ARTICLE IN PRESS

Contact Lens and Anterior Eye xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Contact Lens and Anterior Eye

journal homepage: www.elsevier.com/locate/clae

Does a two-year period of orthokeratology lead to changes in the endothelial morphology of children?

Sin Wan Cheung*, Pauline Cho

School of Optometry, The Hong Kong Polytechnic University, Hong Kong

A R T I C L E I N F O

Keywords:
Children
Endothelium cell density
Orthokeratology
Pleomorphism
Polymegathism

A B S T R A C T

Purpose: To compare changes in endothelial morphology in the central and superior cornea in subjects wearing single-vision spectacles and orthokeratology lenses over two years.

Methods: Endothelial images of the two locations of 99 subjects (6–12 years) from completed myopia control studies were analysed. Endothelial cell density (ECD), coefficient of variation in cell size (CV), and hexagonality (HEX) before and two years after treatment were compared between the two groups of subjects.

Results: Baseline ECD and CV in the central cornea were slightly lower than those in the superior cornea, but no significant difference in HEX was found in the two corneal locations. After two years, reduction in ECD and increase in CV were only significant in the central cornea, but not in the superior cornea. Reduction in HEX was significant in both corneal locations. Subjects receiving orthokeratology had smaller reduction in ECD in the central cornea compared to the controls (orthokeratology: 56 ± 94 cells/mm^2; control: 98 ± 91 cells/mm^2, p = 0.024), otherwise, there were no significant differences in the changes in endothelial morphology in the two corneal locations between the two groups of subjects.

Conclusions: The current study confirmed that there were differences in endothelial morphology of central and superior cornea of Chinese children aged 6–12 years. The morphological response to normal ageing differed between the two corneal locations as reduction in cell density and polymegathism were found only in the central cornea whilst pleomorphism was found in both locations. Orthokeratology lens wear had minimal effect on the developmental changes in endothelial morphology.

1. Introduction

Clinical evidence has shown that orthokeratology (ortho-k) is an effective and safe treatment to slow axial elongation in children [1–9]. One of the indicators for safety in ortho-k lens wear is corneal endothelial morphology. A few longitudinal studies have evaluated the long term effects of ortho-k on the corneal endothelium [10–14]. Three of these studies [10–12] did not find any significant change in endothelial cell density (ECD), pleomorphism in terms of percentage of hexagonal cells (HEX), and polymegathism in terms of coefficient of variation in cell size (CV) 1–7 years after treatment. Hiraoka et al. [10] reported no changes in ECD, CV, and HEX in 52 eyes of 31 subjects aged 10–44 years (mean ± SD: 17 ± 9 years) before and after one year of ortho-k lens wear. Zhong et al. [11] conducted a cross-sectional study to compare corneal thickness and morphology in subjects after one night and five years of ortho-k lens wear (mean ± SD age: one night = 23 ± 4 years; 5 years = 19 ± 5 years). Data collected 8 h prior to lens wear from subjects on one-night treatment were used as control. The authors used data collected from the two eyes and reported no significant difference in ECD and HEX after either one night or 5 years of lens wear. In the retrospective study conducted by Guo and Xie [12], there were no significant changes in ECD, CV, and HEX in 30 subjects aged 8–20 years before and after seven years ortho-k lens wear. In contrast, Cheung and Cho [13] found a significant reduction in ECD without any changes in polymegathism or pleomorphism in children aged 7–17 years (median: 10 years) after two years of lens wear. On the other hand, Nieto-Bone et al. [14] observed an increase in polymegathism without any changes in ECD or pleomorphism after one year of lens wear in 15 adults aged 18–30 years. These studies varied with respect to study designs, age of subjects, duration of study, and lack of proper control subjects. Thus, there is a need to confirm if ortho-k leads to changes in corneal endothelium.

It is known that ECD reduces with age, starting at birth [15–22]. The rate of reduction is most rapid in the first five years of age, slows down during childhood and the adolescent period, and finally becomes stable in adulthood. Of the five studies on the effect of ortho-k on the

* Corresponding author.
E-mail address: orpeggy@gmail.com (S.W. Cheung).

http://dx.doi.org/10.1016/j.clae.2017.10.006
Received 1 June 2017; Received in revised form 1 October 2017; Accepted 6 October 2017
1367-0484/

Please cite this article as: Cheung, S.W., Contact Lens and Anterior Eye (2017), http://dx.doi.org/10.1016/j.clae.2017.10.006

Table 1
Demographic data and baseline ocular and corneal endothelial parameters of the subjects.

