Myopia is now a major public health problem, and high myopia is ranked second as the leading cause of visual impairment globally. Moreover, the onset of visual complications from myopia occurs much earlier than other causes of blindness and thus its impact on quality of life is also seen earlier. The economic burden of myopia is also great, with expenditures on myopia-related optical corrections estimated more than $2 billion annually in the United States alone. For those reasons alone, methods for preventing myopia and controlling its progression are urgently needed.

Myopia Control and OrthoK

Owing to the severity of ocular complications associated with high myopia, tremendous efforts have been put into the investigation of interventions that may retard the progression of myopia in children, thus decreasing the severity of myopia at maturity. It has been consistently demonstrated in various animal models including primates that optical interventions have a strong impact on refractive error development. OrthoK, among other novel contact lens designs being investigated, has been shown in multiple clinical studies as effective in slowing down myopic progression. Combining its unique advantage of providing clear unaided vision during daytime, overnight
OrthoK has become one of the most popular choices among children for refractive correction. However with the rapid increase of the utilization of OrthoK worldwide, potential complications associated with this treatment, especially used as overnight modality, have become a significant concern.

OBJECTIVES

The objective of this study was to systematically compile the current evidence from relevant peer-reviewed publications both in English and Chinese to evaluate the safety of OrthoK for the temporary treatment of myopia. Because the visual side effects were related to the design of the lens, the baseline myopia, and practitioners’ clinical expertise in fitting evaluation, this review only focuses on ocular side effects of the treatment rather than visual complications, such as undercorrection of myopia, daytime vision regression, induced astigmatism, and induced higher order aberration.

METHODS

Selecting Studies for This Review

Types of Studies

Data from all types of relevant clinical studies including case series, case reports, patient/practitioner surveys, retrospective and prospective cohort studies, and clinical trials were included in the review. Because the focus of the review was on the incidence of side effects related to OrthoK, there was no limitation on the primary objective of the studies, that is, whether the treatment was used for myopia correction or for myopia control. Similarly, publications on OrthoK lenses used as overnight or daytime wear modalities were both included in the review.

Search Methods for Identification of Studies

As a large proportion of previously published OrthoK-related complications were from East Asia, especially from China, the literature published both in English and Chinese were identified from the Cochrane Library, MEDLINE, EMBASE, CNKI, CQVIP, and WANFANG DATA using the following strategies.

(1) orthokeratolog* OR orthok* OR corneal reshaping OR reverse geometry lens
(2) myopia AND correct* OR control OR retardation OR therapy* OR treatment*
(3) keratitis OR safety OR side effects OR adverse effects OR complications OR risk
(4) (1) AND (2) AND (3)

The publication type is restricted to clinical studies and the material of the OrthoK lens was limited to gas-permeable material only.

The titles and abstracts were assessed and full copies of all potentially or definitively relevant studies were obtained to determine whether the studies met the criteria for inclusion in this review. References of all included publications were also reviewed.

Validity Assessment

Owing to the retrospective nature of the studies reporting treatment-related side effects, most reviewed studies were subject to some level of biases such as selection bias, performance bias, attrition bias, and/or detection bias. As a result, none of the relevant publications were excluded from the review based on the risks of bias.

DESCRIPTION OF STUDIES

The original electronic searches identified 378 abstracts, of which 133 were in English language and 245 were in Chinese. For further assessment, 269 potentially relevant publications were retrieved, and 99 were subsequently excluded, leaving a total of 58 English and 112 Chinese literature in the final review. 17,19,49,50–80,81–110,111–149,141–165,166–189

RESULTS

Microbial Keratitis

Microbial keratitis (MK) remains as the most serious and sight-threatening complication of OrthoK. Van Meter et al.66 provided a comprehensive review of the MK cases published in English since 1998, with most cases reported in Taiwan, Hong Kong, and Mainland China and presented as sporadic pattern without significant association with the baseline level of myopia, gender, or the specific brand of the OrthoK lenses. The sporadic pattern of MK was similarly reported in earlier Chinese publications and the attributable factors of the cases included lack of training of practitioners and wearers, improper fitting procedures, poor compliance to lens care regimens, and lost to routine follow-ups.38,41,49,58,185 A more recent large-scale multicentered retrospective study reported the estimated incidence rate of MK as 7.7 cases per 10,000 patient years (95% CI, 0.9–27.8), and risk of MK with overnight OrthoK was similar to other overnight modalities.54 Since the publication of the aforementioned two major reviews, there had been few sporadic cases of MK reported, mostly in a tertiary eye care hospital in Hong Kong.56

