

# Ocular signs and symptoms of orthokeratology patients associated with povidone iodine-based disinfecting solution

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## ABSTRACT

**Purpose:** To determine the frequency and severity of ocular symptoms and signs in new orthokeratology (*ortho-k*) subjects using a povidone iodine (PI) disinfecting system compared to those present before lens wear, and whether these were associated with cleaning regimes.

**Methods:** This study recruited 80 subjects from two myopia control studies, who used a PI disinfecting solution for routine use. Ocular symptoms and signs at baseline, one- and six-month after lens wear were reported via questionnaires and ocular examination, respectively. To determine if rates of occurrence were attributable to differences in cleaning regime, subjects were randomly assigned into four groups with respect to routine care procedures, which involved various combinations of rubbing and use of a daily and/or enzymatic cleaner.

**Results:** Sixty-eight subjects completed all aspects of the study. As there were no significant differences in incidence of signs and symptoms between the four groups before and after lens wear (Friedman tests,  $p > 0.07$ ), data were combined for further analysis. Prior to lens wear, itchiness (69 %) and dryness (53 %) were the most commonly reported symptoms. The frequency and severity of all symptoms remained similar after lens wear ( $p > 0.10$ ). Presence of follicles in the lower tarsal conjunctiva (22 %) and conjunctival injection (15 %) was frequently observed, but reduced significantly after lens wear ( $p < 0.01$ ). Mild corneal staining, noted in 13 % of subjects at baseline, did not change significantly over time ( $p = 0.17$ ). Ocular signs were not necessarily reflected in symptoms and vice versa.

**Conclusion:** Use of a PI-based solution did not increase the frequency or severity of ocular signs and symptoms observed before lens wear. Absence of a difference in occurrence of ocular discomfort with respect to cleaning regimes indicated that the use of the PI-based solution may adequately clean the lenses over a 6-month period.

## 1. Introduction

Contact lens discomfort, defined as ‘a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear’ [1], is an important consideration in contact lens wear [2,3]. Several factors have been suggested to be important contributors to such discomfort, including the lens material, care solutions, and biophysical tear film properties [3]. Incorporation of surfactants in contact lens solutions, acting as wetting agents and surface cleaners, may reduce discomfort [1,4]. However, most studies investigating discontinuation have focused on conventional soft and RGP contact lenses and adult participants.

Orthokeratology (*ortho-k*) is a well-accepted practice to slow the progression of myopia in children [5–9]. However, as this treatment involves the use of rigid lenses, acceptance of a certain degree of discomfort, especially at the commencement of therapy, is necessary for success. Stringent adherence to care procedures is essential as overnight lens wear reduces oxygen tension and tear flow, which can increase the risk of adverse events [10]. Thus, in contrast to conventional soft and RGP contact lens wear, more frequent monitoring of ocular health and myopia progression are important for successful therapy. During these follow-up visits, review and reinforcement of use and care routines are performed to minimize risks of complications, if necessary. Thus, solutions and other cleaning preparations must be effective not only in removing microorganisms, but also not lead to any ocular symptoms due to irritation or sensitivity. This is especially important for *ortho-k* lenses, as these are worn overnight and less frequently replaced. As lenses age,

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scratches and deposit tend to accumulate, increasing attachment of microorganisms and rendering disinfection less effective [11,12]. In practice, this may be overcome with daily cleaning and regular enzymatic treatment.

For several years, there had been few advancements in solutions for rigid lenses due to the declining use of conventional rigid lenses, but the increasing popularity of *ortho-k*, especially in East and South-East Asia, and scleral lenses, has led to revived interest in oxidative care systems [13]. As components of contact lens solutions may contribute to contact lens discomfort [3], it is essential that components of these solutions do not cause irritation to the eye. The use of iodine as a disinfectant is well known, acting as an effective oxidative agent [14]. Whilst its use was reduced due to widely circulated reports of iodine allergy, leading to skin irritation and blistering [15], several studies have contested the role of iodine in such allergic reactions and attributed the adverse effects to other ingredients added to the medications [16]. Since the addition of povidone to the formulation, reports of adverse effects have been extremely rare [17]. Evaluation of toxicity of povidone iodine-based (PI) in the sinonasal and oral cavities reported that PI at concentrations up to 1.25 % could safely be used at these sites for up to five months without any adverse events. PI-based soft contact lens solutions have been available for several years [18] and shown to be effective for disinfection. A study investigating adverse events associated with this solution reported only 0.8 % per 100 participant-months in 40 participants. [19].

More recently, a rigid lens version of a PI-based lens disinfection solution, cleadewGP (Ophtecs Inc., Japan), was introduced. Its antimicrobial efficacy and ability to kill organisms, including those in established biofilms, and its effect on conjunctival colonization have been reported [20,21]. In addition to PI, this solution also contains an anionic surfactant, which can remove surface deposits and reduce surface tension, enhancing comfort. Neutralization of PI is achieved via a time-release neutralizing tablet, containing sodium sulfite and a proteolytic enzyme for protein removal. However, the clinical performance of this care system has not been extensively evaluated. This paper reports the frequency and severity of adverse effects over a 6-month period of PI-based solution use in children receiving *ortho-k* therapy and employing different cleaning regimes.

## 2. Methods

Before commencement of lens wear, subjects (aged 6–10 years old) in two myopia control studies employing *ortho-k* treatment were also invited to enrol in this study of adverse events. One of these studies was investigating whether addition of 0.01 % atropine to *ortho-k* therapy enhanced the treatment effect [22], so to remove any confounding effect due to atropine use, only subjects receiving *ortho-k* alone were recruited. The second study merely investigated a minor change in lens design [23], which was not considered likely to have any impact on occurrence of adverse effects. This study received approval from The Hong Kong Polytechnic University (PolyU) (approval number: HSEARS20170430002) and registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (registration number: NCT03193255). Informed consent from the parents and assent from the subjects were obtained before the commencement of study.