	All (N = 99)	Orthokeratology (N = 50)	Control (N = 49)	Between groups p-value[+]
Age (y), median (range)	9 (6–12)	9 (6–12)	9 (6–12)	0.367[a]
Gender, female	57%	56%	57%	0.909[b]
Sphere (D)	−2.13 ± 0.99	−2.25 ± 1.05	−2.00 ± 0.92	0.221
Cylinder (D)	−0.90 ± 0.93	−0.82 ± 0.88	−0.98 ± 0.98	0.437[a]
Spherical equivalent (D)	−2.58 ± 1.12	−2.66 ± 1.22	−2.49 ± 1.02	0.465
Axial length (mm)	24.3 ± 0.8	24.4 ± 0.7	24.2 ± 0.9	0.162
Central cornea				
ECD (cells/mm^2)[#]	3271 ± 215	3241 ± 178	3302 ± 246	0.160
CV (%)[#]	24.49 ± 1.92	24.67 ± 1.96	24.31 ± 1.88	0.346
HEX (%)	71.47 ± 7.11	71.06 ± 7.34	71.90 ± 6.92	0.560
Superior cornea				
ECD (cells/mm^2)	3475 ± 287	3461 ± 226	3488 ± 341	0.648
CV (%)	26.70 ± 3.26	26.95 ± 2.89	26.45 ± 3.62	0.451
HEX (%)	71.07 ± 7.45	69.24 ± 6.48	72.94 ± 7.97	**0.013**

ECD: endothelial cell density; CV: coefficient of variation in cell size; HEX: hexagonality.
[+] Probability values for between group differences using unpaired *t*-tests (unless otherwise specified); bold for p-values < 0.05.
[a] Mann-Whitney *U* tests.
[b] Pearson Chi-square.
[#] Significant differences in ECD and CV between the central and superior cornea using paired *t*-tests, p-values < 0.001.

endothelium, three were longitudinal studies. Hiraoka et al. [10] and Nieto-Bone et al. [14] included adults in their studies and they did not find significant change in ECD, whereas Cheung and Cho [13] reported ECD reduction in the children. As ECD can be affected by normal ageing in children, without information from control subjects, the change or lack of change in corneal endothelial morphology after ortho-k can be due to ageing or ortho-k lens wear, or both.

Previous studies mainly focused on changes in the central cornea, but little is known about the effects on the peripheral cornea. As the ortho-k lens is large and covers over 90% of the cornea, its use may lead to changes in the peripheral cornea which may differ from those observed in the central cornea. The primary objective of the current study was to compare the changes in endothelial morphology in the central and superior cornea over two years in children wearing ortho-k and controls wearing single-vision spectacles. The secondary objectives were to determine the morphological differences between the central and superior locations, and to determine factors affecting the endothelial morphology.

2. Methods

Endothelial images of subjects who had completed the Retardation Of Myopia In Orthokeratology (ROMIO) [4] and Toric Orthokeratology – Slowing Eye Elongation (TO-SEE) [7] studies were evaluated. These two studies investigated the effectiveness of orthokeratology for myopia control in children. The lenses and solutions used in these studies have been described elsewhere [4,7]. Endothelial images for the central and four peripheral corneal locations were captured using a specular microscope, TOPCON SP-2000P, but only images from the central and superior cornea were analysed. The superior cornea was selected as the peripheral site because pilot results showed a significantly highest ECD in this corneal location whereas there were no significant differences in ECD in the inferior, temporal and nasal cornea compared to the central cornea [13]. This may be related to the increased coverage of this part of the cornea by the upper eyelid in Asian eyes. For each subject, at least three images were captured for each corneal location and the clearest image was selected for analysis. The first image was selected if the image quality was similar for all the three captures [23]. Data from eyes with poor image quality or in which the cell count was less than 100 were excluded. Endothelial cells were manually retraced by one masked examiner (JW) trained to use the TOPCON IMAGEnet software (version 1.54). Endothelial cell morphology of the right eyes, including ECD, HEX, and CV, captured at baseline and after two years of the myopia control studies were compared between the ortho-k and control groups.

2.1. Statistical analysis

Commercially available software (SPSS 23.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. Paired *t*-tests were used to compare the baseline endothelial morphology in the two corneal locations for all subjects. Stepwise multiple linear regression was used to evaluate the association between baseline endothelium morphology and demographic data and baseline ocular parameters.

The baseline characteristics between the ortho-k and control subjects were evaluated to ensure that there was no between-group difference at the beginning of the study. The comparisons were performed using unpaired *t*-tests, Mann-Whitney *U* tests, or Pearson Chi-Squares, depending on the type of the data and the normality of the distribution of data. Repeated measures ANOVAs (or ANCOVAs) were used to compare the endothelial morphology at the baseline and the 24-month visits in the two study groups after controlling for covariates identified in the multiple linear regression models for the baseline characteristics. Unpaired *t*-test for between-group comparison of changes in the endothelial morphology was performed if significant interaction was found between time and study group. Factors affecting changes in the endothelial morphology were evaluated for the two study groups using stepwise multiple linear regression.

3. Results

Of the 136 participants who completed the two studies, data from 37 subjects were excluded (16 missing baseline; 21 poor image quality). For the remaining 99 subjects, approximately 50% had used ortho-k. There were no significant differences in the demographic data, including initial age and gender, and baseline ocular parameters, including refractive error and axial length, between the two groups of subjects (Table 1).

3.1. Baseline endothelial morphology

Baseline endothelial morphology for all subjects showed a higher ECD and CV in the superior cornea compared to the central cornea (unpaired *t*-tests, p < 0.001), but no significant difference in HEX