OK groups in either DC amplitudes (multivariate analysis of variance, p=0.82) or IC amplitudes (p=0.24), as well as DC peak times (p=0.87) or IC peak times (p=0.36). The electrophysiological results were also independent of the baseline age (correlation, p=0.14), refraction (p=0.18) and AL (p=0.25). The test–retest results of SV group after 12 months are included in online supplemental tables 1 and 2, showing correlation matrices; and in online supplemental figure 1, displaying Bland-Altman plots.

Interaction between OK and electroretinography on AE

Consistent with previous results, the Ring 1 IC amplitude at baseline was negatively associated with AE in SV group participants without any myopia control intervention in the subsequent follow-ups. This relationship was consistently significant at 12 months (r=−0.44, p=0.02) and 24 months (r=−0.44, p=0.03), after controlling for age and baseline SER. In contrast, in children treated with OK, the Ring 1 IC amplitude was independent of AE at both 12 months (r=−0.19, p=0.21) and 24 months (r=0.15, p=0.33), indicating a weak central retinal response was no longer a risk factor for rapid AE in children receiving OK treatment (figure 3). Additionally, Fisher's transformation revealed a significant difference in correlation coefficients between OK and SV at 24 months (p=0.02), but not at 12 months. Detailed statistics are shown in table 2.

From the ROC analysis using the baseline Ring 1 IC amplitude to predict a rapid AE, the area under the curve for the SV group was 0.82 at 12 months, generating 94.4% sensitivity and 75% specificity, and 0.77 at 24 months, generating 87.5% sensitivity and 77.2% specificity. In contrast, the areas under the curve for the OK group were 0.55 and 0.69 at 12 and 24 months, respectively.

DISCUSSION

Consistent with previously reported findings, a weak central inner retinal function predisposed rapid AE at both 12 and 24 months for school-aged children, in terms of Ring 1 IC amplitude as measured by global flash multifocal electroretinogram. In contrast, in children receiving OK treatment, this relationship between retinal electrophysiology and AL elongation was absent. The Breath-O-Correct OK lens lowered this myopiagenic risk factor and significantly reduced AE in 24 months in school-aged children, when compared with those wearing SV lens spectacles.

OK reshapes the corneal profile via overnight wearing of rigid gas permeable lenses, which flatten the central zone to reduce refractive error, and steepen the paracentral zone to create an annular zone of increased refractive power.[23] Being one of the most commonly adopted means of controlling myopia progression, the general belief of its mechanism is that the paracentral annular zone creates positive defocus for the peripheral vision,[24] as it has been demonstrated in animal studies that peripheral myopic defocus could minimise AE.[25 26] It has been demonstrated that the retina is sensitive to defocus stimulation. Positive defocus could enhance, while negative defocus could inhibit retinal electrophysiological responses, particularly in the paracentral regions.[27 28] Further to whole-field defocus, the retina was also sensitive to simultaneous dual-focus. The dual-focus contact lens, which has also been shown to be applicable in myopia control,[29] consists of a central clear zone with full corrective power and alternating concentric rings of in-focus and defocus powers. Our team previously reported a significant increase in IC amplitudes in the central and paracentral regions when wearing this dual-focus contact lens.[30] Whether this increase in retinal electrophysiological response is indeed a factor in myopia control effectiveness of peripheral positive defocus, as observed with the OK and dual-focus lenses, requires further studies.

Our previous study revealed that 0.01% atropine was unable to slow down the overall myopia progression in schoolchildren compared with placebo. In terms of the progression rate and retinal electrophysiology, children using placebo exhibited similar readings to the untreated children in this study, that is, a weakened retinal response was associated with faster progression. Interestingly, an opposite trend appeared in children using 0.01% atropine. The pharmacological intervention was more effective in controlling myopia for children with a weaker baseline retinal function. However, for children with a stronger retinal function at baseline, that is, predicted to have slow myopia progression if untreated, stratified analysis revealed that 0.01% atropine appeared to have accelerated their myopia progression. In the current study using OK as the intervention,

