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The safety of orthokeratology contact lens wear in slowing the axial elongation of the eye in children

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ABSTRACT

Purpose: To evaluate the safety of orthokeratology contact lens wear in slowing the axial elongation of the eye in myopic children.

Methods: Safety data from three prospective studies, which evaluated the use of orthokeratology for slowing myopia progression in children in comparison to a parallel control group of single-vision spectacle lens wearers over a 2-year period, were pooled together for analysis. The primary and secondary safety endpoints are the comparisons of adverse events and slit-lamp findings grades ≥ 2 between orthokeratology and control groups, respectively.

Results: Collectively, data from 125 orthokeratology and 118 control subjects were analyzed in this study. Of these, 101 (81 %) and 88 (75 %) orthokeratology and control subjects completed the 2-year follow-up period, respectively. Nineteen orthokeratology subjects experienced 28 adverse events, of which 6 were significant, whereas just one adverse event was found in the control group; this difference was statistically significant ($p < 0.001$). Most adverse events found in the orthokeratology group were corneal in nature, primarily corneal abrasion/staining, accounting for around 40 % of all adverse events. Of the 28 adverse events, only 18 (3 significant) are likely to be contact lens-related, leading to incidence rates of total and device-related adverse events per 100 patient years of lens wear (95 % confidence intervals) of 13.1 (9.2–18.2) and 8.4 (5.4–10.7), respectively. No significant differences were found between groups in the total number of silt-lamps findings with grades ≥ 2 ($p > 0.05$).

Conclusion: Around 13% of eyes wearing overnight orthokeratology contact lenses are likely to experience an adverse event over one year of lens wear, with this figure being lower when considering device-related adverse events alone. No serious adverse events were found, with most being non-significant. These results inform eye care practitioners on the safety of orthokeratology lenses when prescribed for slowing myopia progression to myopic children.

1. Introduction

Orthokeratology contact lenses are becoming a relative popular form of vision correction in children, primarily driven by growing evidence supporting the use of this contact lens type for slowing myopia progression.[1] As such, most current research in orthokeratology is focused in understanding both the mechanism underlying the myopia control effect and improving treatment outcomes [2].

Although many studies have documented the efficacy of orthokeratology in slowing myopia progression, [3–6] fewer studies have assessed the safety associated with this modality of contact lens wear.[7–10] Review of previous studies that assessed ocular adverse events associated with orthokeratology lens wear in children indicates that the incidence of such events might be around 20 percentage of patients per annum.[7–10] However, most of these studies have not provided adequate definition of what's considered an 'adverse event' and have limited safety assessment to just a few types of adverse events. As orthokeratology contact lenses are commonly used for slowing

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myopia progression [1], these lenses might be worn for many years, potentially throughout childhood and adolescent years while the risk of myopia progression remains, and perhaps throughout adulthood as well for refractive error correction. Therefore, it is important to further understand the safety of this modality of contact lens wear in children, so eye care practitioners are better informed about the safety issues that might be encountered when orthokeratology lenses are prescribed for slowing myopia progression to myopic children, thus allowing them to better counsel patients, and their parents, on the risks and benefits of orthokeratology as an option for myopia control. As such, this study pooled together safety data from three prospective clinical trials to assess differences in incidence rates of adverse events and slitlamp findings between myopic children wearing overnight orthokeratology contact lenses and distance, single-vision spectacles over a 2-year period [11–13].