Corneal Staining, Lens Binding, and Tear Film Stability

Corneal staining was commonly reported in patients wearing OrthoK lenses.77,55,61,65,96,103,107,130,149,164,185,187 Commonly reported grading systems included Efron scale, Cornea and Contact Lens Research Unit scale, and Oxford scheme. Although mild corneal staining was also a common ocular finding in non-contact lens wearers, OrthoK has been reported to increase both the frequency and the severity of staining. Higher baseline myopia was reported to be positively associated with the level of staining103,107,130,149,164,185,187; however, age did not seem to be a significant factor in observed corneal staining after OrthoK treatment. Lens binding was another most commonly seen complication in overnight OrthoK and was significantly associated with central corneal staining.103,107,130,149,185 Chronic wear of OrthoK lenses was also significantly associated with reduced basal tear secretion187 and tear film stability, however with limited information reported dry eye symptoms.185,187,196

Epithelial Iron Deposit/White Lesion/ Fibrillary Lines

Pigmented iron ring or arcs and adjacent white linear lesions had often been reported as a result of chronic wear of OrthoK lenses, and the incidences of the lesions were significantly associated with the duration of OrthoK treatment.24,31,34,40,45,54,59 The findings were reported to be in subepithelial layer and usually were clinically
insignificant. Prominent fibrillar white lines were also reported in long-term OrthoK treatment and were thought to represent nerve fibers in the subbasilar plexus.59

**Endothelium**

None of the studies investigating the short-term or long-term impact of OrthoK lenses on corneal endothelium reported evidence of OrthoK lenses worn overnight or during daytime had significant impact on the density or the morphologic features of corneal endothelial cells.96,101,110,111,141,190

**Corneal Thickness**

Significant central corneal thinning up to 20 microns associated with mid-peripheral thickening up to 25 microns has been commonly reported. The onset of significant central thinning was reported as quickly as 24 hour after initiation of lens wear and usually peaked at 1 week after overnight treatment.1,3,109,110 The central thinning was predominantly in epithelial layer; however, the mid-peripheral thickened involved both epithelial and stromal components.27,35,36,44,48,93,96,110,115,127,141,190

**Intraocular Pressure/Corneal Hysteresis/Corneal Resistance Factor**

Corneal compensated intraocular pressure (IOP) and Goldmann-correlated IOP decreased and reached trough level around 1 week of OrthoK treatment.124,173,184,191 Significant decreases in corneal hysteresis (CH) and corneal resistance factor (CRF) were also reported within the first week after the treatment; however, both IOP and CH gradually returned to baseline level at 1 month of lens wear.124,191

**DISCUSSION**

OrthoK, either worn overnight or during daytime, is considered a viable option for temporary myopia correction and myopia control. With the drastic increase in the prevalence of myopia worldwide and the overall earlier onset of myopia, the popularity of OrthoK also increases significantly accordingly. Potential complications significantly associated with OrthoK include MK, corneal staining, and lens binding. There are other clinically insignificant side effects such as epithelial pigment deposit and increasing visibility of fibrillary lines, and transient changes of corneal biomechanical properties.

**Microbial Keratitis**

Owing to potentially serious consequence, infectious keratitis remains the most concerning complication related to OrthoK. At least three factors have been shown to increase the risks of MK of overnight OrthoK. Extended/overnight lens wear remains the most significant risk factor for infection.15,20,67 It is likely that overnight modality allows more time “for bacteria to colonize the contact lens and adapt to the environment to become appropriately virulent.”70 Additionally, it is also suggested that overnight lens wear may reduce ocular surface’s defense against infection as it could compromise tear mixing between the pre- and post-lens tear compartments during blinking.191 Furthermore, the reverse geometry design was hypothesized to further reduce the epithelial surface integrity likely because of its compressive hydraulic effect exerted on the cornea, hence increasing its susceptibility to infection.40

