Ophthalmic Technology Assessment

Safety of Overnight Orthokeratology for Myopia

A Report by the American Academy of Ophthalmology

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Objective: To review the published literature to evaluate the safety of overnight orthokeratology (OOK) for the treatment of myopia.

Methods: Repeated searches of peer-reviewed literature were conducted in PubMed (limited to the English language) and the Cochrane Central Register of Controlled Trials (no language limitations) for 2005, 2006, and 2007. The searches yielded 495 citations. The panel reviewed the abstracts of these articles and selected 79 articles of possible clinical relevance for review. Of these 79 full-text articles, 75 were determined to be relevant to the assessment objective.

Results: No studies were rated as having level I evidence. Two premarket applications to the Food and Drug Administration were rated as having level II evidence. There were 2 studies rated as having level II evidence. The main source of reports of adverse events associated with OOK was 38 case reports or noncomparative case series (level III evidence).

Conclusions: The prevalence and incidence of complications associated with OOK have not been determined. Complications, including more than 100 cases of infectious keratitis resulting from gram-positive and gram-negative bacteria and *Acanthamoeba*, have been described in case reports and case series representing observations in undefined populations of OOK users. Data collection was nonstandard. Risk factors for various complications cannot be determined. Because OOK puts patients at risk for vision-threatening complications they may not encounter otherwise, sufficiently large well-designed cohort or randomized controlled studies are needed to provide a more reliable measure of the risks of treatment and to identify risk factors for complications. Overnight orthokeratology for slowing the progression of myopia in children also needs well-designed and properly conducted controlled trials to investigate efficacy. Because of variations in orthokeratology practice, a wide margin of safety should be built into OOK regimens.

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The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to evaluate the peer-reviewed scientific literature, to distill what is well established about the technology, and to help refine the important questions to be answered by future investigations. After appropriate review by all contributors, including legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements.

Background

Orthokeratology is the reduction, modification, or elimination of refractive anomalies by the programmed application of contact lenses.[1] Although permanent changes frequently are desired, investigators generally agree that overnight orthokeratology (OOK) changes of the cornea are only temporary and that to maintain OOK changes, retainer lenses must be worn during the day or during sleep. Orthokeratology has generated both successful outcomes and concern over reported complications. The purpose of this review was to examine the safety of OOK so that those interested in the subject can make a rational assessment of the risks associated with the technique. This assessment does not provide a systematic review of the effectiveness of OOK.

There is worldwide interest in OOK as an alternative to refractive surgical procedures to treat myopia, particularly in young people. The attractiveness of reducing myopia without surgery at perhaps a lower price and using conventional methodology (contact lenses) has not been overlooked by the world market. Children frequently present as

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candidates for OOK because of the parents' desire to prevent myopia progression and age contradictions to refractive surgery. Eye care providers who do not offer surgical options for refractive errors may offer OOK as an additional treatment option to their patients.

The prevalence of myopia is particularly high in certain ethnic populations. Myopia has been reported in 37% of 7560 children in Hong Kong age 5 to 16 years.[2] Myopia prevalence rates of 56% to 85% have been reported in teenagers[3] and young adults[4] in Singapore.

The popularity of various refractive surgical procedures, starting with radial keratotomy in 1980 and subsequently epikeratophakia, excimer laser photorefractive keratectomy and laser in situ keratomileusis, intrastromal corneal ring segments, and intracorneal and intraocular lens implantation demonstrates that many myopic patients are willing to undertake some degree of risk to reduce their dependence on eyeglasses or contact lenses. Although it has been suggested that orthokeratology can slow the progression of myopia in children, 2 controlled, prospective studies have demonstrated a lack of effect of conventional rigid gas-permeable (RGP) contact lenses on the progression of myopia, and it is generally agreed that OOK produces only a temporary effect.[5,6] A pilot study of OOK for myopia control showed less increase in axial length in the OOK group compared with eyeglass wearers.[7] However, this study used historical controls and there was no standardized protocol for fitting the contact lenses for OOK, possibly contributing to the somewhat unpredictable published results for individual children.

History

Multiple methods to eliminate myopia have been recorded historically. Unconfirmed stories suggest that in ancient China, some individuals slept with small weights or sand bags on their eyelids to reduce myopia.[1] In the 19th century, personal necessity prompted August Muller-Gladback, a German ophthalmologist with −14.00 diopters (D) of myopia, to grind corneal contact lenses for himself, and he coined the term *cornea lens*.[8] Although the optics of his contact lenses were satisfactory, unfortunately, he could not wear the contact lenses for more than 30 minutes because of discomfort. In 1888, Eugene Kalt in Paris, France, used glass contact lenses to flatten the keratoconic cornea into a more normal shape.[9]

The first plastic corneal contact lens was designed by Kevin Tuohy in California in 1945[8] and was fit flatter than the anterior corneal curvature (keratometric curvature or K) to encourage exchange of tears. It subsequently was noted that the flat fit of the contact lenses induced irregularities of the cornea surface in wearers, a fact borne out subsequently by the observations of multiple clinicians. Those using the contact lenses themselves reported that their vision was affected by the contact lenses even when they were not wearing them.