A total of 80 subjects agreed to participate and, before being dispensed with *ortho-k* lenses (Katt BE free *ortho-k* lenses; Precision Technology Services, <https://www.ptsoptics.com/>), were randomized into four groups using different cleaning regimes. All groups disinfected their lenses with the PI-based solution, following the manufacturer's instructions, with or without cleaning before disinfection. Whilst Group 1 subjects merely disinfected the lenses, the remaining subjects all rubbed their lenses prior to disinfection, of whom Group 3 additionally used a separate daily cleaner (O2 Daily Care Solution; Ophtecs Inc., <https://ophtecs.com>), Group 4 both a daily cleaner and a weekly protein removal treatment (Progent A + B; Menicon Co, <https://www.menicon.com/product/lens-care/>), and Group 2 only rubbed their lenses with the PI-based solution as described previously [18]. Before lens insertion,

each subject was instructed to rub and rinse their lenses with the Cleadew Dissolving and Rinsing Solution (Ophtecs Inc., <https://ophtecs.com>) and use unpreserved artificial tears (Teare; Ophtecs Inc., <https://ophtecs.com>) to cushion the lenses. A similar pre-lens insertion routine is recommended for all *ortho-k* lens wearers attending the PolyU clinic using other care systems.

All subjects underwent thorough examinations for vision, ocular assessments at baseline, 1-month, and 6-month visits, and, with assistance from their parents, completed a questionnaire (Appendix A) reporting the frequency and severity of ocular symptoms, including discomfort, dryness, itchiness, burning, visual disturbance, redness, and tearing. The questionnaire was modified from previously validated questionnaires for contact lens wear [24,25]. It was translated into Chinese and back-translated into English for accuracy by an independent observer. Visual symptoms and symptoms related to lens wear, including discomfort, dryness, itchiness, and burning sensation, redness, and tearing were assessed.

### 2.1. Data analysis

Differences in frequencies and severity of symptoms were evaluated between groups and over time. Kruskal-Wallis test was used to compare the groups at each visit. Friedman tests were used to compare reports of symptoms over the study period. In the absence of significance between groups, data was pooled for the Friedman tests for changes due to lens wear. Chi-squared tests were used to compare symptoms between completed and excluded subjects as well as incidence of symptoms before and after lens wear among the asymptomatic and symptomatic subjects.

## 3. Results

Of the original 80 randomised subjects, one subject withdrew before commencing lens wear. Of the remaining 79 subjects, four did not complete the study, and a further seven failed to complete all questionnaires (see Fig. 1). These 11 subjects were excluded from the final analysis, leaving 68 subjects. There were no differences in the baseline symptoms between the completed and excluded subjects (Chi-squared,  $0.91 > p > 0.15$ ). However, data collected from all subjects was included in the descriptive table in Table 1. The mean (SD) age of the subjects was 9.05 (1.14) years, of whom 66 % were female.

### 3.1. Ocular symptoms

There were no significant between-group differences either in baseline age and gender, or individual symptoms at any study visit (Kruskal-Wallis tests,  $0.95 > p > 0.11$ ) (Table 2), so data from the four groups were combined for further analysis. Although there were no significant changes in frequency or severity of symptoms during the study period (Friedman tests,  $p > 0.10$ ), analysis of symptoms revealed a variety of patterns, with most subjects remaining consistent, but others experiencing transient periods of discomfort and only a few having more problems at the end of the 6-month study period. An example of this can be seen in the diagrammatic representation of the whole day symptoms for the 39 baseline asymptomatic subjects (Fig. 2). Diagrammatic representation became too complicated for symptomatic subjects with variation of transient improvement and decline, and so are not presented.

Table 3 shows data for subjects who did not experience any symptoms before lens wear. For the 39 subjects reporting no ocular discomfort at baseline, as shown in Fig. 2, the majority experienced no discomfort after lens wear and 82 % were symptom-free at the 6-month visit. Similar results were seen for the end-of-day discomfort. With respect to dryness, 31 % of previously asymptomatic subjects experienced dryness after six months of lens wear, although this was reported to occur rarely in eight of these 10 subjects. Somewhat fewer subjects

