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Contrast Sensitivity in Emmetropic Presbyopes with Small-Aperture Inlay Implantation: Normative Values and Postoperative Outcomes

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Introduction

Contrast Sensitivity (CS) is an important measure to research quality of vision, complementing high-contrast visual acuity which assesses visual quantity, and it integrates both optical and neural processing components of vision in a single function [1-2]. CS under different lighting conditions provides particularly important information about quality of vision for post-surgery populations and for presbyopia patients as they are affected by age-related changes to both crystalline lens and neural processing [2-5]. Presbyopia is the most common eye disease, naturally occurring for every person as a result of aging, currently affecting 1 billion adults worldwide [6]. It is age-related loss of accommodation resulting from the crystalline lens' inability to focus at near vergence [7]. The KAMRA® inlay (AcuFocus Inc., Irvine, CA, USA), a small-aperture intra-corneal inlay medical device aiming at correcting presbyopia, can be monocularly implanted into a lamellar pocket in the non-dominant eye of a patient. Its mechanism of action is to restrict unfocused peripheral light rays to provide increased depth of focus and an extended range of continuous vision expanding from near to far [8,9].

The CS function is generally measured using a chart comprised of sine wave gratings at various contrast levels (e.g. the Functional Acuity Contrast Test (FACT) chart in the Optec 6500 Vision Tester (Stereo Optical Co., Chicago, IL, USA), the CSV-1000 Contrast Testing Instrument (VectorVision, Greenville, OH, USA) at a set of spatial frequencies under photopic or mesopic lighting with or without a glare source, Despite a large body of literature on CS [1,10-13]. There is an unmet need for a normative CS database that covers all contrast testing conditions for the presbyopia population, as most reported CS norms either do not pertain to presbyopia population or do not test under mesopic or with-glare conditions. The study aims to establish normative CS curves for emmetropic presbyopes tested monocularly and binocularly under photopic and mesopic conditions with and without glare and to use the normative curves to compare to postoperative outcomes in KAMRA inlay implanted subjects.

Materials and Methods

Subjects and inlay design

In this prospective, multi-center, open-label, single-arm US IDE clinical trial (http://www.clinicaltrials.gov, NCT00819299 and NCT00850031), 507 subjects at 24 clinical sites (15 US and 9 non-US) were implanted with the KAMRA intra-corneal inlay in their non-dominant eyes. Pre-determined subgroup of 335 subjects (47% females and 53% males; mean age, 51.6 ± 3.6 years; race, 90% Caucasian, 7% Asian, 2% Hispanic and less than 1% African American and others) participated in the CS sub-study that was analyzed and presented in this paper. The study was approved by the institutional review board or the ethics committee of each investigational site and was performed in accordance with the Declaration of Helsinki. Subjects provided informed consent before screening and participation.

The inclusion criteria included age between 45 and 60 years, distance visual acuity correctable to 20/20 in both eyes, uncorrected near visual acuity between 20/40 and 20/100 and a preoperative spherical equivalent cycloplegic refraction between +0.50 to -0.75 D with no more than 0.75 D of refractive cylinder in the study eye.

The design of small-aperture KAMRA inlay, the surgical preparation and the technique for KAMRA inlay implantation have been reported in detail [14]. The inlay from the anterior angle is depicted in Figure 1. The inlay is made from a highly biocompatible material polyvinylidene difluoride (PVDF). The inlay is 6 microns thick, 3.8 mm in outer diameter, 1.6 mm in inner diameter, 7.5 mm in spherical radius, and microperforated with 8,400 holes between 5 and 11 µm in diameter allowing for 5% light transmission through the annulus of the inlay.