Optometrists fitting contact lenses in the 1950s observed similar flattening changes in the corneal curvature and refraction, which led them to note that myopia could be reduced by the type of fit of the contact lens on the cornea.[10–12] In 1957, Morrison[13] reported fitting 1000 young myopic patients with flat-fitting polymethyl methacrylate contact lenses; none showed any progression of myopia over 2 years of follow-up.

Before 1960, publications had noted only the reduction in myopia from contact lenses fit flatter than the corneal curvature. The first advocacy of orthokeratology occurred at the Second World Contact Lens Congress in Chicago in 1962.[14] At that meeting, the proclaimed father of orthokeratology, George Jessen, lectured on Orthofocus, or The Use of Contact Lenses to Reduce Myopia.[15] In 1967, Nolan reported a successful therapeutic plan to reduce myopia using rigid contact lenses.[16]

Widespread use of flat-fitting contact lenses to reduce myopia began, and complications related to this practice soon followed. In 1968, Hartstein argued that keratoconus, or warping, could be caused by hard contact lenses.[17] In 1970, Hartstein and Becker examined a small series of long-term contact lens wearers and suggested that low scleral rigidity was associated with corneal warping; keratoconus or astigmatism was more likely to develop in patients with low rigidity than in those with high scleral rigidity.[18] In 1976, Ing reported irregular astigmatism or corneal warping in 131 patients wearing hard contact lenses.[19]

Reports of corneal irregularities made controversial the use of flat-fitting contact lenses to reduce myopia. Four studies evaluating the safety and effectiveness of orthokeratology with polymethyl methacrylate contact lenses were published between 1977 and 1984. At the University of Houston College of Optometry, Kerns[20–27] conducted a controlled clinical trial over 1000 days comparing 36 eyes subjected to orthokeratology with 26 eyes treated with conventionally fitted rigid contact lenses. Overnight orthokeratology patients experienced marked flattening of the cornea as expected, but the corneal flattening stopped changing after 300 days. Patients showed progressive corneal steepening of the vertical meridian to levels steeper than baseline values, producing long-lasting with-the-rule corneal astigmatism. Changes in refractive error from a 2.6-D decrease to a 1.0-D increase were noted for the OOK group, with induction of average cylinder of 0.42 D. Kerns also noted variability in the fitting process and patient response. Binder et al[28] compared 23 OOK patients and 16 rigid contact lens patients and found unpredictable and uncontrolled responses to OOK. Binder concluded that the risk of resulting corneal warpage was small but that it did exist on a short-term basis. The Berkeley Orthokeratology Study assessed safety by monitoring corneal thickness, keratometry, refraction, corneal edema, corneal astigmatism, and endothelial cell density. Reduction in myopia in the OOK group was 1.01±0.87 D, compared with 0.54±0.58 D in the control group. There were minimal changes between control patients and OOK patients in all parameters and no statistical difference in any category, except that the OOK group required 1.25 times as many office visits.[29,30] The Pacific University study reported effective reduction in myopia of 1.3 D, but results varied from patient to patient.[31,32]

In 1982, Levy reported the first case of permanent loss of vision in a patient being treated with OOK. Vision loss was attributed to scarring from microbial keratitis.[33] Over the next 25 years, the effectiveness of orthokeratology became

more accepted, but the paucity of data on long-term safety did not allow quantitation of the risk of possible complications associated with widespread use.

The Introduction of Modern Overnight Orthokeratology. Three improvements in technology between 1982 and 2000 led to the reemergence of orthokeratology in 2000. One improvement was the advent of highly oxygen-permeable materials. The first of these new materials was 3M fluoropolymer plastic (3M, St. Paul, MN), which could be used for contact lenses and which provided a significantly higher oxygen transmission, or Dk, value than previously seen, enabling safer contact lens wear during sleep.[34] The second improvement was the availability of computer-assisted videokeratography to analyze the surface of the cornea and color-coded maps to provide more information to clinicians on the geographic apical center of the cornea, the optical center of the cornea, and the elevation and curvature of the cornea.[35–38] Practitioners then could monitor the effects of contact lens wear on corneal topography more accurately.[39–41] The third improvement was the advent of reverse geometry contact lenses, typified by a flat-back central optical zone and steeper intermediate zone, which permitted more rapid flattening of the central corneal zone than conventional contact lens designs had permitted in the past.[42–45]

Orthokeratology with reverse-geometry–designed contact lenses reduces myopia by flattening the central cornea. The amount of central cornea flattening measured topographically correlates closely with the amount of myopic reduction. After overnight wear of reverse-geometry contact lenses, histologic and in vivo studies have shown that the corneal epithelium is thinned centrally, which reduces the corneal sagittal height and is responsible for the reduction in myopia.[46] Overnight wear of reverse-geometry contact lenses has been shown to inhibit central corneal swelling because of central pressure of the flat lens on the central cornea; the peripheral space outside the central flat zone permits stromal edema, accentuating the central corneal flattening with peripheral elevation.[47] With reverse geometry contact lenses, the secondary curve junction of the posterior lens surface is steep and the periphery of the lens forms a tear reservoir over the midperipheral cornea, effectively redistributing the central edema to the peripheral epithelium.[48] Thinning of the central epithelium has been demonstrated by optical coherence tomography.[49]