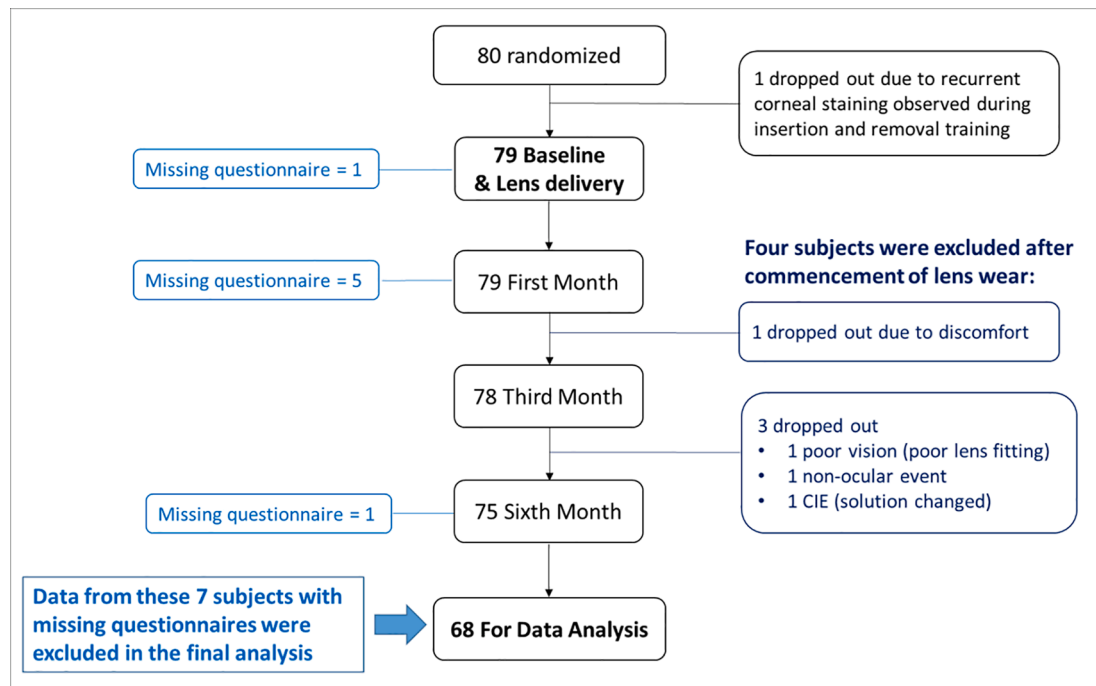


Fig. 1. Study flow chart.

reported problems at the end of the day. Itchiness was the most commonly reported symptom at baseline, with only 21 subjects being asymptomatic. This was also the only symptom that increased significantly after lens wear (Chi-squared,  $p < 0.001$ ), with almost two-thirds of these previously asymptomatic subjects reporting itchiness at the 6-month visit, seven of whom experienced this sometimes or frequently. This problem was somewhat reduced at the end of the day. Whilst most subjects did not report burning, redness or tearing at baseline, a total of 15 %, 17 %, and 19 %, respectively, reported such problems, mostly occurring rarely, at the 6-month visit.

Table 4 shows data for subjects who reported symptoms at baseline. Of these subjects, over half (50–60 %) reported improvement in at least one symptom. For ocular discomfort, 17 out of 29 symptomatic subjects revealed a reduction or no symptom after six months of lens wear. Of the remaining 12 subjects, symptoms of eight were unchanged with only four experiencing symptoms more frequently. Slightly more than half (36/68) of the subjects initially reported dryness, although this appeared to be reduced at the end of the day. Interestingly, 56 % of these subjects reported an improvement in the frequency of experiencing dryness after lens wear, 44 % becoming asymptomatic. Only five subjects reported increased frequency of dryness at the end of the study.

Itchiness was the most commonly reported symptom of ocular discomfort at baseline, being experienced by 47 (69 %) of the subjects. However, once again, there was an improvement of 60 % after lens wear, with only five reporting more frequent symptoms. Only eight subjects reported a burning sensation before lens wear, of whom four improved. Redness and tearing were initially experienced by 15 (22 %) and 21 (31 %) subjects, respectively, of whom 47 % and 67 % improved, and the symptoms of only one and two subjects, respectively, worsened after lens wear.

For vision, despite having myopia, 39 (57 %) subjects were happy with their vision at baseline, most of whom had habitual vision aids. Ten of these subjects experienced blurred vision at the 6-month visit, but this rarely occurred in nine. Among the 29 subjects complaining about vision at baseline, 72 % reported improved vision after lens wear and none reported their vision getting worse.

### 3.2. Ocular signs

There were no differences in ocular signs among the four cleaning regimens before and after lens wear (Friedman tests,  $p > 0.07$ ). Overall, except for follicles in the lower eyelids, very few ocular signs above Grade 1 were observed throughout the study (Table 5). The frequency of corneal staining, which was most often observed in the inferior region, did not change significantly over the study period (Friedman test,  $p = 0.17$ ). In all cases, this was categorized as Grade 1. The incidence reduced during the early period of lens wear, but returned to somewhat above baseline by the 6-month visit.

Of the 13 % of subjects with conjunctival injection at baseline, only two presented with Grade 2 injection, one of whom reported mild blurry vision after lens wear and the second had no symptoms. Mild conjunctival injection (Grade 1) observed at baseline was not present after three months of lens wear. Two subjects with Grade 2 conjunctival injection at baseline intermittently displayed this sign over the period of lens wear. Follicles were present in the lower eyelid of 22 % subjects at baseline. The prevalence reduced significantly over the study period (Friedman test,  $p = 0.002$ ). At baseline, 13 % displayed Grade 2 follicles and one subject, Grade 3. Throughout the study period, ocular examination for the presence of follicles revealed clinically significant findings (Grade 3 or above) in only two subjects. One subject with Grade 3 + follicles at baseline, which persisted throughout the period of the study, displayed slight improvement at the 6-month visit, but reported mild itchiness and blurred vision at this time. Follicles were only noted in the second subject at the 6-month visit.

## 4. Discussion

This study evaluated adverse effects associated with the use of a PI-based disinfecting solution for rigid lenses in children undergoing ortho-k treatment. As there was some concern about the advice given by the manufacturer that rubbing of lenses was not required, the study incorporated four cleaning and disinfecting methods, which were randomly allocated to the subjects. Subjects were monitored for a period of six months, with data collection visits after one and six months of lens wear. The results showed that there were no significant differences between

**Table 1**

Frequency of symptoms of the 68 completed and 10 excluded subjects\* at the baseline visit.