2. Methods

Three prospective studies conducted in Hong Kong and Spain evaluated the use of an overnight orthokeratology contact lens for the purposes of slowing myopia progression in children. The studies' designs have been previously described in detail [11–13]. In one study, a total of 102 eligible Hong Kong Chinese subjects, ranging in age from 6 to 10 years, with myopia between −0.50 and −4.00 D and astigmatism not more than −1.25D, were randomly assigned to wear orthokeratology lenses or distance, single-vision spectacles for a period of 2 years (ClinicalTrials.gov number: NCT00962208) [11]. In a second study, 61 White European subjects 6 to 12 years of age with myopia −0.75 to −4.00 D and astigmatism ≤ 1.00 D were prospectively allocated to orthokeratology contact lenses or distance, single-vision spectacles for 2-years (ClinicalTrials.gov number: NCT00978692) [12]. In a third study, 80 Hong Kong Chinese subjects (aged 6–12 years) with myopia of −0.50 to −5.00 D and with-the-rule astigmatism of −1.25 to −3.50 D were fitted with orthokeratology lenses or single-vision spectacles for a period of 2 years (ClinicalTrials.gov number: NTC04806763) [13]. In all three studies, inclusion criteria included: neophyte contact lens wearers with no previous exposure to any myopia control treatment; good health with no regular ocular medications; and no history of ocular or systemic disease that could interfere with contact lens wear or influence refractive development. In all three studies, the same orthokeratology lens (*Menicon Z Night*, Menicon Co., Ltd, Nagoya, Japan) and care solutions, including *MeniCare Plus* and *Menicon Progent* (Menicon Co., Ltd, Nagoya, Japan), were prescribed according to the manufacturer's recommendations. Subjects were seen at baseline and then followed (at least) after 1 day, 1 month and then at 6-month intervals for the remaining 2-year period (i.e., 6-, 12-, 18- and 24-months). All three studies were conducted with written informed consent and in accordance with the tenets of the Declaration of Helsinki and were approved by Ethical Committee Review boards.

Safety data from these three studies were pooled together for analysis. The primary safety endpoint is the comparison of adverse events between the test (i.e., orthokeratology) and control (i.e., distance, single-vision spectacles) groups. The secondary safety endpoint is the comparison of slit-lamp findings grades ≥ 2 between the test and control groups. Data from the three studies were audited to identify any potentially missing safety data. In all three studies, children and parents were advised on the signs and symptoms that could indicate a possible adverse response and were instructed on steps to take in the event of an adverse reaction. Subjects were instructed to report to the clinic immediately should a reaction appear to be abnormal (e.g., red eye, pain, unusual discomfort, or eye secretions). Unscheduled visits were arranged as needed. In this report, subjects who discontinued the study were further classified as adverse and non-adverse dropouts. Adverse dropout refers to subjects who did not complete the study because of an adverse event. All adverse events, whether they occurred in subjects who completed or discontinued the study, were recorded and classified into serious, significant or non-significant according to Table 1 using previously reported methodology,[7,14] which is based largely upon ISO11980:2012: Contact Lens and Lens Care Products – Guidance for Clinical Investigations [15]. More specifically, serious, significant or non-significant adverse events were classified based on symptomatology and on the clinical concern to potentially produce significant visual impairment that might warrant discontinuation from lens wear. Thus, serious adverse events were considered those symptomatic and with the potential to produce significant visual impairment to warrant permanent discontinuation from lens wear; significant events were those commonly asymptomatic and of sufficient clinical concern to warrant clinical intervention and perhaps temporal discontinuation from lens wear; whereas non-significant adverse events were those typically asymptomatic and of no immediate clinical concern to warrant discontinuation from lens wear.

Recurrences of the same adverse event(s) in the same or fellow eye at any of the subsequent study visits were classified as separate events; bilateral events of the same condition were counted as independent events. Patient-years of lens wear was calculated for each individual subject from the time of dispensing to the time of discontinuation or completion of the 2-year visit. No discounting was performed for temporary discontinuation of lens wear during the trials. The crude incidence of adverse events was calculated per 100 patient years of lens wear (i.e., [total number of events/number of patient-years of wear]* 100), and the 95 % confidence intervals were calculated using the Wilson's method [16].

2.1. Statistical analysis

Mean and standard deviations were calculated for all continuous variables, and frequencies were reported for categorical variables. Differences between groups in baseline demographics (i.e., age, mean spherical refractive error and axial length) were tested using unpaired t-tests, except for the male/female and Hong-Kong Chinese/White European ethnicity ratios, which were tested using a Chi-square test. Differences between groups in the number of discontinuations, adverse events, and slit-lamp findings were tested using Chi-squared or Fisher's exact tests.