The effectiveness of OOK generally is accepted as a temporary treatment for the reduction of mild myopia.[1,50,51] Two manufacturers of OOK contact lenses, Paragon Vision Sciences (Mesa, AZ) and Euclid Systems Corporation (Herndon, VA), reported reductions in myopia of up to 1.50 D with no induction of astigmatism in their premarket approval applications to the U.S. Food and Drug Administration (FDA).[52,53]

Food and Drug Administration Status

In June 2002, Paragon Vision Sciences received FDA approval for the Paragon Corneal Refractive Therapy (CRT), CRT 100, Quadra RG, and Quadra RG 100 (paflufocon B, paflufocon D) RGP contact lenses for the reduction of myopia.[52] The Paragon CRT was indicated for overnight wear to correct myopia of up to −6.00 D in eyes with astigmatism of up to 1.75 D, and the Quadra RG was indicated for overnight wear to correct myopia up to −3.00 D in eyes with astigmatism of up to 1.50 D. Approval was granted based on a premarket study of 281 subjects followed up for 9 months. Adverse events reported in the premarket application are listed in Table 1; 4 patients with adverse events left the study. Final approval was given by the FDA without any age restriction, although the FDA advisory panel suggested that approval be limited to individuals 18 years old and older.

In June 2004, Euclid Systems received FDA approval for OOK, and the lens material was subsequently acquired by Bausch & Lomb (Rochester, NY), which now markets the Boston Equalens (BE) material in different designs manufactured by different laboratories.[53] The Euclid lens was indicated for overnight wear for temporary reduction of myopia of up to −5.00 D in eyes with astigmatism of up to 1.50 D. One design is the Boston Orthokeratology Oprifocon A shaping contact lens for overnight wear. Other designs in the Bausch & Lomb Vision Shaping Treatment Method include the Contex OK series (Sherman Oaks, CA), the BE Retainer lens (BE Enterprises, Vancouver, Canada), the Dream Lens (DreimLens, Inc., Indian Harbor Beach, FL), and the Emerald Lens (Euclid Systems). Adverse events reported in the premarket application are listed in Table 1; none were serious.

The FDA requires that all practitioners in the United States be certified to a minimum standard of orthokeratology education. The contact lens manufacturers provide online education and a certification course for practitioners using these lenses. For example, Bausch & Lomb provides an Internet-based training program.[54] The BE Retainer lens Web site states: "There is a requirement imposed by the HPFB (Health Product Food Branch of Health Canada) and the FDA (Food and Drug Administration in the United States) that all practitioners are certified to a minimum standard of orthokeratology education. To meet this requirement, BE Enterprises and Bausch & Lomb have made an online certification course and test available. It takes around 15 minutes to review and complete the certification course."[55] A popular contact lens journal noted: "Becoming certified in corneal reshaping is straightforward. Learning the dynamics of reverse-geometry lenses will set you apart from the average contact lens practitioner. Certification courses cost nothing but a few hours of well-spent time."[56]

Resource Requirements

The cost of OOK varies. For simple cases, the cost can range from $1500 to $2500, depending on the length of treatment and the number of contact lenses prescribed.

Questions for Assessment

The focus of this assessment is to address the following question: Is OOK safe for the temporary treatment of myopia?

Table 1. Data Reported to the Food and Drug Administration in Premarket Approval Application for Orthokeratology Lenses (Level II Evidence)

Company	No.	Reported Adverse Event/Complication	Comments
Boston Orthokeratology Oprifocon A shaping lenses for overnight wear for Bausch & Lomb Vision Shaping Treatment (P10062;S001-S004)*	191 (378 eyes)	1 eye: BSCVA reduced to 20/50 (decentered lens) 1 eye: BSCVA reduced to 20/60 (central staining) 1 eye: BSCVA reduced to 20/60 (no reason given) 12 adverse events reported by 10 subjects: 2 eyes: bilateral grade 4 staining with vision decrease to 20/80 1 eye: grade 3 corneal staining (dislodged lens) 1 eye: corneal distortion with vision decrease to 20/200 and rippling on the cornea 2 eyes: bilateral iritis with trace cells and flare in both eyes 1 eye: corneal infiltrates 2 eyes: abrasion (grade 3 staining)	Study period was 9 mos; 29% (110 eyes) discontinued lens wear during the study period. All eyes with acuity reduction reported as returning to normal vision except 2 eyes of 1 subject with ≥2 lines loss of BSCVA. Return to pretreatment VA for this subject was not reported on the study form but was reported verbally. 4 patients reporting adverse effects discontinued the study. No age restriction, but boxed warning states that the safety and efficacy has not been studied clinically in adolescent and pediatric subjects (study population was 18 years or older).
Paragon CRT, CRT 100, Quadra RG, Quadra RG 100 (paflufocon B, paflufocon D) rigid gas permeable contact lenses for corneal refractive therapy (P870024/S43)†	205 (408 eyes)	28 eyes (12%): 1 line loss of BSCVA 2 eyes (1%): 2 lines loss of BSCVA 5 eyes (2%): >2 lines loss of BSCVA 1 eye: scratched with lens plunger and/or lens 1 eye: diffuse subepithelial infiltrative keratitis 1 eye: tearing/discomfort	Study enrolled 205 subjects (408 eyes); 121 completed 9 months of treatment; safety analysis was conducted on all eyes. 24 subjects were between the age of 12 and 18 years. The FDA advisory panel recommended that the approved labeling indication should be ≥18 years; the FDA did not concur with this recommendation. 83 subjects (40%) discontinued lens wear during the study period: 44 for unacceptable vision; 3 for reasons of comfort; remainder for lack of interest, lost to follow-up, missed visits, other.