	Whole day						End of day					
	All		Completed		Excluded		All		Completed		Excluded	
Discomfort												
Never	46	(59 %)	39	(57 %)	7	(70 %)	57	(73 %)	48	(71 %)	9	(90 %)
Rarely	26	(33 %)	23	(34 %)	3	(30 %)	19	(24 %)	18	(26 %)	1	(10 %)
Sometimes	6	(8 %)	6	(9 %)	0	(0 %)	1	(1 %)	1	(1 %)	0	(0 %)
Frequently	0	(0 %)	0	(0 %)	0	(0 %)	1	(1 %)	1	(1 %)	0	(0 %)
Dryness												
Never	38	(49 %)	32	(47 %)	6	(60 %)	54	(69 %)	47	(69 %)	7	(70 %)
Rarely	28	(36 %)	25	(37 %)	3	(30 %)	20	(26 %)	18	(26 %)	2	(20 %)
Sometimes	11	(14 %)	10	(15 %)	1	(10 %)	3	(4 %)	3	(4 %)	0	(0 %)
Frequently	1	(1 %)	1	(1 %)	0	(0 %)	1	(1 %)	0	(0 %)	1	(10 %)
Itchiness												
Never	28	(36 %)	21	(31 %)	7	(70 %)	37	(47 %)	32	(47 %)	5	(50 %)
Rarely	18	(23 %)	16	(24 %)	2	(20 %)	23	(29 %)	19	(28 %)	4	(40 %)
Sometimes	23	(29 %)	22	(32 %)	1	(10 %)	14	(18 %)	14	(21 %)	0	(0 %)
Frequently	9	(12 %)	9	(13 %)	0	(0 %)	4	(5 %)	3	(4 %)	1	(10 %)
Burning												
Never	68	(87 %)	60	(88 %)	8	(80 %)	67	(86 %)	59	(87 %)	8	(80 %)
Rarely	9	(12 %)	7	(10 %)	2	(20 %)	9	(12 %)	7	(10 %)	2	(20 %)
Sometimes	1	(1 %)	1	(1 %)	0	(0 %)	2	(3 %)	2	(3 %)	0	(0 %)
Blurred vision												
Never	48	(62 %)	39	(57 %)	9	(90 %)	58	(74 %)	49	(72 %)	8	(80 %)
Rarely	19	(24 %)	18	(26 %)	1	(10 %)	13	(17 %)	12	(18 %)	2	(20 %)
Sometimes	8	(10 %)	8	(12 %)	0	(0 %)	6	(8 %)	6	(9 %)	0	(0 %)
Frequently	2	(3 %)	2	(3 %)	0	(0 %)	0	(0 %)	0	(0 %)	0	(0 %)
Constantly	1	(1 %)	1	(1 %)	0	(0 %)	1	(1 %)	1	(1 %)	0	(0 %)
Redness												
Never	61	(78 %)	53	(78 %)	8	(80 %)						
Rarely	11	(14 %)	9	(13 %)	2	(20 %)						
Sometimes	6	(8 %)	6	(9 %)	0	(0 %)						
Tearing												
Never	54	(69 %)	47	(69 %)	7	(70 %)						
Rarely	19	(24 %)	16	(24 %)	3	(30 %)						
Sometimes	4	(5 %)	4	(6 %)	0	(0 %)						
Frequently	1	(1 %)	1	(1 %)	0	(0 %)						

\* One excluded subject did not have baseline questionnaire resulting in 10 excluded subjects at baseline.

Differences in symptoms between the completed and incomplete subjects were statistically insignificant (Chi-square,  $0.91 > p > 0.15$ ).

the groups with respect to symptoms, indicating that the disinfecting solution adequately removed deposits without additional cleaning steps, probably due to the presence of a surfactant in the solution and/or a proteolytic enzyme incorporated in the neutralizing tablet. However, as deposits do tend to accumulate over time and *ortho-k* lenses are routinely replaced only on an annual, or even longer, basis, practitioners may wish to err on the side of caution and advise their patients accordingly.

As there were no significant between-group differences in frequency or severity of symptoms, combined data was used to investigate frequency and severity of symptoms and changes over time. Although ocular discomfort is one of the most frequently reported reasons for contact lens wear discontinuation [1], in the current study, there were minimal changes over time in reporting of overall discomfort by 82 % of baseline asymptomatic subjects. This agrees with the findings of previous studies, which reported that serious adverse effects were rarely observed in *ortho-k* lens wearers [5,26–28], which may be attributable to *ortho-k* not involving open eye lens wear, hence not leading to changes to tear film associated with evaporation and incomplete blinking [29–31]. In the current study, the majority of subjects had no overall change in symptoms during lens wear, with the exception of

itchiness. Most symptoms were reported to occur rarely, with only one subject each reporting dryness or itchiness occurring frequently. The severity of symptoms was generally considered to be mild with moderate severity of itchiness reported by only two subjects (one of whom was the frequent sufferer mentioned above).

Overall discomfort also improved in 60 % of those subjects symptomatic at baseline. Similar reductions in reporting of individual symptoms also fell by at least 47 % for these subjects (Table 4). A similar reduction in ocular discomfort over a 6-month period of *ortho-k* lens wear was reported by Wang et al. [31]. However, an extended study [28] reported somewhat more adverse effects occurring after six months of lens wear, although not all may have been associated with lens wear. It is possible that wearers become complacent with proper care routines over time and fail to replace lenses as appropriate. Lens deposits can build up, especially in the scratches, on older lenses. Such deposits, if not adequately removed, can take up solution during disinfection, which can leach out during lens wear, increasing the risk for discomfort and solution-induced corneal staining [32].

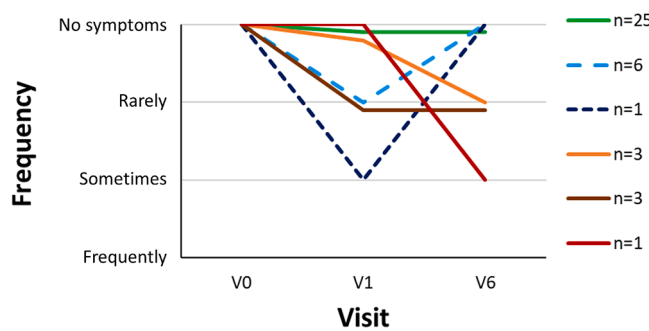
Although dryness was one of the most frequently reported symptoms during lens wear, over 50 % of subjects had reported this problem before commencing treatment. In the majority of these subjects, dryness

**Table 2**

Frequency of whole day symptoms among the four cleaning groups at baseline, one month and six months of lens wear.