A large proportion of earlier reported complications, especially the more visually threatening cases such as MK, were originated from East Asia such as Mainland China and Taiwan. This was at least partially related to bigger population undergoing the OrthoK treatment, resulting in higher number of total incident cases. More importantly, in Mainland China, the overall incidence of MK decreased significantly after 2002, when China Food and Drug Administration posted regulations regarding the rigorous inspection and registration of OrthoK lenses, the training and certification of OrthoK practitioners, and the minimal requirements of instrumentation and fitting/follow-up procedures.192 With the combined efforts from government agencies, administration of hospitals/clinics, industry partners, practitioners, and individual patients/parents, the use of OrthoK in Mainland China both for myopia correction and myopia control has entered a fast growing stage with improved standardized protocols, close monitoring system for the long-term efficacy and safety of the treatment, and better awareness and compliance of lens wearers.79,128

Although it has been reported that the incidence of MK tends to be slightly higher in children than in adults,24 the data need to be interpreted with caution. First of all, the total number of incident cases was small, resulting in a bigger variance of the outcome estimate. Furthermore, most studies were subject to significant patient selection and participation bias because of the age difference of the patients. Although the exact magnitude of effect due to bias was difficult to evaluate because of the retrospective nature of most studies, the direction of the overall effect estimate will be biased toward younger aged patients, assuming better parental attention and a higher probability of seeking follow-up visits comparing to that of young adults.

In summary, considering the vision-threatening potential of MK and the direct association between the age and the expected OrthoK-wearing duration of the patients, practitioners should use great caution in fitting children with OrthoK lenses and it is important to provide extensive education to both patients and parents on rigorous compliance to lens caring regimen. It is also worth noting that *Pseudomonas aeruginosa* and *Acanthamoeba* were the most commonly reported pathogens for OrthoK-associated infectious keratitis, both of which require early diagnosis and prompt treatment to minimizing the risks of permanent vision loss. As a result, both patients and parents should remain high vigilance of possible related signs and symptoms; and to seek routine and timely follow-ups to minimize the risk of irreversible vision loss due to the complication.

**Corneal Staining/Lens Binding**

It is noteworthy that corneal staining could present in several distinctive patterns: sporadic or diffuse punctate staining; patchy central staining, especially the whorl shaped staining; and peripheral indentation rings. In authors’ own experience, peripheral punctate staining was more commonly associated with preexisting conditions such as misdirected lashes, lid margin disorders, lagophthalmos, and sensitivity to contact lens solution and care products. However, persistent central staining was more associated with suboptimal OrthoK fitting and lens adherence to the corneal surface. Recurrent lens binding and superficial corneal abrasion on lens removal is one of the most common reasons for urgent care visits in OrthoK treatments. Several factors have been proposed to promote lens binding in overnight OrthoK, such as coated lens,
decreased thickness and increased viscosity of post-lens tear film with overnight wear, eyelid pressure on OrthoK lens toward cornea, and the negative hydraulic pressure in post-lens tear film associated with reverse geometry lens designs pulling the lens closer to the central corneal surface.\textsuperscript{37,61,107} Recurrent lens binding can often be resolved by improving the fitting and promoting tear exchange through lens adjustment. Although mild-to-moderate corneal staining does not always require cessation of daytime GP lens wear, it is strongly indicated to discontinue overnight OrthoK treatment temporarily if persistent central corneal staining worsens than grade 2 (Efron scale) is observed, to avoid more serious complications such as chronic corneal abrasion and/or corneal ulcer.

**Epithelial Iron Deposit/White Lesion/ Fibrillar Lines**

Pigmented ring shaped corneal deposition is a common finding in chronic OrthoK treatment and there seemed to be no evidence suggesting an ethnicity predisposition to this finding. Although the exact etiology of the sign is unclear, it has been hypothesized that the pigmented ring might be related to the stress forces applied to epithelium and/or tear stagnation underneath the reverse geometry zone.\textsuperscript{24,31,45,54,73} All reported cases of pigmented corneal rings and adjacent white lesions were not near visual axis and were not visually significant and there was no treatment necessary. However considering the chronic nature of OrthoK treatment, careful photograph documentation and routine evaluation of both the density and the extent of the findings are recommended.