BSCVA = best spectacle-corrected visual acuity; FDA = Food and Drug Administration; VA = visual acuity.
*U.S. Food and Drug Administration Center for Devices and Radiological Health. Euclid Systems Corporation. Summary of safety and effectiveness data from premarket approval application number P010062. 2004. Available at: http://www.fda.gov/cdrh/pdf/p010062b.pdf. Accessed May 22, 2008.
†U.S. Food and Drug Administration Center for Devices and Radiological Health. Paragon Vision Sciences. Summary of safety and effectiveness data from premarket approval application supplement number P870024/S43. 2002. Available at: http://www.fda.gov/cdrh/pdf/P870024S043b.pdf. Accessed May 22, 2008.

Description of Evidence

The peer-reviewed, English language literature was reviewed on December 22, 2005, September 15, 2006, and October 15, 2007, in PubMed (limited to English language) and on January 5, 2006, September 15, 2006, and October 15, 2007, in the Cochrane Library (no language limitations). Key words in the search were the MeSH headings *contact lenses* and *myopia/therapy* or *myopia/rehabilitation* combined with the text word *orthokeratology*. There were no date restrictions on the initial literature search. The authors assessed the 495 citations resulting from the electronic searches and selected 79 citations that definitely or potentially met the inclusion criteria. Any publication on adverse effects or complications in individuals who underwent treatment with overnight use of rigid contact lenses to produce a change in refraction during the day was included; regardless of publication type; patient age; or country of origin. The reviewers were not masked to either trial results or publication details. Abstracts of meeting presentations are not subject to peer review and are not included in the analysis. Additional studies were identified after the literature searches by surveillance of the literature.

The authors reviewed the full text of the 79 articles and selected 75 that met the inclusion criteria. Under the guidance of the panel methodologist, one of the following ratings of level of evidence was assigned to each of the selected articles. The rating scale is based on the one developed by the British Centre for Evidence-Based Medicine. A level I rating was assigned to well-designed and well-conducted randomized clinical trials; a level II rating was assigned to well-designed case-control and cohort studies and poor-quality randomized studies; and a level III rating was assigned to case series, case reports, and poor-quality cohort and case-control studies. No studies were rated as level I evidence. Information from the premarket applications to the FDA was rated as level II evidence.

There were 2 studies rated as level II evidence.[57,58] Of the other articles reviewed, 38 were case reports or series (level III evidence) reporting adverse effects from OOK.[33,59–95] Fourteen articles[20–30,96–98] reported on orthokeratology in the late 1970s to early 1980s. Thirteen articles were reviews, editorials, commentary, or letters to the editor[1,2,99–111] and there was one other study[112] of microbial flora in tears with OOK. Three articles[46,47,113] studied the mechanism of action of orthokeratology and 2 articles were experimental.[114,115] Two articles[116,117] were not specifically about OOK, but they reported corneal changes in long-term contact lens wearers.

Assessing the safety of treatment usually is more difficult than assessing the benefits, because adverse events can be multiple and generally are not identifiable in advance. Adverse events often are not reported or are reported inconsistently, and reports are difficult to retrieve from the published literature because of poor indexing.[118] Case reports and case series represent observations for an undefined population of OOK users and are not collected in a standardized manner. Without knowledge of the number of users, an accurate rate of adverse events is impossible to calculate. Only long-term prospective studies and randomized controlled trials, wherein the number of patients experiencing an adverse event and the total number of patients undergoing OOK are known, can provide a more reliable measure of risk. Unfortunately, none of the peer reviewed literature on OOK could be rated as level I evidence, thus limiting the quality of any safety and risk assessment for OOK.

Published Results

Table 1 lists adverse events from the premarket approval applications to the FDA. In randomized controlled studies of OOK rated as level II evidence, Lipson et al[57] reported no adverse events in 15 months of follow-up of 65 adult patients, and Lui and Edwards[58] reported no adverse events in 100 days of follow-up of 14 patients. In level III-rated evidence, Mika et al[60] reported no adverse events in 6 months of follow-up of 16 girls (age range, 10–16 years), and Soni and Nguyen[61] reported 9 adverse events in 1 year of follow-up (n = 201). One patient had recurrent corneal erosions and the other 8 events were not sight threatening and resolved completely.[61] In an article identified by surveillance of the literature, Lipson reported results of a retrospective review of 296 patients undergoing OOK over a 4-year period.[119] There were 3 adverse events (defined as microbial keratitis or a corneal ulcer, a corneal abrasion requiring medical treatment, or a corneal scar) during the study period that did not result in a loss of best-corrected visual acuity. There was no difference in safety and efficacy of OOK in children younger than 12 years compared with children and adults older than 12 years of age.[119]

Table 2 lists reports of infectious keratitis. Some corneal ulcers were reported in more than 1 publication, and care was taken to eliminate duplications in review articles and to list each adverse event only once. As previously noted, the value of the data is limited, because no denominator exists for the treatment population and the total number of patients undergoing OOK is unknown. Table 3 lists reports of other adverse events associated with OOK; these additional complications are discussed below.