3. Results

Collectively, the three studies enrolled 125 orthokeratology and 118 control subjects. Of these, 101 (81 %) and 88 (75 %) test and control subjects completed the 2-year follow-up period, respectively. As such, 24 and 30 subjects from each group discontinued the study at different time points. Of the 24 orthokeratology and 30 control subjects that discontinued the study, 19 and 29 were non-adverse dropouts, respectively thus leaving 5 and 1 adverse dropouts, respectively. The overall pooled retention rate for the three studies was 77.8 %. No significant differences were found between groups in the number of subjects that discontinued or completed vs. the total number of subjects collectively enrolled in the three studies (both $p > 0.05$). No significant differences were found between groups in any of the baseline demographics (Table 2).

The reasons and timeline for non-adverse and adverse dropouts are reported in Table 3. Most reasons for discontinuation in the orthokeratology group (N = 24) were related to lens fitting issues (i.e., 10 under-response to target myopic correction and 5 poor lens centration), whereas the majority of discontinuations found in the control group (N = 30) were related to subjects seeking myopia control treatment (N = 14) and lost to follow-up (N = 14), thus accounting for 63 % and 93 % of all discontinuations, respectively. No significant differences were found between groups neither in the rate of non-adverse dropouts ($p = 0.620$) nor in the rate of adverse dropouts ($p = 0.071$).

The five adverse dropouts found in the test group included three subjects who had mild rhinitis, resulting in persistent and significant

Table 1
Adverse events classification. BSCVA, best-corrected visual acuity.

Classification Symptomatology	Serious Symptomatic	Significant Commonly symptomatic	Non-significant Asymptomatic
Description	An adverse event that produces or has the potential to produce significant visual impairment and might warrant permanent discontinuation from lens wear	An adverse event of sufficient clinical concern to warrant clinical intervention and perhaps temporal discontinuation from lens wear	An adverse event which is of no immediate clinical concern and does not warrant discontinuation from lens wear
Condition	Presumed microbial keratitis /infectious corneal ulcer Permanent decrease of ≥ 2 lines of BCVA Central or paracentral corneal opacity Corneal warpage Epithelial wrinkling Hypopyon Pentration of the anterior limiting lamina Neovascularization within the central 6 mm of the cornea Persistent epithelial defect Corneal abrasion requiring medical intervention Uveitis Endophthalmitis Hyphaema Iritis	Peripheral non-infectious corneal ulcers/scars Symptomatic corneal infiltrative events Corneal scarring Corneal abrasion requiring no medical intervention Corneal staining ≥ grade 3 Corneal neovascularization ≥ grade 2 Any temporary loss of ≥ 2 lines of BCVA (for ≥ 2 weeks) Any event which necessitates temporary lens discontinuation ≥ 2 weeks	Asymptomatic corneal infiltrative events Deep stromal opacities Localized allergic reaction Corneal white lines Corneal epithelial iron lines Corneal staining ≥ grade 2 Disorders of the eyelids and lashes (e.g., blepharitis, meibomitis, hordeolum) conjunctivitis

Table 2
Baseline demographics of subjects who completed the 2-year follow-up period. N, number of subjects; HK, Hong Kong Chinese; WE, White European; MSE, mean spherical refractive error; D, diopters. Variables are expressed as mean ± standard deviation.

	Orthokeratology N = 101	Control N = 88	Statistical significance (p-value)
Age (years)	9.12 ± 1.36	9.16 ± 1.43	0.973
Male/female ratio	51/50	43/45	0.823
Ethnicity ratio (HK/WE)	72/29	64/24	0.826
MSE (D)	−2.70 ± 1.20	−2.55 ± 1.06	0.723
Axial length (mm)	24.43 ± 0.79	24.29 ± 0.92	0.256

inferior-nasal corneal staining; one subject who showed increased conjunctival hyperemia after failing to comply with care procedures despite reeducation; and the remaining subject developed chalazion in the right eye; all these adverse dropouts occurred following between 18 and 24 months of lens wear. None of these five adverse dropouts could be attributed to adequate orthokeratology contact lens wear. All discontinuations, including non-adverse and adverse dropouts, resolved successfully upon contact lens discontinuation and vision was unaffected. One recurrent corneal inflammation was reported in the control group and the subject was excluded from the study.