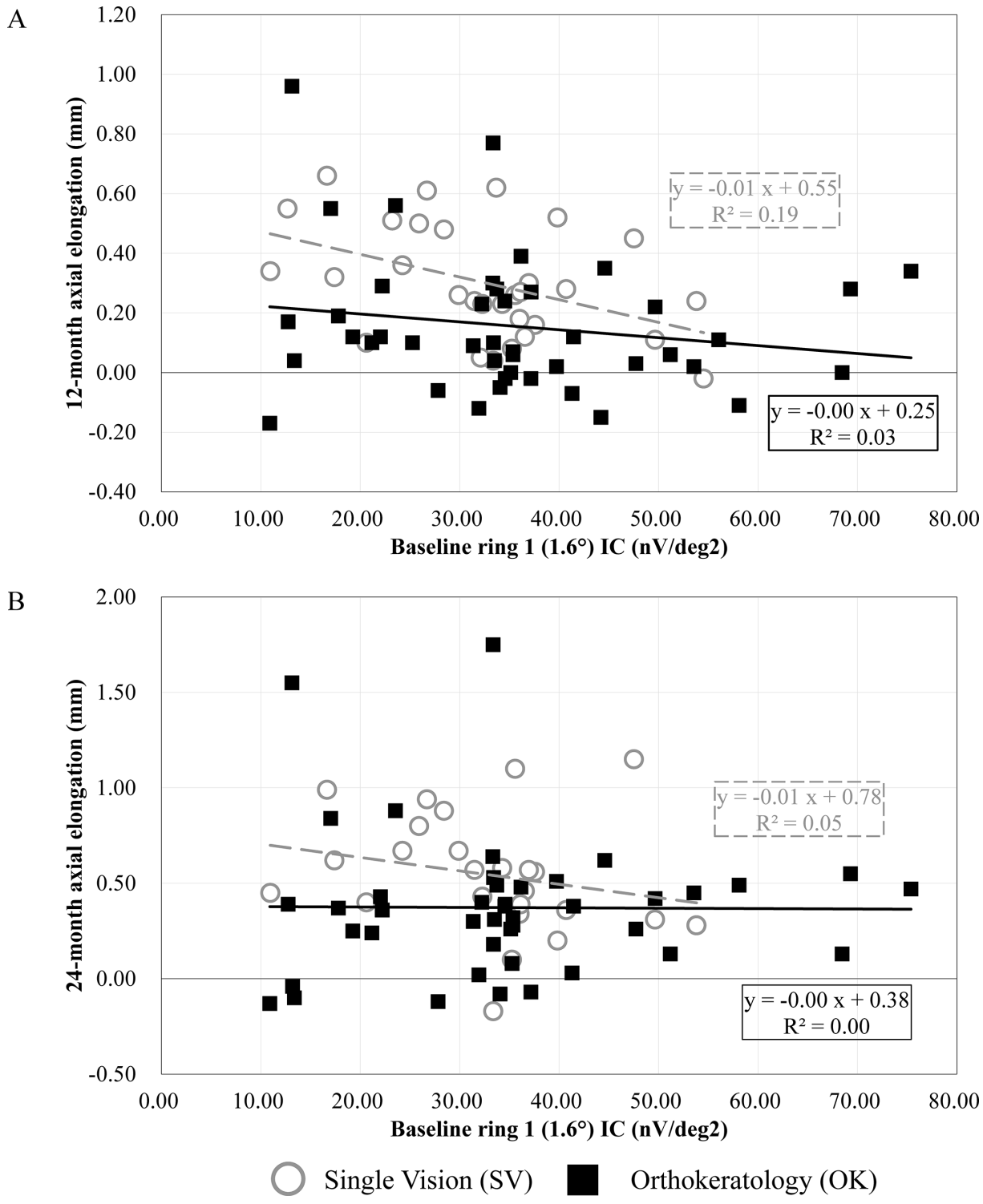

Figure 3 Axial elongation against baseline central inner retinal response measured by global flash multifocal electroretinography. (A) 12-month results. (B) 24-month results. IC, induced component.

the treatment effect on myopia control was not differentiated by the retinal electrophysiological response. OK treatment was shown to have a similar myopia control effect on children with either strong or weak baseline central retinal function. In addition to helping children with weak central inner retinal response to control myopia, OK did not accelerate myopia progression for those with strong retinal function as occurred with 0.01% atropine, creating an overall significant control of AE over 12- and 24-month periods. The difference in myopia control effect between OK and 0.01% atropine may be related to their modes of application, that is, optical and pharmacological regimens, respectively. A review of the literature revealed that optical regimens appeared to provide more stable myopia control efficacy than 0.01% atropine.[12 14] It may be speculated that optical intervention by OK exerts a defocus stimuli to the paracentral retina, while the pharmacological effect of 0.01% atropine would act on the entire retina. The sparing of the central retinal region during OK treatment may be a key in

Table 2 Correlation between baseline global flash multifocal electroretinography and axial length elongation at 12 and 24 months