Infectious Keratitis

Reports of microbial keratitis associated with the use of OOK lenses from 5 different centers on 3 different continents were published simultaneously in the journal *Cornea* in 2005.[59,72,87,90,91] The accompanying commentary raised 3 significant concerns about the undue occurrence of infectious microbial keratitis in these reports.[106] Most of these infections were central and severe, caused by aggressive organisms such as gram-negative rods or *Acanthamoeba* that are capable of causing significant vision loss from corneal scarring. Second, most cases occurred in children or adolescents. Third, the infections were associated with multiple brands of RGP contact lenses and occurred in different countries. These simultaneous reports of cases of microbial keratitis instigated safety concerns about OOK and scrutiny of the procedure.

Ladage et al[115] reported a statistically significant increase in binding of *Pseudomonas aeruginosa* to the rabbit cornea in the presence of contact lens wear. They noted greater cornea *Pseudomonas* binding to hyper-oxygen transmitting polymer RGP contact lenses when fitted as OOK lenses compared with the alignment fit RGP lenses supporting exposed risk for OOK versus alignment-fit RGP contact lenses, even with the highest Dk value (most oxygen permeable) materials. Under alignment fit conditions, clinical RGP contact lens wear of the highest Dk material showed no increase in *P. aeruginosa* binding after 30 nights of human wear.[120] This evidence suggests that the OOK fit produces the higher risk for microbial keratitis compared with just the overnight wear. Ladage et al also noted an increase in central corneal epithelial thinning, stromal thickening, and surface cell damage with overnight contact lenses.

Asbell[114] reported that *P. aeruginosa* binding was more common in smooth epithelial cells found in deeper cell layers and less in mature cells with microvilli. In individual cells with both smooth and villous surfaces, *Pseudomonas* preferentially bound to the smooth areas of the cells.

Boost and Cho[112] studied flora in 41 students with multiple conjunctival cultures before and during OOK, finding no significant difference in levels or type of pathogens over time with contact lens wear. They concluded that ocular flora was not altered by OOK, but variations in contact lens care and cleaning and disinfection regimens were more likely to influence bacteria present. Microbial keratitis, then, likely results from the introduction of opportunistic pathogens already present on the ocular surface into compromised corneal epithelial cells.

More than 100 cases of infectious keratitis associated with OOK have been reported since 2001 in the literature reviewed for this assessment; the listing in Table 2 shows the case reports and offending organisms. Of these, *Pseudomonas* was the leading pathogen, with 39 documented cases. In addition, there were 32 patients with *Acanthamoeba*, 4 with *Serratia* species, 3 with fungal ulcers, 2 with *Staphylococcus* species, and 1 with *Nocardia*. Approx-

Table 2. Infectious Keratitis Associated with

Author, Year	Country	Level of Evidence	No. (Patients)	Age (yrs)
Araki-Sasaki et al, 2005[59]	Japan	III	1	17
Chen et al, 2001[64]	Taiwan	III	1	9
Hsiao et al, 2004[73]	Taiwan*	III	6	Average, 13 (range, 9–17)
Hsiao et al, 2005[72]	Taiwan*	III	20 patients/21 eyes	Average, 14 (range, 9–21)
Hsiao et al, 2007[74]	Taiwan*	III	8	Mean, 11.2
Hutchinson & Apel, 2002[75]	Australia	III	2	60 29
Lang & Rah, 2004[77]	USA	III	2	29 12
Lau et al, 2003[78]	Taiwan	III	2	11 11
Lu et al, 2001[80]	China	III	16	—
Macsai, 2005[81]	USA	III	2	9 11
Poole et al, 2003[82]	UK	III	1	22
Priel et al, 2006[83]	Israel	III	1	16
Robertson et al, 2007[122]	USA	III	1	19
Sun et al, 2006[86]	China	III	28	Average, 16 (range, 10–21)
Tseng et al, 2005[87]	Taiwan	III	9/10 eyes	Mean, 12.3 (range, 8–17)
Wang & Lim, 2003[88]	Singapore	III	1	14
Watt et al, 2007[89]	Australia	III	7	Average, 17 (range, 12–22)
Wilhelmus 2005[90]	USA	III	1	16
Xuguang et al, 2003[95]	China	III	4	Average, 17 (range, 15–19)
Yepes et al, 2005[91]	Canada	III	3	41 14 12
Ying-Cheng et al, 2006[92]	Taiwan	III	1	16
Young et al, 2003[94]	Hong Kong	III	1	37
Young et al, 2004[93]	Hong Kong	III	6	Mean, 12.1 (range, 9–14)

BCVA = best-corrected visual acuity; BSCVA = best spectacle-corrected visual acuity; UK = United Kingdom; USA = United States of America; VA = visual acuity.
*These studies report cases at the Chang Gung Memorial Hospital, Taipei, and may be duplicated reports.