	Baseline					First month					Sixth month				
	All	G1	G2	G3	G4	All	G1	G2	G3	G4	All	G1	G2	G3	G4
<b>Discomfort</b>															
Never	39 (59 %)	9	11	10	9	42 (62 %)	8	13	10	11	45 (66 %)	9	12	12	12
Rarely	23 (34 %)	4	6	5	8	20 (29 %)	5	3	7	5	16 (24 %)	6	2	3	5
Sometimes	6 (9 %)	2	0	3	1	6 (9 %)	2	1	1	2	7 (10 %)	0	3	3	1
Frequently	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Dryness</b>															
Never	32 (47 %)	6	8	8	10	37 (54 %)	6	9	11	11	38 (56 %)	7	10	10	11
Rarely	25 (37 %)	6	6	6	7	20 (29 %)	3	4	6	7	21 (31 %)	5	6	7	3
Sometimes	10 (15 %)	3	3	3	1	8 (12 %)	5	3	0	0	6 (9 %)	2	1	1	2
Frequently	1 (1 %)	0	0	1	0	3 (4 %)	1	1	1	0	3 (4 %)	1	0	0	2
<b>Itchiness</b>															
Never	21 (31 %)	6	5	5	5	23 (34 %)	6	7	3	7	22 (32 %)	8	4	4	6
Rarely	16 (24 %)	2	7	4	3	27 (40 %)	2	7	10	8	24 (35 %)	2	9	8	5
Sometimes	22 (32 %)	5	3	6	8	13 (19 %)	5	2	3	3	16 (24 %)	4	3	4	5
Frequently	9 (13 %)	2	2	3	2	4 (6 %)	2	0	2	0	6 (9 %)	1	1	2	2
Constantly	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0
<b>Burning</b>															
Never	60 (88 %)	12	16	15	17	55 (81 %)	12	15	14	14	54 (79 %)	13	16	13	12
Rarely	7 (10 %)	3	1	2	1	13 (19 %)	3	2	4	4	10 (15 %)	1	1	3	5
Sometimes	1 (1 %)	0	0	1	0	0	0	0	0	0	3 (4 %)	1	0	2	0
Frequently	0	0	0	1	0	0	0	0	0	0	1 (1 %)	0	0	0	1
<b>Blurred</b>															
Never	39 (57 %)	9	8	14	8	46 (68 %)	9	13	10	14	44 (65 %)	9	13	11	11
Rarely	18 (26 %)	3	8	1	6	18 (26 %)	4	3	8	3	23 (34 %)	6	4	7	6
Sometimes	8 (12 %)	2	1	2	3	3 (4 %)	1	1	0	1	1 (1 %)	0	0	0	1
Frequently	2 (3 %)	1	0	1	0	1 (1 %)	1	0	0	0	0	0	0	0	0
Constantly	1 (1 %)	0	0	0	1	0	0	0	0	0	0	0	0	0	0
<b>Redness</b>															
Never	53 (78 %)	10	15	14	14	54 (79 %)	13	14	12	15	49 (72 %)	12	16	10	11
Rarely	9 (13 %)	4	2	2	1	11 (16 %)	1	3	6	1	13 (19 %)	2	1	7	3
Sometimes	6 (9 %)	1	0	2	3	2 (3 %)	1	0	0	1	6 (9 %)	1	0	1	4
Frequently	0	0	0	0	0	1 (1 %)	0	0	0	1	0	0	0	0	0
<b>Tearing</b>															
Never	47 (69 %)	11	13	10	13	55 (81 %)	13	15	14	13	50 (74 %)	11	14	10	15
Rarely	16 (24 %)	3	4	6	3	8 (12 %)	1	2	1	4	15 (22 %)	2	3	8	2
Sometimes	4 (6 %)	0	0	2	2	3 (4 %)	0	0	2	1	2 (3 %)	1	0	0	1
Frequently	1 (1 %)	1	0	0	0	1 (1 %)	0	0	1	0	1 (1 %)	1	0	0	0
Constantly	0	0	0	0	0	1 (1 %)	1	0	0	0	0	0	0	0	0

G1: Group 1 (N = 15); G2: Group 2 (N = 17); G3: Group 3 (N = 18); G4: Group 4 (N = 18).

Insignificant differences in symptoms among the four groups at all study visits (Kruskal-Wallis tests,  $0.95 > p > 0.11$ ).**Fig. 2.** Frequencies of whole day discomfort for the 39 subjects who were asymptomatic at baseline (V0), 1-month (V1), and 6-month (V6) visits.

decreased somewhat over the first month and then remained steady over the rest of the study. Complaints of dryness, the most common reason for discontinuation of soft contact lens wear [2,3], were far less frequent, which again may be attributable to the mode of lens wear. The reduction of dryness in initially symptomatic subjects was consistent with the findings of reduced symptoms by Carracedo et al. [33] whose subjects reported less dryness after changing from silicone hydrogel to *ortho-k* lens wear. The authors attributed this to an increase in goblet cell density observed after commencing *ortho-k* lens wear. Such improvement may continue over longer term lens wear (>six months), as a study in China revealed only 23 % of patients reporting dry eye [9]. Wang et al. also observed a reduction in reports of dryness after six months of *ortho-k* lens wear [31]. Their study did report some changes in meibomian gland secretion after commencement of lens wear, but these did not reach significance. Similar to the current study, some subjects had symptoms of dryness at baseline, which worsened after commencement of lens wear. The authors suggested that their subjects may have suffered from mild allergic conjunctivitis, which was aggravated by lens wear

**Table 3**

Symptoms reported by subjects, who were asymptomatic at the baseline visit, for the whole day (WD) and at end of day (ED) after one month (M1) and six months (M6) of lens wear.