Table 3
Reasons and timeline for non-adverse and adverse dropouts. *, indicates adverse dropouts.

Time (months)	Orthokeratology	Spectacles
0 to ≤ 1	–	10 Sought myopia control treatment
>1 to ≤ 3	6 Under-response to treatment	–
> 3 to ≤ 6	1 Unknown reason 5 Poor lens centration 4 Under-response to treatment 1 Poor compliance	1 Recurrent ocular inflammation* 1 Sought soft contact lenses 1 Sought orthokeratology 8 Lost to follow-up
> 6 to ≤ 12	1 Poor compliance	1 Lost to follow-up 2 Sought myopia control treatment
> 12 to ≤ 18	1 Discomfort	2 Lost to follow-up 1 Sought myopia control treatment
> 18 to 24	3 Mild rhinitis* 1 Increased conjunctival hyperemia* 1 Chalazion*	3 Lost to follow-up
Total	**24**	**30**

3.1. Adverse events

Nineteen orthokeratology subjects experienced 28 adverse events throughout the course of the three studies, of which 6 were significant, whereas just one adverse event was reported in the control group; this difference was statistically significant ($p < 0.001$) (Table 4). Of the 28 adverse events found with overnight orthokeratology, three male subjects experienced 2 adverse events each at different time points (i.e., peripheral non-infectious corneal ulcer and dimple veiling; corneal abrasion and hordeolum; and conjunctival staining and corneal abrasion) and 1 female subject experienced 3 adverse events (i.e., corneal abrasion, papillary conjunctivitis, corneal staining). Two female and 2 male subjects experienced bilateral adverse events at the same time points (i.e., papillary conjunctivitis, blepharitis, bacterial conjunctivitis, and conjunctival hyperemia). The remaining adverse events were unilateral and occurred exclusively in one subject each. Five adverse events found with orthokeratology were adverse dropouts. Fewer adverse events were found in Hong-Kong Chinese in comparison with White European subjects ($p < 0.001$), and there were similar adverse events in males in comparison with females ($p = 0.951$). No severe adverse events were found in any of the studies. No cases of reduced visual acuity were found at the occurrence of any of the adverse events found. All adverse events resolved successfully, and vision was unaffected in all cases.

The most common adverse events (number in brackets) associated with orthokeratology lens wear were corneal abrasion (6), papillary conjunctivitis (3), rhinitis (3), corneal staining (2), corneal infiltrative events (2), blepharitis (2), bacterial conjunctivitis (2), hordeolum (2), conjunctival hyperemia (2), conjunctival staining (1), corneal neovascularization (1), dimple veiling (1), and chalazion (1) (Table 4). Most adverse events associated with orthokeratology contact lens wear were

Table 4
Type and timeline of adverse events for both subjects who completed and discontinued the study.Type and timeline of adverse events for both subjects who completed and discontinued the study. ♀, female; ♂, male; CU, corneal ulcer; CIE, corneal infiltrative event; *significant adverse events; ג required temporary contact lens wear discontinuation (≥2 weeks); גג required permanent contact lens wear discontinuation (i.e., adverse dropout).

Time (months)	Orthokeratology	Control
0 to ≤ 1	1 Corneal abrasion ♀ 2 Corneal staining ♀♀	–
>1 to ≤ 3	2 Papillary conjunctivitis ♀	–
> 3 to ≤ 6	**1 Peripheral non-infectious CU** *ג♂	1 Recurrent ocular inflammation ♀ג
> 6 to ≤ 12	3 Corneal abrasion ♀♀♂ **1 Corneal abrasion** *♀ 2 Blepharitis ♀ 2 Bacterial conjunctivitis ♂ 1 Hordeolum ♂ 1 Conjunctival staining	
> 12 to ≤ 18	1 Corneal abrasion ♀ **1 Corneal neovascularization** *♀ **1 Hordeolum** *ג♀ **1 Papillary conjunctivitis** *♂ 1 Dimple veiling ♂ **1 Symptomatic CIE**	–
> 18 to 24	3 Rhinitis ♂ג♂♂ 2 Conjunctival hyperemia ♂ג 1 Chalazion ♂ג	–
Total	28 (**6 significant***)	1 (**1 significant***)