Orthokeratology in Published Reports

Type of Study	Reported Pathogen	Comments/Visual Acuity after Treatment
Case report	*Pseudomonas*	Glycocalyx biofilm formation confirmed on contact lenses No loss of BCVA
Single case report	*Serratia marcescens*	9 yr-old had 6 mos orthokeratology in USA; BCVA after treatment, 20/20
Noncomparative case series	*Pseudomonas*	BCVA range 20/20 to 20/200; 4 lost BCVA Cases occurred from January 2001 through December 2002
Retrospective noncomparative case series	9, *Pseudomonas* 2, *Staphylococcus* 1, *Serratia* 1, *Acanthamoeba* 8, negative culture results	Final VA range 20/20 to 20/100; 4 lost BCVA Cases occurred from April 2000 to March 2003; there is an overlap with cases reported in Hsiao 2004
Case series	4, gram-negative bacteria 4, negative culture results	Cases occurred from July 1, 1998, through December 31, 2002; there is an overlap with cases reported in Hsiao 2004 and Hsiao 2005
Case report	1, *Pseudomonas* 1, *Acanthamoeba*	BCVA, 20/40 (unchanged) BCVA, 20/120
Noncomparative case series	1, unknown 1, *Serratia*	No loss of BCVA
Case report	*Pseudomonas*	BCVA left eye, 20/200 BCVA, 20/25
Noncomparative case series	7, *Pseudomonas* 8, *Acanthamoeba* 1, Mycotic keratitis	9 required lamellar keratoplasty or penetrating keratoplasty
Case report	1, *Pseudomonas* 1, *Haemophilus influenzae*	BCVA, 20/30 Each patient lost 2 lines of BCVA
Single case report	Unknown	BCVA 20/30
Single case report	*Pseudomonas*	BSCVA 20/50
Single case report	*Acanthamoeba*	BCVA, light perception with projection. Additional complications: secondary angle-closure glaucoma, mature cataract
Noncomparative case series	13, *Acanthamoeba* 8, *Pseudomonas* 2, Fungus 1, *Nocardia* 1, *Providencia stuartii* 1, gram-negative rods 2, negative	Cases occurred from March 2000 through August 2001; 3 of the cases reported here are in the time range for the cases reported in Xuguang 2003 (same first author) VA after treatment was not available for the fourth case.
Noncomparative case series	Microbial keratitis; 90% with central corneal infiltrates 3, *Acanthamoeba* 1, *Pseudomonas* 1, gram negative 4, negative results	Denominator unknown; type of lens and details of wear unknown 4 eyes BCVA 20/30 or worse; 1 eye with hand movements only
Single case report	*P. aeruginosa* keratitis; stellate-shaped central corneal infiltrate	BCVA 20/25
Survey	3, *Pseudomonas* 1, *Acanthamoeba* 3, Unknown	2 cases were previously reported by Hutchinson and are not included here No loss of BCVA
Single case report	*Acanthamoeba*	VA 20/100
Case report	*Acanthamoeba*	Cases occurred in June 2001 (n = 1), August 2001 (n = 2), and February 2002 (n = 1) 1 case no VA impairment; VA in other cases from 20/50 to 20/75
Case report	1, *Acanthamoeba* 1, *Serratia* 1, *Pseudomonas*	BCVA, hand movements BCVA, 20/80 BCVA, 20/20
Single case report	*P. aeruginosa* *P. putida* *Burkholderia cepacia*	BCSVA, 20/20
Single case report	*Pseudomonas*	BCVA, 20/30
Noncomparative case series	5, *Pseudomonas* 1, unknown	All lost BCVA; BSCVA range, 20/20–20/200

Table 3. Other Complications of Orthokeratology

Author/Year	Country	Level of Evidence	Number	Type of Study	Adverse Effect/ Complication	Comments
Hiraoka et al, 2004[69]	Japan	III	31 patients/ 52 eyes	Prospective noncomparative case series	None	No endothelial cell loss noted with specular microscopy
Berntsen et al, 2005[63]	USA	III	20	Prospective noncomparative case series	Astigmatism	Higher-order aberrations increased in 5-mm pupils from baseline after 1 month wear ($P < 0.0001$)
Hiraoka et al, 2005[71]	Japan	III	39 patients/ 64 eyes	Prospective noncomparative case series	Astigmatism	Higher-order aberrations in 64 eyes of 39 patients
Joslin et al, 2003[76]	USA	III	9 patients/ 18 eyes	Prospective noncomparative case series	Astigmatism	Higher-order aberrations in 18 eyes of 9 patients
Stillitano et al, 2004[85]	Brazil	III	14 patients/ 26 eyes	Prospective cohort study	Astigmatism	Higher-order aberrations, especially spherical aberration and coma, increased from baseline after night 1 ($P = 0.006$) and night 8 of wear ($P = 0.004$)
Cheung et al, 2006[65]	Hong Kong	III	1	Single case report	Concentric white lines	Concentric white lines in paracentral cornea representing nerve bundles of the sub-basal plexus
Cho et al, 2005[66]	Hong Kong	III	35	Noncomparative case series	Corneal pigmentation	Pigment present in 90% of 35 patients followed for 1 year
Rah et al, 2002[84]	USA	III	6	Noncomparative case series	Corneal pigmentation	5 of 6 patients followed 6 months to 2 years
Liang et al, 2003[79]	Taiwan	III	2	Case report	Corneal pigmentation	2 patients
Cho et al, 2002[67]	Hong Kong	III	1	Single case report	Corneal pigmentation	1 patient
Hiraoka et al, 2004[70]	Japan	III	1	Single case report	Corneal pigmentation	1 patient
Levy et al, 1982[33]	Canada	III	1	Single case report	Recurrent corneal erosion	1983 series, symptoms persisted 1 year
Gupta & Weinreb, 1997[68]	USA	III	1	Single case report	Infected filtering bleb	4-year status post-trabeculectomy with mitomycin-C

imately one third of the infectious keratitis cases were those reported in *Cornea* articles in 2005.