Asymptomatic at baseline	Discomfort		Dryness		Itchiness		Burning		Redness	Tearing	Blurred vision	
	WD	ED	WD	ED	WD	ED	WD	ED	WD	WD	WD	ED
N (% of out 68 subjects)	39 (57%)	48 (71%)	32 (47%)	47 (69%)	21 (31%)	32 (47%)	60 (88%)	59 (87%)	53 (80%)	47 (69%)	39 (57%)	50 (74%)
<b>(1) No overall change</b>	32 (82%)	45 (94%)	22 (69%)	36 (77%)	8 (38%)	19 (59%)	51 (85%)	50 (85%)	44 (83%)	38 (81%)	27 (69%)	48 (96%)
Remained asymptomatic	25	36	18	28	6	13	46	47	39	33	20	37
Transient at M1 only	7	9	4	8	2	6	5	3	5	5	7	11
<b>(2) Developed symptoms</b>	7 (18%)	3 (6%)	10 (31%)	11 (23%)	13 (62%)	13 (41%)	9 (15%)	9 (15%)	9 (17%)	9 (19%)	12 (31%)	2 (4%)
M1 and M6	3	0	4	6	9	3	1	1	4	2	6	2
M6 only	4	3	6	5	4	10	8	8	5	7	6	0
Frequency at M6												
Rarely	6	2	8	9	6	8	8	8	6	9	11	1
Sometimes	1	1	2	1	6	5	1	1	3	0	1	1
Frequently	0	0	0	1	1	0	0	0	0	0	0	0
Severity at M6												
None	0	0	1	2	0	0	0	0	0	0	2	0
Very mild	6	3	8	6	9	8	6	5	5	8	7	1
Mild	1	0	1	3	2	5	3	4	4	0	3	1
Moderate	0	0	0	0	2	0	0	0	0	0	0	0

**Table 4**

Symptoms reported by subjects, who were symptomatic at the baseline visit, for the whole day (WD) and at end of day (ED) after one month (M1) and six months (M6) of lens wear.

Symptomatic at baseline	Discomfort		Dryness		Itchiness		Burning		Redness	Tearing	Blurred vision	
	WD	ED	WD	ED	WD	ED	WD	ED	WD	WD	WD	ED
N (% of out 68 subjects)	29 (43 %)	20 (29 %)	36 (53 %)	21 (31 %)	47 (69 %)	36 (53 %)	8 (12 %)	9 (13 %)	15 (20 %)	21 (31 %)	29 (43 %)	18 (26 %)
<b>(1) Improved</b>	17 (59 %)	11 (55 %)	20 (56 %)	13 (62 %)	28 (60 %)	21 (58 %)	4 (50 %)	5 (56 %)	7 (47 %)	14 (67 %)	21 (72 %)	15 (83 %)
Asymptomatic at M6	13	9	16	11	14	17	3	4	5	12	17	12
Improved at M6	4	2	4	2	14	4	1	1	2	2	4	3
Frequency at 6 months												
Rarely	4	2	4	2	12	4	1	1	2	1	4	3
Sometimes	0	0	0	0	2	0	0	0	0	0	0	0
<b>(2) Remained unchanged</b>	8 (28 %)	7 (35 %)	11 (31 %)	5 (24 %)	14 (30 %)	11 (31 %)	1 (13 %)	2 (22 %)	7 (47 %)	5 (24 %)	8 (28 %)	2 (11 %)
Frequency at 6 months												
Rarely	6	7	9	5	6	5	1	2	5	4	8	2
Sometimes	2	0	2	0	4	5	0	0	2	0	0	0
Frequently	0	0	0	0	4	1	0	0	0	1	0	0
<b>(3) Deteriorating</b>	4 (14 %)	2 (10 %)	5 (14 %)	3 (14 %)	5 (10 %)	4 (11 %)	3 (37 %)	2 (22 %)	1 (7 %)	2 (9 %)	0	1 (6 %)
Frequency at 6 months												
Sometimes	4	2	2	2	4	3	2	2	1	2	0	1
Frequently	0	0	3	1	1	1	1	0	0	0	0	0
Severity at 6 months												
Very mild	1	1	0	0	1	0	0	0	0	0	0	0
Mild	2	1	4	2	4	3	3	2	1	1	0	1
Moderate	1	0	1	1	0	1	0	0	0	0	0	0

[31].

In the current study, itchiness was the most commonly experienced problem in previously asymptomatic subjects, which was usually mild and infrequent. Over two thirds of the total subjects reported itchiness at baseline, of whom five had increased frequency of symptoms, from rarely to sometimes, or severity, from very mild to mild. Significantly increased itchiness was also reported by new *ortho*-k wearers in Nanjing, China [34], experienced by 30 % of long-term wearers in Sichuan, China [9], and 20 % of patients attending private optometry practices in Hong

Kong [35]. Itchiness is most often associated with the presence of allergens, which may attach to the lens surface and cause problems if lenses are not cleaned adequately. Symptoms can usually be relieved by the use of eye drops, but patients should be reminded to ensure they are correctly caring for their lenses.

Itchiness may be accompanied by symptoms of burning, redness, and tearing, which can be exacerbated by rubbing the eyes. These symptoms were experienced at baseline by 12 %, 22 %, and 31 %, respectively of subjects, but were reduced after lens wear in over half of these subjects.



**Table 5**

Ocular signs observed before and after lens wear.