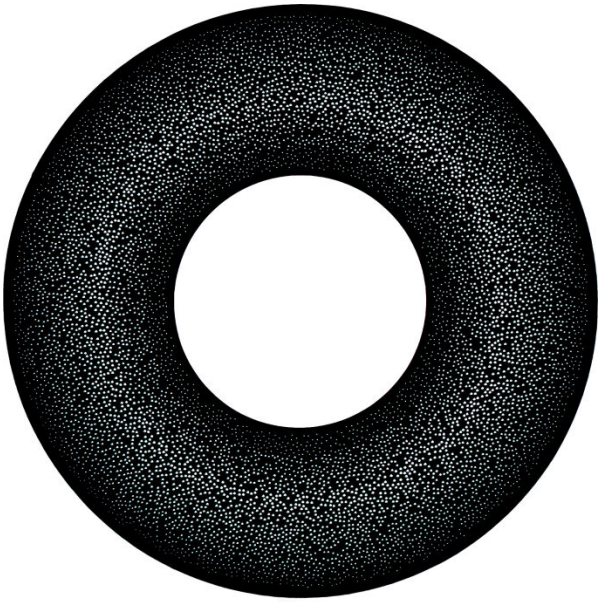

Figure 1: Depiction of the KAMRA® corneal inlay

Contrast sensitivity testing

Contrast sensitivity (CS) was measured using slides of the FACT chart within the Optec 6500 Vision Tester [15]. The back-lit chart was calibrated to 85 cd/m^2 and 3 cd/m^2 for photopic and mesopic testing in luminance, respectively. The FACT chart and the CS measurement process have been discussed in detail [15]. Testing was performed under best distance vision. Five CS conditions were measured (monocular and binocular photopic CS without glare, monocular and binocular mesopic CS without glare, and binocular mesopic CS with glare) and four spatial frequencies were tested in each condition (3, 6, 12, and 18 cycles per degree (cpd) for photopic conditions, 1.5, 3, 6, and 12 cpd for mesopic conditions). Preoperative data were collected and compared to 12, 24, and 36 months postoperatively. Test results were represented in log10 unit of CS (logCS). A logCS score of 0.3 less than the lowest logCS score for a spatial frequency on the FACT chart was assigned when no patches were seen [11,16].

Data analysis

Statistical analysis was performed using the JMP 11.2 (SAS Institute, Inc, Cary, NC, USA). Postoperative mean logCS changes and their upper limits of 95% confidence interval were compared to the preoperative mean logCS values with a non-inferiority margin of -0.15 logCS. This analysis is further confirmed by calculating the within-subject changes and comparing their means to the non-inferiority margin of -0.15 logCS. Mean logCS values from postoperative visits were compared with each other in each combination of spatial frequency and testing condition using Tukey-Kramer HSD test to protect overall error rate across tests between visits. A p-value less than 0.05 were considered statistically significant.

Results

Table 1: The mean logCS values from preoperative to 12, 24 and 36 month postoperative visits and the lower and upper limits of normative values developed from preoperative means in various contrast testing conditions.

Spatial Frequency	Pre-op (n=335)	Month 12 (n=313)	Month 24 (n=286)	Month 36 (n=282)	Low Normal	High Normal
Monocular Photopic without glare						
3	1.85	1.81	1.83	1.81	1.43	2.26
6	1.94	1.88	1.87	1.86	1.54	2.34
12	1.65	1.52	1.52	1.49	1.19	2.11
18	1.23	1.00	1.01	0.99	0.66	1.8
Binocular Photopic without glare						
3	1.98	2.02	2.01	1.98	1.66	2.3
6	2.08	2.11	2.1	2.08	1.77	2.39
12	1.8	1.78	1.79	1.79	1.4	2.21
18	1.41	1.36	1.36	1.36	0.92	1.9
Monocular Mesopic without glare						
1.5	1.68	1.61	1.64	1.63	1.29	2.07
3	1.87	1.74	1.74	1.73	1.49	2.25
6	1.86	1.63	1.65	1.62	1.41	2.3
12	1.41	1.12	1.13	1.12	0.83	2

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Binocular Mesopic without glare						
1.5	1.82	1.8	1.82	1.8	1.48	2.17
3	1.96	1.96	1.97	1.94	1.62	2.3
6	1.96	1.92	1.94	1.91	1.56	2.36
12	1.52	1.48	1.49	1.47	0.99	2.05
Binocular Mesopic with glare						
1.5	1.65	1.61	1.63	1.6	1.2	2.1
3	1.79	1.76	1.79	1.75	1.34	2.24
6	1.8	1.74	1.74	1.72	1.33	2.28
12	1.37	1.28	1.3	1.32	0.75	1.98

Note: The lower and upper normative values are derived from preoperative logCS means ± 1.96 standard deviations at each spatial frequency. The standard deviations are generally between 0.15 to 0.30 logCS and are not presented [15]. Copyright 2016 by SLACK Incorporated. Adapted with permission.

The upper and lower limits of normative values were developed from preoperative CS measurements by taking 1.96 standard deviations (SD) from the mean at each spatial frequency in each testing condition [15] and they demonstrated that the postoperative mean logCS values were well within the high and low normative curves across all postoperative visits (Table 1). The analyses examining changes from preoperative to postoperative revealed that none of the three binocular conditions showed a significant change from baseline: the largest mean change in any condition was -0.08 logCS, half of the clinically significant mean change threshold of -0.15 logCS. In the monocular conditions, the high spatial frequencies in monocular mesopic without glare condition showed the significant loss from preoperative (-0.20 to -0.24 logCS at 6 cpd and 0.29 to -0.30 logCS at 12 cpd across 12-36 months), and the highest spatial frequency in monocular photopic without glare condition also showed a significant loss from preoperative (-0.22 to -0.24 logCS at 18 cpd). The low to intermediate spatial frequencies in both monocular conditions did not show significant losses compared to preoperative mean logCS values with a non-inferiority margin of -0.15 logCS. These results were confirmed by within-subject change analyses. Furthermore, comparisons of mean logCS values between postoperative visits yielded no statistically significant differences ($p>0.05$), indicating stability in CS through three years after surgery.