found to affect the cornea (6 corneal abrasions, 2 corneal staining, 2 corneal infiltrative events, 1 corneal neovascularization, and 1 dimple veiling), followed by the conjunctiva (3 papillary conjunctivitis, 2 bacterial conjunctivitis, 2 conjunctival hyperaemia, and 1 conjunctival staining), and the ocular adnexa (2 blepharitis, 2 hordeolum, and 1 chalazion) accounting for 43 %, 29 % and 18 % of all adverse events, respectively. The remaining three cases of rhinitis were not considered ocular adverse events. Most importantly, no serious adverse events were found with overnight orthokeratology in this study, with most adverse events found being non-significant (79 %). The rate of adverse events was found to peak between 6 and 12 months of lens wear but occurred at a similar rate at the other study visits (i.e., 0- to 6-months: 21.4 %; 6- to 12-months: 32.1 %; 12- to 18-months: 21.4 %; and 18- to 24-months: 25.0 %) (Table 4). Of the 28 adverse events, only 18 (4 significant) were likely to be contact lens-related (i.e., 6 corneal abrasion, 2 corneal staining, 3 papillary conjunctivitis, 1 conjunctival staining, 2

conjunctival hyperemia, 1 dimple veiling, 1 peripheral non-infectious corneal ulcer, 1 symptomatic CIE, 1 corneal neovascularization). When considering device-related adverse events alone, these were found to affect primary the cornea (67 %) followed by the conjunctiva (33 %).

3.2. Incidence of adverse events

One-hundred and twenty-five orthokeratology contact lens subjects and 118 single-vision spectacle subjects were initially recruited from the three studies. Of these, 101 (81 %) and 88 (75 %) orthokeratology and single-vision spectacle subjects completed the 2-year follow-up period, respectively, accounting for 202 and 176 patient-years of wear. Additionally, 24 and 30 orthokeratology and spectacle subjects, respectively discontinued the study at different time points, accounting for additional 12.3 and 11.8 patient-years of wear. Thus, this study evaluates safety data which accounts for 214.3 and 187.8 patient-years of lens wear for the test and control groups, respectively. The total incidence of adverse events and the incidence rates depending on the severity of adverse events for all events and for those likely to be contact lens-related found with orthokeratology lens wear are reported in Table 5. One single subject from the control group was reported to experience an adverse event (Table 4), which leads to an incidence (95 % confidence intervals) of 0.5 (0.1 to 3.0) per 100-patient years of lens wear.

3.3. Slit-lamp findings

A greater number of grade $\geq$ 2 of palpebral conjunctival injection was found in the control group in comparison with the orthokeratology group, whereas a greater number of grade $\geq$ 2 of palpebral conjunctival papillae was found in the orthokeratology group in comparison with the control group. However, no significant differences were found between groups in the total number of silt-lamps findings with grades $\geq$ 2 ($p > 0.05$) (Table 6). Six slit-lamp findings grade $\geq$ 3 were found in the orthokeratology group (0.6 %), consisting of 4 palpebral conjunctival papillae (0.4 %) and 2 palpebral conjunctival follicles (0.2 %), but no slit-lamp findings grade $\geq$ 4 were found in this group. No slit-lamp findings grade $\geq$ 3 were found in the control group. No significant differences were found between groups in the total number of slit-lamp findings grades $\geq$ 3 ($p = 0.269$).

Table 5
Crude incidence rates of adverse events per 100 patient years of lens wear (95% confidence intervals) found with orthokeratology lens wear for all events and for those likely to be contact lens-related.