Interpreting these data to evaluate the safety of OOK is difficult, because the denominator of all orthokeratology patients is unknown. After the first reported cases in China, Taiwan, Hong Kong, and Japan, government regulation of orthokeratology was instituted for the expressed purpose of reducing complications of OOK.[1,110,111] In China, reported complications led to the registration of approved contact lenses and government authorization of orthokeratology providers.[110]

Endothelium

Overnight orthokeratology use for 1 year does not influence density or the morphologic features of corneal endothelial cells when assessed by specular microscopy, although the range of insult that could be detected by specular microscopy is not known.[69] The coefficient of variation of endothelial cell density was 22.3, a large number but consistent with conventional specular microscopy data. Corneal thickness is not a useful measure of corneal health because the intentional flattening of the central epithelium makes pachymetry measurements artifactually low. There was no change in polymegethism or polymorphism noted in study patients compared with normal subjects. The Berkeley Study reported that the endothelium was not adversely affected by orthokeratology during the 1-year follow-up.[29] Only longer-term studies can establish the risks of endothelial dysfunction.

Induced Astigmatism

Higher-order positive spherical aberration is induced by OOK.[63,76,85] Hiraoka et al[71] reported that 64 eyes of 39 patients undergoing OOK had successfully reduced myopia from −2.6 D to −0.17 D, but increased third- and fourth-order aberration significantly in the vertical and horizontal corneal axis. The increase of higher-order aberration is similar to that observed after radial keratotomy and LASIK (i.e., surgically induced).

Concentric White Lines

Fine concentric white lines in the paracentral epithelium were described by Cheung et al.[65] These fibrillary lines were similar to those seen in patients with keratoconus and were thought to represent nerve bundles in the subbasilar plexus. In 1975, Bron[121] reported single lines in normal patients that ultimately were determined to be corneal nerves. These concentric lines are of no known clinical significance other than that they were induced by OOK.

Corneal Epithelial Iron Lines

Multiple observers have reported pigmented iron lines in the paracentral cornea in a number of patients. Cho et al[66] reported corneal pigmented iron lines in 35 patients undergoing OOK who were followed up for 12 months. The lines were noted in 17% of patients at 3 months, 49% of patients at 6 months, and 90% of patients at 12 months in both eyes. Rah et al[84] noted an iron line in 5 of 6 patients fitted with OOK lenses; 5 patients were fitted with CRT lenses (Paragon), and 4 of 5 iron lines were in patients with the CRT lens. One patient fitted with the Dream lens design also had an iron line. Additional iron lines similar to Hudson-Stähli lines were reported in OOK patients by Liang et al,[79] Cho et al,[67] and Hiraoka et al.[70] The clinical significance of the iron line is probably minimal.

Recurrent Corneal Erosion

Recurrent corneal erosion syndrome after OOK was reported by Levy in 1980.[33] Symptoms persisted for 2 weeks and the patient experienced further recurrences during the next 12 months. Before beginning orthokeratology treatment, the patient had been examined by an ophthalmologist who found that the examination showed normal results except for a slightly low Schirmer test score. Soni and Nguyen[61] reported on 1 patient who had recurrent corneal erosions in the left eye only. The small punctate abrasions cleared in several days and the OOK treatment was stopped.

Infected Filtering Bleb

In 1997, Gupta and Weinreb[68] reported an infected filtering bleb in a patient who began an orthokeratology program 10 weeks earlier. The patient was fitted with a flatter pair of contact lenses 1 week before seeking treatment for an avascular bleb with a yellowish infiltrate. The patient responded to treatment with fortified topical antibiotics and systemic antibiotics, and 1 month later seemed to be normal.

Discussion

The safety of orthokeratology is difficult to assess. In the 2 premarket applications, 1 did not study patients younger than 18 years, and in the other, the FDA advisory panel recommended approval for individuals 18 years of age and older.

Early case reports of complications, especially in children, may reflect local rather than national practices. Details of individual complications such as the specific contact lens, wear regimen, and compliance with the cleaning regimen frequently are not reported. As with most clinical diseases, underreporting of complications is assumed. After initial reports, journal editors may not consider additional reports as having much value after the first cases are in print.

Many cases of infectious keratitis occurred in teenagers and children. The large number of children and adolescents in these series and the risk of sight-threatening complications necessitate the highest level of vigilance. The wide variation in organisms, treatment, and patients led to wide variation in outcomes, with some patients losing vision and other patients retaining good vision. Therein lies one difficulty of evaluating the safety of OOK: not all patients who had infectious keratitis sustained damage because of the complication. However, damage assessment is only one aspect of evaluation of risk, and the OOK process puts a number of patients at risk for potentially vision-threatening complications that they may not encounter otherwise. The severity of the adverse event often is determined by the speed of diagnosis and the effectiveness of therapy administered by the treating physician.