**Endothelium**

OrthoK, owing to its predominantly overnight wearing modality and the long-term nature of the treatment, and also its common utilization among pediatric patients, has raised concerns of its possible short-term and long-term impact on corneal endothelium. As a result, baseline and annual evaluation of endothelial integrity by specular microscopy has been commonly incorporated as part of the standard routine in OrthoK treatment in Mainland China. Evidence from large sample, longitudinal studies showed no significant short-term or long-term changes of endothelial cell density, corneal pomygelemthitis, or polymorphism, reassuring the long-term safety of overnight OrthoK on endothelium.

**Corneal Thickness**

Significant central corneal thinning accompanied by mid-peripheral thickening has been consistently reported with fairly quick onset and usually stabilized after several weeks of OrthoK lens wear. There had been elevated concerns of secondary corneal ectasia because of OrthoK induced central corneal thinning; however, due to the small magnitude (<20 microns) of central corneal thinning and its predominant epithelial origin, the risk of OrthoK induced ectasia is minimal.\textsuperscript{3,39,103} Mid-peripheral corneal thickening and steepening has been postulated as the main “myopia-controlling” stimulus, as it imposes significant myopic shift on peripheral retinal defocus, which has been considered as a potent myopia-inhibiting signal.\textsuperscript{7-15} The overall magnitude of mid-peripheral corneal thickening and steepening has been reported to correlate with the level of baseline (pretreated) myopia hence corresponding central thinning and flattening induced by the treatment; however, more recent reverse geometry designs have been attempted on inducing more significant mid-peripheral steepening, that is, independent of central thinning and flattening (Personal communication with proprietary lens designers, Patrick Caroline, 2014).

**Corneal Biomechanics**

CH and CRF are corneal biomechanical properties measured by Reichert Ocular Response Analyzer (http://www.ocularresponseealyzer.com). CH reflects the capacity of corneal tissue to recover back to its original shape after a transient application of external force. Compared with central corneal thickness, CH provides a more complete characterization of the contribution of corneal resistance to IOP measurements. CRF, a derivative from CH, indicates the overall resistance of corneal tissue that is relatively independent of IOP.\textsuperscript{193} Significant decreases in IOP, CH, and CRF were reported within the first week after OrthoK treatment; however both IOP and CH gradually returned to baseline level at 1 month of lens wear and remained unchanged after 6 months.\textsuperscript{124,190} Despite the early temporary reduction of CH, there was no evidence suggesting chronic OrthoK treatment altered corneal microstructure and its biomechanical properties.

**Strength and Limitations and of This Review**

This was the first review on the safety of OrthoK that used a systematic and objective approach to identify as many relevant literature as possible in both English and Chinese, hopefully to provide a comprehensive and balanced presentation of the topic. This review faces several limitations. First of all, despite the large number of studies identified and included in the review, the absolute incidences of OrthoK-associated side effects were difficult to evaluate because of significant potential sampling bias, publication bias, and lost to follow-ups. Additionally, the wide variety of study designs made it difficult to perform meta-analysis so only the results from individual relevant studies were reported. Finally, owing to the time constraints, no further effort was made to contact the investigators of each study to clarify unclear data presentations in the original publications or to acquire necessary raw data to improve the efficiency of the data usage in the analysis.

**CONCLUSIONS**

OrthoK in general is a safe option for myopia correction and retardation. However, the long-term success of the treatment depends on a combination of multiple factors including proper fitting of the lenses, rigorous compliance to lens use and care regimen, adherence to routine follow-ups, and timely and appropriate treatments to complications.

**FUTURE DIRECTION**

To better estimate the absolute prevalence and incidence of OrthoK-related complications, future clinical practice and research should aim at establishing complete and systematic patient database and minimizing the rate of lost to follow-ups in the cases of long-term treatment. It is only with an accurate denominator, that is, the correct estimate of the patient-time in whichever cohort the incident cases were generated can a true incidence rate be accurately calculated. Additionally, more focussed research on the independent effect of each factor, such as patient’s baseline refractive error, corneal physiological and biomechanical profile, lens
design, lens material, and treatment modality, etc., will provide valuable insights into guiding clinical decision making in maximizing the efficacy and safety of OrthoK treatment at individual patient level. Finally, continuous laboratory research on the pathogenesis of OrthoK-related MK, identifying subjective and objective indicators that focus on prediction and prevention of complications, and better understanding of long-term effects of OrthoK treatment are warranted, especially considering the early onset and the chronic nature of the treatment in most patients.

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