Type of adverse event	All events: N = 28 (6 significant)	Likely to be contact lens-related: N = 18 (4 significant)
Serious	**0.0** (0.0 – 1.8)	**0.0** (0.0 –1.8)
Significant	**2.8** (1.3 – 6.0)	**1.9** (0.7 – 4.7)
Nonsignificant	**10.3** (6.9 – 15.1)	**6.5** (3.9 – 7.2)
Total	**13.1** (9.2 – 18.2)	**8.4** (5.4 – 10.7)

4. Discussion

This study pooled together safety data from three prospective clinical trials, which evaluated the use of overnight orthokeratology contact lens wear for the purposes of slowing myopia progression in children in comparison to a control group of single-vision spectacle lens wearers over a 2-year period.

No significant differences were found between orthokeratology and control groups either in the total rate of discontinuation or in the rate of non-adverse and adverse dropouts. Most reasons for discontinuation in the orthokeratology group (N = 24) were related to lens fitting issues (i.e., 10 under-response to target myopic correction and 5 poor lens centration), whereas the majority of discontinuations found in the control group (N = 29) were related to subjects seeking myopia control treatment (N = 14) and lost to follow-up (N = 14), thus accounting for 63 % and 93 % of all discontinuations, respectively. Five adverse dropouts were found in the orthokeratology group, but none of these could be attributed to adequate orthokeratology contact lens wear. All the discontinuations, including non-adverse and adverse dropouts, resolved successfully upon contact lens discontinuation and vision was unaffected. One recurrent corneal inflammation was found in the control group and the subject was excluded from the study. The overall retention rate for the three studies was 77.8 %, which is consistent with that reported in other studies [17].

A greater incidence of adverse events was found with orthokeratology in comparison with spectacle lens wear (Table 4). Nineteen orthokeratology subjects experienced 28 adverse events throughout the course of the three studies, of which 6 were significant, whereas just one adverse event was reported in the control group. Of the 28 adverse events, only 16 (3 significant) are likely to be contact lens-related, leading to incidence rates of total and device-related adverse events (95 % confidence intervals) of 13.1 (9.2 – 18.2) and 8.4 (5.4 – 10.7) per 100 patient years of lens wear, respectively (Table 5). Most adverse events related to orthokeratology contact lens wear were found to affect the cornea followed by the conjunctiva accounting for two-thirds and one-third of all device-related adverse events, respectively. Of note, however, is that despite some adverse events were unlikely to be contact lens-related the lack of any of these types of events in the control group may imply that the handling (i.e., insertion and removal) and wearing of contact lenses may be related to the incidence of these event types. Most importantly, no serious adverse events were found with overnight orthokeratology in this study, with most adverse events found being non-significant (79 %). All adverse events resolved successfully and there were no cases of any loss of best-corrected visual acuity. Slit-lamp findings with grade $\geq$ 2 were relatively rare affecting 15 % and 13 % of the orthokeratology and control groups, respectively. Most importantly,

Table 6
Number of slit-lamp findings (n) found across all study visits (N) in both the orthokeratology and control groups.

	Orthokeratology (N = 1000)	Control (N = 204)	Statistical significance (p-value)
	n (%)	n (%)	
Corneal staining extent ≥ Grade 2	0 (0.0)[a]	0 (0.0)	P = 1.000
Corneal staining depth ≥ Grade 2	2 (0.2)[a]	0 (0.0)	P = 0.566
Limbal Injection ≥ Grade 2	0 (0.0)	0 (0.0)	P = 1.000
Bulbar conjunctival injection ≥ Grade 2	2 (0.2)	2 (1.0)	P = 0.079
Palpebral conjunctival injection ≥ Grade 2	15 (1.5)	9 (4.4)	P = 0.008
Palpebral conjunctival papillae ≥ Grade 2	112 (11.2)	12 (5.8)	P = 0.037
Palpebral conjunctival follicles ≥ Grade 2	21 (2.1)	4 (2.0)	P = 0.901
All ≥ Grade 2	152 (15.2)	27 (13.2)	P = 0.534

% = (n/N)*(100). No slit-lamp findings could be obtained for either the orthokeratology or control groups from the MCOS trial (NCT00978692) [7], with the exception of corneal staining extend and depth which were obtained from the orthokeratology group only accounting for a total number of visits of 239 (i.e., pooled N = 1239[a]). No slit-lamp findings could be obtained from the control group of the TO-SEE clinical trial (NTC04806763) [13].