	Baseline	Month 1	Month 3	Month 6	p-value*
<b>Corneal staining</b>					
<b>Overall</b>	<b>9 (13 %)</b>	<b>5 (7 %)</b>	<b>6 (9 %)</b>	<b>12 (18 %)</b>	0.17
Grade 1	9 (13 %)	5 (7 %)	6 (9 %)	12 (18 %)	
<b>Location</b>					
Central	1	1	0	3	
Inferior	6	2	5	7	
Superior	1	0	0	2	
Nasal	1	1	1	3	
Temporal	0	2	0	2	
<b>Conjunctival injection</b>					
<b>Overall</b>	<b>10 (15 %)</b>	<b>9 (13 %)</b>	<b>1 (1 %)</b>	<b>1 (1 %)</b>	< 0.001
Grade 1	8 (12 %)	8 (12 %)	0	0	
Grade 2	2 (3 %)	1 (1 %)	1 (1 %)	1 (1 %)	
<b>Location</b>					
Inferior	1	0	0	1	
Superior	1	0	0	1	
Nasal	10	9	1	1	
Temporal	10	9	1	1	
<b>Follicles Lower eyelid</b>					
<b>Overall</b>	<b>15 (22 %)</b>	<b>8 (12 %)</b>	<b>6 (9 %)</b>	<b>7 (10 %)</b>	< 0.01
Grade 1	4 (6 %)	5 (7 %)	3 (4 %)	1 (1 %)	
Grade 2	9 (13 %)	2 (3 %)	2 (3 %)	4 (6 %)	
Grade 3–4	1 (1 %)	1 (1 %)	1 (1 %)	2 (3 %)	
<b>Location</b>					
Inner central	4	2	3	3	
Tarsal	5	2	3	3	
Lid margin	3	3	2	2	
Nasal	5	4	3	2	
Temporal	14	8	6	7	

\* Friedman tests for changes over time.

This may be attributable to the use of eye drops or improved hand hygiene. Interestingly, only a very small number of previously asymptomatic patients reported any of these symptoms after commencement of lens wear. Increased tearing was reported in the Nanjing study [34], but the increase did not reach significance. The prevalence of red eye in long term wearers in Chengdu was 29 % [9].

With regard to vision, of those who had no problems at baseline, 31 % (12/39) reported problems after six months of lens wear with daytime vision, although interestingly, only two of these subjects reported vision problems at the end of the day. Problems with vision would be expected to increase at the end of the day with regression. It is possible that the higher demand of good vision in the classroom led to the complaint of poor daytime vision, which may not be applicable in the smaller home environment in the evening. In addition, the severity was scored as mild or less and, as such, may not be clinically significant (Table 3). For those who reported blurred vision at baseline, the majority reported improvements at six months, with none reporting worsening of symptoms (Table 4). This low level of vision problems is similar to those previously reported by studies on long-term *ortho-k* wearers [8,9]. This is to be expected as *ortho-k* patients are mainly children undergoing therapy for myopia control, whose vision will be carefully monitored and lenses replaced if appropriate [8,9,37].

In contrast to soft contact lens wear, in which symptoms tend to increase over time, leading to reduced wearing time and possible temporary or even permanent discontinuation of lens use [36], overall symptoms reported in this study tended to reduce over time. This may be attributable to the overnight wear modality. This was reflected in the

low number of dropouts in the two parent studies from which the subjects were recruited: after commencement of lens wear, only one subject discontinued due to lens-related problems. Of the initial 80 subjects in this study, one was considered as unsuitable for lens wear during the lens insertion and removal training, and a further three discontinued lens wear during the course of the study. However, only one of these was due to lens discomfort, whilst the second was attributable to persistent poor vision. In general practice, major reasons for discontinuation of *ortho-k* lens wear are more likely to be cost and inconvenience, rather than adverse effects [38,39]. Overall discontinuation of *ortho-k* lens wear is low [26–28,40]. However, the cited study is fairly old and newer options for myopia control have been developed in the last decade [41]. This allows transfer to alternative therapies, which tend to be more economical in case of discontinuation of *ortho-k* treatment.

Ocular examination revealed few signs. In agreement with most other studies [39,42,43], the frequency of the most commonly reported adverse effect of *ortho-k* lens wear, corneal staining, varied little over the study period and was very mild in all cases. Santodomingo-Rubido et al. observed that staining occurred most commonly in the central cornea during the early months of *ortho-k* lens wear and reduced subsequently [28]. In contrast, a recent report indicated that corneal staining significantly increased over 2-year *ortho-k* lens wear [31]. However, in their study, contact lens disinfection was achieved using a care solution containing DMDM hydantoin, which is reported to cause contact allergy in some users and may explain the increase in corneal staining observed. Increased levels of staining have been reported with PHMB-based solutions in soft lens users [44], but was not associated with discomfort. It was suggested that PHMB may decrease corneal sensitivity, which may account for the lack of discomfort [45], although this has not been confirmed by other researchers. One study has suggested that, although there were no differences with respect to discomfort between PHMB- and Polyquad-containing solutions in contact lens wearers, the latter was associated with more corneal staining [46]. However, contrary results were reported by several studies [47,48]. In contrast to solutions containing quaternary ammonium compounds, oxidising solutions lead to less grittiness, dryness, and irritation [49,50], as well as reduced levels of corneal staining and corneal infiltrative events [51].

As the use of iodine had previously been associated with adverse effects, in particular, irritation and itchiness, this study aimed to determine whether signs and symptoms increased following the commencement of *ortho-k* lens wear. Tan et al. had reported less staining in adults wearing soft contact lenses using cleadew for soft lenses than patients using other products [19]. They reported no solution-induced staining and significantly better end-of-day comfort, but slightly more low-level itchiness. This agrees with the results of the current study using cleadewGP, indicating that povidone iodine-based solutions are not associated with increased signs and symptoms.