Discussion

Floor effects in CS testing

The floor and ceiling effects of the FACT chart are well-documented in the literature [13,17]. This study measured mesopic CS from 1.5 to 12 cpd and photopic CS from 3 to 18 cpd to maximize sensitivity and to minimize floor and ceiling effects in all conditions. This study further assigned a score of the lowest CS score minus 0.3 at each spatial frequency when a subject could not see any contrast patches to alleviate the impact of the floor effect and closely estimate the CS population means. This method was applied in similar sinusoidal grating contrast test such as CSV-1000 Contrast Testing Instrument [11,16]. Another method assigning half of the lowest logCS value to subjects with zero patches seen [12,18] uses the same principle even though deriving slightly different logCS scores. Some other methods to treat the floor effect could overestimate the group means if they exclude subjects who couldn't see any patches or assign them with the lowest logCS score, and some other methods could underestimate the group means if they assign those subjects a zero value.

CS after KAMRA inlay surgery

The results showed some mild reductions at the highest spatial frequencies in monocular CS following KAMRA inlay surgery, but showed CS maintained in low to intermediate spatial frequencies in monocular CS conditions and across all spatial frequencies in binocular conditions. Additionally, the postoperative CS was maintained within normative range established from preoperative means in all CS conditions throughout 36 months. These results were generally comparable to a report on another presbyopia-correcting intra-corneal device [19]. Whitman et al. reported that there was some CS loss in the Raindrop Near Vision Inlay ("Raindrop") eye at high spatial frequencies (-0.19 logCS at 12 cpd and -0.23 logCS at 18 cpd) in monocular photopic condition and a smaller loss at high spatial frequencies in monocular mesopic condition. That study [19] also measured CS using Optec 6500 Vision Tester but did not specify how they scored subjects who could not see any patches to account for the floor effect. The postoperative CS loss in KAMRA inlay eyes was smaller compared to Raindrop eyes in the photopic condition, and was a little bigger in mesopic conditions. This reversed impact from lighting condition can be explained by the different mechanisms of action of these two inlays: KAMRA inlay is a 3.8 mm opaque annular ring with a 1.6 mm central aperture and provides extended depth of focus from near through far by restricting unfocused light from reaching the retina; Raindrop Near Vision Inlay is a 2 mm meniscus-shaped inlay whose volume biomechanically raises anterior corneal surface over the inlay and it creates a profocal power profile to provide near vision in the most steeply curved central area, intermediate vision around the central area, and distance vision

in the periphery beyond approximately a 3-mm diameter [19]. Theoretically, KAMRA inlay eyes may experience only a very mild impact on distance vision and photopic distance CS due to diffraction from the 1.6 mm central aperture, similar to the report of constricted pupils mildly reducing CS [20], and the reduced illumination on the retina in KAMRA inlay eyes may additively exemplify its impact on CS under low light. In comparison, Raindrop inlay implanted corneas are multifocal, similar to central multifocal LASIK [21], with an area of central corneal steepening splitting light energy between near and far and inducing approximately 1 diopter myopic shift along with negative spherical aberration [22]. As shown in simulations, this hydrogel inlay creates a pupil-dependent trade-in image quality in exchange for enhanced depth of focus [23] similar to what has been found with center near multifocal contact lenses [24] thus affects distance vision and photopic distance CS. With this optical design, however, the negative impact on CS may be less evident under mesopic conditions where the pupil enlarges, because distance vision is viewed through the periphery of the cornea, that is, the area of available peripheral distance zone increases with larger pupils and as a result reduces the loss of mesopic distance CS [19].

The CS results in KAMRA inlay eyes appear to be on the same scale as those after other corneal refractive surgeries. Significant and prolonged CS reduction was reported after radial keratotomy (RK) and photorefractive keratectomy (PRK) through six months or even one year after surgery [25,26]. Some CS reduction after laser *in situ* keratomileusis (LASIK) was reported from 6 to 18 cpd in one month postoperative while showing the most loss at 12 cpd [27]. When compared to intraocular lens (IOL), KAMRA inlay subjects demonstrated better monocular CS than multifocal IOL eyes and better binocular CS than multifocal IOL subjects and Crystalens Advanced Optics accommodative IOL subjects [28].

Conclusion

We established the CS normative values in monocular and binocular mesopic with and without glare conditions for the young presbyopia population based on a large sample. We demonstrated that the mild reductions in monocular CS in KAMRA inlay eyes were within the normative ranges and were comparable to those from other presbyopia-correcting procedures such as shape-changing corneal inlay [19]. Binocular CS in KAMRA inlay subjects were well maintained after surgery and CS has been stable through three years postoperatively. Practitioners in the ophthalmic care community can use these results as reference CS curves for their patients if their patients are in similar age range and are being measured with sinusoidal grating contrast-based test such as FACT CS chart.

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