Table 7
Crude incidence rates of anterior eye (i.e., cornea, conjunctiva and ocular adnexa) adverse events calculated per 100 patient years of lens wear (95% confidence intervals) from studies reporting adverse events associated with overnight orthokeratology and daily soft contact lens wear in minors. N.R., not reported (i.e., no details were reported to make incidence calculations).

Wearing Modality	**OVERNIGHT ORTHOKERATOLOGY**				**DAILY SOFT CONTACT LENS WEAR**			
Study	This study	Hiraoka et al. 2018 [8]	Hu et al. 2021 [9]	Lu et al. 2022 [10]	Hiraoka et al. 2018 [8]	Cheng et al. 2020 [23]	Woods et al. 2021 [30]	Giannoni et al. 2022 [31]
Number of subjects	101	53	260	1,001	39	663	144	294
Subjects' age range (years)	6 to 12	8 to 16	8 to 15	8 to 15	8 to 16	7 to 15	8 to 12	7 to 11
Patients/years of lens wear	214	530	260	1501	390	816	653	865
Type of adverse event								
Serious	0.0 (0.0 – 1.8)	0.0 (0.0 – 0.7)	0.0 (0.0 – 1.5)	0.0 (0.0 – 0.3)	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.5)	0.2 (0.0 – 0.9)	0.2 (0.1 – 0.8)
Significant	2.8 (1.3 – 6.0)	6.2 (4.5 – 8.6)	13.1 (9.5 – 17.7)	N.R.	5.9 (4.0 – 8.7)	0.0 (0.0 – 0.5)	0.3 (0.1 – 1.1)	17.7 (15.3 – 20.4)
Nonsignificant	8.9 (5.7 – 13.4)	16.2 (13.3 – 19.6)	29.6 (24.4 – 35.4)	N.R.	20.5 (16.8 – 24.8)	10.5 (8.6 – 12.8)	5.7 (4.1 – 7.7)	7.1 (5.5 – 9.0)
TOTAL	**11.7 (8.0 – 16.7)**	**22.5 (19.1 – 26.2)**	**42.7 (17.4 – 48.8)**	**13.7 (12.1 – 15.5)**	**26.4 (22.3 – 31.0)**	**10.5 (8.6 – 12.8)**	**6.1 (4.5 – 8.2)**	**25.0 (22.2 – 28.0)**
Likely to be contact lens-related	8.4 (5.2 – 12.9)	7.7 (5.8 – 10.3)	42.7 (17.4 – 48.8)	N.R.	8.7 (6.3 – 11.9)	4.5 (3.3 – 6.2)	3.4 (2.2 – 5.0)	20.7 (18.1 – 23.5)

no significant differences were found between groups in the total number of slit-lamp findings (Table 6).

The fewer adverse events found in Hong-Kong Chinese in comparison with White European subjects is not well understood, but this might be related to differences in compliance with lens wear between ethnicities as well as to differences between study sites in the methodology used for assessing and recording adverse events. It is possible that Hong-Kong Chinese subjects might be more compliance with myopia control treatment in comparison with European subjects due to the higher myopia prevalence [18] and greater rate of myopia progression [19] typically found in Asian Chinese in comparison with white European subjects. Also, whist the methodology employed for assessing and recording adverse events in White European subjects was designed *a priori*, [7] the adverse events found in Hong Kong Chinese subjects were classified using the former methodology in this study *a posteriori*.

The greater incidence of adverse events found with orthokeratology contact lens wear in comparison with spectacle lens wear was anticipated as sleeping in lenses is a risk factor for the development of adverse events with contact lens wear [20,21]. However, the latter has been shown to be particularly the case with extended wear soft contact lenses, where patients continuously wear lenses day and night for 7 to 30 consecutive days [21]. Different from extended wear, overnight orthokeratology contact lenses are solely worn during sleeping hours and eyes are free from contact lens wear during the waking hours.