The *Acanthamoeba* keratitis cases were severe and sight-threatening and can be bilateral.[122] The *Acanthamoeba* keratitis cases in children may be the result of deficient levels of tear film immunoglobulin A,[123] which have been shown to be reduced in patients with clinical *Acanthamoeba* keratitis. This evidence suggests that exposing children as young as 8 years to the possibility of bilateral *Acanthamoeba* keratitis infection from OOK requires a solid rationale for use in that group of patients.

Rinsing RGP contact lenses with tap water is a common practice and is mentioned on the package insert of RGP contact lenses. The use of nonsterile water (e.g., tap water) by children and adults on RGP contact lenses and contact lens cases should be discouraged in favor of commercially available multipurpose contact lens solutions, and practitioners should recommend strongly the complete elimination of tap water from all steps in OOK regimens.[124]

Fitting reverse-geometry contact lenses according to K-readings and fluorescein patterns is subject to wide clinical variation from practitioner to practitioner. The interpretation of fluorescein patterns requires skill and experience; the central flat zone of a reverse-geometry contact lens is more discernible to experienced practitioners. As with any technique, a learning curve for practitioners influences the effectiveness and the safety of OOK for individual patients.

Because specific risks associated with OOK have not been elucidated or quantified, it becomes imperative that patients, families, and practitioners realize that the risk factors associated with orthokeratology are poorly understood and extend throughout the use of the contact lenses. In the studies reviewed, many patients wore hard contact lenses for more than 2 years before encountering vision loss resulting from microbial keratitis.

The prevalence and incidence of complications associated with OOK have not been determined. Complications have been described only in case series and case reports representing observations in undefined populations of OOK users. Furthermore, both data collection and reporting lack standardization. The large number of children and adolescents in these series and the risk of sight-threatening complications in children and adolescents necessitates the highest level of vigilance.

Risk factors for various complications of OOK cannot be determined because there is variation in patient characteristics, provider credentialing and training, contact lens type, contact lens fitting practice, wear regimen, care regimen, compliance, and follow-up among the various case reports and series and in clinical practice. Clinician training, skill,

and experience also may be factors in the safety of OOK. For these reasons, a wide margin of safety should be built into OOK practice, and regulation by governmental or other appropriate bodies may play a role in ensuring that appropriate standards of care are followed.

There are insufficient data to compare the risks of OOK with those associated with other types of contact lenses or refractive surgery. The increased risk of infectious keratitis with overnight contact lens wear compared with daytime contact lens wear is addressed in the Refractive Errors & Refractive Surgery Preferred Practice Pattern.[125] The risk standard that myopia correction is judged against is eyeglass wear, which carries little risk. Comparing OOK with surgical correction, such as LASIK, is not appropriate because LASIK is an invasive procedure. LASIK is intended to alter the shape of the cornea permanently by removing corneal tissue and has its own risks and complications; it is not FDA-approved for use in children. Practitioners who offer other treatments to correct myopia should evaluate the risks of OOK with respect to the other treatments commensurate with their abilities and local standards.[105] Ultimately, safety is more likely to be achieved with ethical and knowledgeable practitioners and educated patients. The application of OOK in children and adolescents should be undertaken very cautiously, and the practice of OOK should be pursued in all patients with these goals in mind.

Future Research

Future research should be directed at assessing the rate of infectious keratitis among OOK users and whether the rate varies by age or clinical characteristics such as contact lens type, wear regimen, or fitting parameters. Sufficiently large, well-designed cohort or randomized controlled studies are needed to provide a more reliable measure of the risks of treatment and to identify risk factors for complications. Overnight orthokeratology for slowing the progression of myopia in children also needs to be assessed by well-designed and properly conducted controlled trials to determine efficacy. Research also should consider contact lens material, contact lens design, and treatment schedule to optimize refractive effect and to minimize the risk of infectious keratitis. Finally, continuing basic science research into the pathogenesis, prevention, and treatment of microbial keratitis is warranted, with the goal of saving vision in patients affected by this complication.

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	L	Alcon Laboratories, Inc., Allergan, Inc.
William J. Reinhart, MD	N	
Ira J. Udell, MD	C	Alcon Laboratories, Inc., InSite Vision, Inc., Vistakon

Code	Category	Specific Financial Relationship
C	Consultant/Advisor	Consultant fee, paid advisory boards or fees for attending a meeting.
E	Employee	Employed by a commercial entity.
L	Lecture Fees	Lecture fees (honoraria), travel fees or reimbursements when speaking at the invitation of a commercial entity.
O	Equity Owner	Equity ownership/stock options of publicly or privately traded firms (excluding mutual funds) with manufacturers of commercial ophthalmic products or commercial ophthalmic services.
P	Patents/Royalty	Patents and/or royalties that might be viewed as creating a potential conflict of interest.
S	Grant Support	Grant support.
N	None	No financial interest. May be stated when such interests might falsely be suspected.