Cleaning of contact lenses is essential for safe lens wear. Burnham et al. reported problems of cellular debris leading to *Pseudomonas* adherence to contact lens and storage cases [52]. The importance of adherence to routines to avoid adverse effects allows safe use of *ortho-k* [42,53]. It has been previously reported that cleadewGP can kill the FDA panel of organisms and significantly reduce levels of *Acanthamoeba castellanii* [54], as well as effectively kill organisms present in established biofilms in lens cases [55], thus making cleadewGP an appropriate care solution for *ortho-k* wearers. Whilst having a strong disinfecting effect on lenses and lens cases, use of the solution did not significantly change the organisms in the ocular microbiome, indicating that it is a safe option. In contrast to PHMB-containing solutions, to which resistance may develop if not correctly used [56,57], as development of resistance to iodine has not been reported, loss of effectiveness is unlikely to occur.

Follicles, which were present in the subjects at baseline, are a common occurrence in children of Chinese ethnicity, as 33 % of children aged 6–15 years, who did not wear contact lenses, were found to have follicles in the lower lids [58]. The prevalence of follicles tends to decrease over time [58] and this was also observed in the current study.

Of the two subjects with Grade 3 follicles at baseline, their presence was persistent at all visits for one subject, whilst for the second, were absent at 1-month and 3-month, but returned at the 6-month visit. Both subjects had no self-reported symptoms at any visit. It is thought that follicles may be related to developing immunity in young children [58].

A major limitation of this study was that it could not be extended beyond six months, although it is recognized that the development of signs and symptoms may occur more frequently if the originally prescribed lens is still in use after this time. This is most often due to build-up of lens deposits and scratches on the lens surface. However, for many subjects, their lenses would have been replaced by this time due to damage, scratches, and changes in prescription, as the subjects were recruited from myopia control studies. Nevertheless, as the major issue with povidone iodine-based solution is the perception that iodine may be an irritant, the results strongly indicate that there were no significant adverse effects with its use and were comparable or superior to use of other care systems. Sample size for the current study was relatively small and this may have prevented detection of differences between cleaning regimes. However, comparison of each of the five elements examined each on three occasions revealed that none of the differences between groups reached significance and, interestingly, the highest frequency of symptoms was seen in the groups using the more intensive cleaning regimes. This study did not include a control group using an alternative disinfecting solution. The side effects of other systems, especially PHMB-based and hydrogen peroxide, have been investigated and reported in a number of published papers. Hence, to avoid repetition and to enable recruitment of an adequate sample size, a case series design was adopted.

In conclusion, this study showed that the use of cleadewGP, a PI-based disinfecting solution, did not lead to any increase in overall ocular discomfort and little or no change in both signs and symptoms, suggesting it is suitable as a disinfecting solution for *ortho-k* or other rigid lenses. For *ortho-k* wear to be successful, it needs to be not only

effective for myopia control, it also has to be safe and comfortable. Different cleaning regimes did not appear to affect the frequency and severity of signs and symptoms of *ortho-k* wearers, which may be attributable to the inclusion of a surfactant and an enzymatic cleaner. However, as this was a fairly short-term study observing only the first 6-month of lens wear, it may not reflect longer term use, especially if the lenses are not replaced regularly.

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## 6. Commercial relationship

The authors have declared that no commercial relationship with any products used in this report.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A

Have you experienced the following problems during a typical day in the past 2 weeks? Please circle the most appropriate answer.

	0	1	2	3	4
<b>Frequency</b>	Never	Rarely	Sometimes	Frequently	Constantly
<b>Severity</b>	None	Very Mild	Mild	Moderate	Severe

### 1. How often did your eyes feel discomfort? When your eyes felt discomfort, how intense was this feeling of discomfort?

	Whole Day						End of Day (before insertion)				
Frequency	0	1	2	3	4	Frequency	0	1	2	3	4
Severity	0	1	2	3	4	Severity	0	1	2	3	4

### 2. How often did your eyes feel discomfort? When your eyes felt discomfort, how intense was this feeling of discomfort?

	Whole Day						End of Day (before insertion)				
Frequency	0	1	2	3	4	Frequency	0	1	2	3	4
Severity	0	1	2	3	4	Severity	0	1	2	3	4

### 3. How often did your eyes feel itchy? When your eyes felt itchy, how intense was this feeling of itching?

	Whole Day						End of Day (before insertion)				
Frequency	0	1	2	3	4	Frequency	0	1	2	3	4
Severity	0	1	2	3	4	Severity	0	1	2	3	4

### 4. How often did your eyes feel burning and stinging? When your eyes felt burning and stinging, how intense was this feeling of burning and stinging?

	Whole Day						End of Day (before insertion)				
Frequency	0	1	2	3	4	Frequency	0	1	2	3	4
Severity	0	1	2	3	4	Severity	0	1	2	3	4

### 5. How often did your vision change between clear and blurry or foggy? When your vision was blurry, how noticeable was the changeable, blurry or fogging vision? ☐ with glasses ☐ without glasses

	Whole Day					End of Day (before insertion)			
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(continued)

Frequency	0	1	2	3	4	Frequency	0	1	2	3	4
Severity	0	1	2	3	4	Severity	0	1	2	3	4

**6. How often did your eyes look red? When your eyes were red, how much did the red eyes bother you?**

	Whole Day						End of Day (before insertion)				
Frequency	0	1	2	3	4	Frequency	0	1	2	3	4
Severity	0	1	2	3	4	Severity	0	1	2	3	4

**7. How often did your eyes look or feel excessively watery? When your eyes were watery, how much did the watery eyes bother you?**

	Whole Day						End of Day (before insertion)				
Frequency	0	1	2	3	4	Frequency	0	1	2	3	4
Severity	0	1	2	3	4	Severity	0	1	2	3	4

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