A greater incidence of adverse events has been also reported with daily disposable soft contact lenses in comparison with spectacle lens wear [22,23]. Thus, to put the safety of the overnight orthokeratology into the context of overall contact lens wear, the incidence of anterior eye adverse events found with orthokeratology contact lens wear was compared with that reported with other daily wear soft contact lens types worn by children (Table 7). Despite special care was taken to make fair comparisons between studies in anterior eye adverse events (i.e., cornea, conjunctiva and ocular adnexa) only, as these are the ones typically reported in most contact lens studies, differences in study design, observation period, and the methodology employed for recording and classifying adverse events among studies may partly account for differences in the incidence rate of adverse events between studies. To account for differences in study designs and methodologies in the comparison of adverse events between studies, incidence rates of adverse events were calculated per 100 patient years of lens wear for all studies, thus allowing comprehensive comparisons in incidence rates between studies potentially enhancing interpretability. Of note, however, is that given the rare occurrence of serious adverse events, comparing the incidence of such events between studies is challenging. The comparison in the incidence of anterior eye adverse events between children wearing overnight orthokeratology and daily soft contact lenses reveals that between 10 and 20 % of eyes wearing overnight orthokeratology and daily wear soft contact lenses are likely to experience an adverse event over the course of one year of lens wear. Previous prospective studies conducted with orthokeratology contact lenses have also failed to find serious adverse events associated with the wear of these lenses [7–10,24]; this is further supported by a recent study which reported the rate of microbial keratitis associated with orthokeratology lens wear in children to be 4.9 (95 % confidence intervals: 2.1 to 11.4) per 10,000 patient/years of lens wear [25], with the latter rate being remarkably similar to that recently found with daily soft contact lens wear in children, which has been reported to be around 4.8 per 10,000 patient/years (95 % confidence intervals: 1.6 to 16.0) [26].

A limitation of this study is that subjects were randomized to receive either overnight orthokeratology or spectacle lens wear in just one of the three studies pooled together for analysis. Likewise, only one of the three studies used a single-masked study design (i.e., investigator-masked). Nonetheless, of notice is that randomisation makes difficult recruitment due to parents not wanting their child to risk receiving the placebo (most discontinuations found in the control group in this study were related to this reason), and whereas investigator masking is difficult, masking subjects to wear either overnight orthokeratology or spectacles is just not possible [27]. Another limitation of the safety analysis of this study includes a relatively short total subject-time exposure to orthokeratology contact lens wear (i.e., 214 patient-years of lens wear) and thus the incidence rate of adverse events associated to the prescription of this medical device in normal clinical practice is yet to be established, but this is also typically the case for other lens types and it is commonly managed through post-approval studies [28–30]. Notwithstanding the above, a strength of this study is that all safety data were collected from three well-controlled clinical trials in which subjects were closely monitored. All three studies employed almost identical study designs in that they were prospective clinical trials designed to assess the clinical performance of overnight orthokeratology contact lens wear in slowing the axial elongation of the eye in myopic children in comparison to a parallel control group of distance, single-vision spectacle lens wearers over a 2-year period. Both study groups were well balanced as no significant differences were found between groups in any of the baseline demographics, and all three studies assessed the safety of the same orthokeratology contact lens design and material.

In conclusion, this study informs eye care practitioners as to safety issues that might be encountered when orthokeratology lenses are prescribed for slowing myopia progression to myopic children. More specifically, around 20 % of orthokeratology lens wearers are likely to discontinue lens wear primarily because of lens fitting issues, principally under-response to treatment and poor lens centration. This study also found that between 10 and 20 % of eyes wearing overnight orthokeratology contact lenses are likely to experience adverse events over one year of lens wear, with this figure going below 10 % when considering device-related adverse events alone. Most importantly, most adverse events were non-significant and resolve successfully with no cases of any loss of best-corrected visual acuity, thus supporting overnight orthokeratology as a relatively safe option for myopia management in children [1].

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jacinto Santodomingo-Rubido is a full-time employee of Menicon Co., Ltd. The authors alone are responsible for the content and writing of the paper. Menicon Co., Ltd funded the publication costs of this study.

Appendices.

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