	12-month axial elongation			24-month axial elongation		
	Partial correlation (controlled for baseline SER and age)		Fisher's test R-to-Z transformation	Partial correlation (controlled for baseline SER and age)		Fisher's test R-to-Z transformation
	$OK(R_{OK}(p))$ (N=46)	$SV(R_{SV}(p))$ (N=32)	R_{OK} vs $R_{SV}(Z(p))$	$OK(R_{OK}(p))$ (N=43)	$SV(R_{SV}(p))$ (N=27)	R_{OK} vs $R_{SV}(Z(p))$
Direct component						
Ring 1 (1.6°)	−0.03 (0.86)	−0.25 (0.18)	0.94 (0.34)	0.05 (0.76)	**−0.47 (0.02)**	**2.17 (0.03)**
Ring 2 (5.3°)	0.01 (0.97)	−0.16 (0.42)	0.71 (0.48)	0.10 (0.54)	−0.42 (0.04)	2.12 (0.03)
Ring 3 (10.1°)	−0.15 (0.32)	−0.24 (0.21)	0.39 (0.70)	0.14 (0.37)	−0.38 (0.06)	2.10 (0.04)
Ring 4 (15.6°)	0.08 (0.59)	−0.12 (0.52)	0.84 (0.40)	0.16 (0.30)	**−0.49 (0.02)**	**2.62 (0.01)**
Ring 5 (21.8°)	−0.11 (0.50)	−0.24 (0.22)	0.56 (0.58)	0.04 (0.79)	**−0.56 (0.004)**	**2.61 (0.02)**
Induced component						
Ring 1 (1.6°)	−0.19 (0.21)	**−0.44 (0.02)**	1.17 (0.24)	0.15 (0.33)	**−0.44 (0.03)**	**2.41 (0.02)**
Ring 2 (5.3°)	−0.10 (0.53)	**−0.55 (0.002)**	**2.16 (0.03)**	0.11 (0.50)	−0.32 (0.13)	1.71 (0.08)
Ring 3 (10.1°)	−0.11 (0.49)	−0.05 (0.79)	−0.25 (0.80)	0.05 (0.75)	0.12 (0.58)	−0.27 (0.79)
Ring 4 (15.6°)	−0.04 (0.79)	−0.07 (0.74)	0.13 (0.90)	0.09 (0.58)	0.03 (0.90)	0.23 (0.81)
Ring 5 (21.8°)	0.05 (0.76)	0.08 (0.68)	−0.13 (0.90)	0.18 (0.26)	−0.08 (0.71)	1.02 (0.31)

R_{OK}: correlation coefficient for the OK group; R_{SV}: correlation coefficient for the SV group

Bold denotes statistical significance after Hochberg's adjustment.
OK, orthokeratology; SER, spherical equivalent refraction; SV, single vision.

halting excessive AE, as demonstrated in our SV control group. Recently, various researchers have proposed the use of higher concentrations of atropine to provide a better myopia control effect.[9] Whether a higher concentration of atropine, as well as other optical myopia control interventions, would interact with the retinal electrophysiological function warrants further investigation. Furthermore, as MOFO mfERG is not a common clinical protocol for general ophthalmic practice, especially in the assessment of children, a set of electroretinographic normative data of a paediatric-friendly protocol may be helpful in clinically determining an optimal myopia control regimen for children.[31] Further studies are warranted to develop and verify these retinal electrophysiological measurement protocols.

To conclude, a weak central inner retinal response was shown to be a risk factor for rapid AE and myopia progression for children not receiving a myopia control intervention. In contrast, use of OK reduced the effect of this risk factor and effectively controlled AE in school-aged children over 24 months. Combined with our previous results on effects of 0.01% atropine, these findings provide evidence for clinical judgement on selecting an optimal myopia control regimen for individual patients.

Contributors GTKW, SS-HC and KYC conducted the experiments; KYC analysed the data, wrote the draft and revised the manuscript; TCL and HH-lC designed the research and obtained funding. All authors have read and agreed to the published version of the manuscript. HH-lC is the guarantor.

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Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and written consent and assent were obtained from the parent/guardian and the participant, respectively, before commencement of any study-specific procedures. All procedures adhered to the Tenets of Declaration of Helsinki and were approved by the Institutional Review Board of The Hong Kong Polytechnic University (Reference Number: HSEARS20181108001).

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Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID iDs
Kai Yip Choi http://orcid.org/0000-0002-0443-3028
Sonia Seen Hang Chan http://orcid.org/0000-0002-9900-9245
Thomas Chuen Lam http://orcid.org/0000-0002-3511-5620
Henry Ho-lung Chan http://orcid.org/0000-0002-8516-4711

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