Title: Investigating the mechanism of action of the Tetraflex 'accommodative' intraocular lens

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ABSTRACT

PURPOSE: To investigate the mechanism of action of the Tetraflex (Lenstec Kellen KH-3500) 'accommodative' intraocular lens (IOL).

METHOD: Thirteen eyes of eight patients implanted with the Tetraflex 'accommodating' IOL at least two years previously had an assessment of their objective amplitude-of-accommodation by autorefraction, anterior chamber depth and pupil size with optical coherence tomography and IOL flexure with aberrometry, each viewing a target at 0.0 to 4.0 D of accommodative demand.

RESULTS**:** Pupil size decreased by 0.62 ± 0.41 mm on increasing accommodative demand, but the Tetraflex IOL was relatively fixed in position within the eye. The ocular aberrations of the eye changed with increased accommodative demand, but not in a consistent manner between individuals. Those aberrations that appeared to be most affected were defocus, vertical primary and secondary astigmatism, vertical coma, horizontal and vertical primary and secondary trefoil and spherical aberration.

CONCLUSIONS**:** Some of the reported near vision benefits of the Tetraflex 'accommodating' IOL appear to be due to changes in the optical aberrations due to flexure of the IOL on accommodative effort rather than forward movement within the capsular bag.

The Tetraflex (KH3500, Lenstec, St Petersburg, Florida, USA) intraocular lens (IOL) is one of the currently marketed ‘accommodating’ IOLs, whose original proposed principal action was an anterior shift on contraction of the ciliary muscle.[1] However, the lens is designed to move as a whole in the capsular bag rather than through the hinge optics of IOLs such as the 1CU (1 component unit, HumanOptics AG, Erlangen, Germany).[1] Saunders and Saunders described the Tetraflex IOL as having “extremely flexible 5° angulated closed-loop haptics”, finding the lens to provide enhanced near vision with good distance vision 6 months after surgery, although no control group was examined.[2] The same authors found the Tetraflex allowed most of their subjects (88%) to read newspaper and telephone directory print compared to 7% of those implanted with a monofocal IOL.[3] Our prior study on the Tetraflex IOL showed 0.39 ± 0.53 D of physiological objective accommodation at 3 weeks after implantation, although this decreased a little by 6 months.[1]

The mechanism of action of the first generation ‘accommodating’ IOLs is not fully understood. To address this issue, Marcini and colleagues studied patients implanted 6 months previously with the Crystalens AT-45 ‘accommodative’ IOL (Bausch and Lomb, Rochester, NY).[4] The range of eye focus that allowed corrected distance visual acuity to be maintained (on average 1.1 D) on 3.3 D stimulation of the contralateral eye was correlated with a decrease in anterior chamber depth (r=0.40) and the ciliary-scleral process angle (r = 0.77).[4] However, the Crystalens IOL differs substantially from the Tetraflex, such as having grooves in the surface of the plate adjacent that act as hinges. The authors also noted the possible contribution of gravity to the findings as ultrasound biomicroscopy was performed with the patient supine. Most studies with these first generation IOLs have found a forward shift on average with pharmacologically induced accommodation.[5] However, the results are variable with some eyes showing a backwards shift despite apparently good distance-corrected near visual acuity, particularly with the Crystalens AT-45.[5] Also the Tetraflex has not been examined. In addition, pharmacologically induced lens movement has been shown to overestimate the anterior segment changes that can be utilised physiologically.[6]

Most aberrometers have a closed field-of-view and a fixed focal length target designed to relax accommodation to measure the distance viewing wavefront. Hence they are unable to investigate any changes in wavefront with accommodative effort. An adapted instrument (dynamic stimulation aberrometry, Optana, attached to a WASCA; Carl Zeiss meditec AG) has recently been used to demonstrate changes in aberrations over a range of focal distances in 8 patients, one of whom was implanted with a dual-optic accommodating IOL (Synchrony, Visiogen, Irvine, CA).[7] Unlike autorefractors and IOL biometry techniques, aberrometers offer the potential to investigate the optical effects of IOL flexure in-vivo to attempts to focus at near.

This study examines the objective accommodation achieved in eyes implanted with an ‘accommodating’ IOL (Lenstec Tetraflex KH-3500), compared to changes in pupil size, anterior chamber depth and ocular aberrations.

METHODS

This study consisted of physiological measurements of patients previously implanted with the Tetraflex IOL. Informed consent was obtained from the subjects prior to inclusion in the study after explanation of the nature and possible consequences of the study. The research followed the tenets of the Declaration of Helsinki and was approved by the Solihull Local Research Ethics Committee. The enrolment criteria were patients who had undergone routine cataract surgery to remove a lenticular opacity affecting the vision of the patient, no other eye disease or previous ocular surgery, no ocular surface problems or dry eye, no medication with known accommodative effects, and had been implanted with the Tetraflex IOL for two years or more.

The Tetraflex 'accommodating' IOL is a single-piece, spherical optic, acrylic IOL with a refractive index of 1.46. The central optic portion is 5.75 mm and the overall size 11.5 mm in diameter. Its design is shown in figure 1.

Thirteen eyes of eight unselected patients aged 45-81 years (mean 68.4 ± 11.7 years) were assessed. Five had been implanted with the Tetraflex IOL binocularly and 3 monocularly. Retinoscopy and subjective refraction (maximum plus correction without a drop in visual acuity) was performed and all subsequent measures were taken with an optimum distance correction. Objective accommodative responses were assessed using the open-field NVisionK-5001(NVision-K; Shin-Nippon Commerce Inc., Tokyo, Japan) through undilated pupils.[8] Zernike polynomial aberrations up to 8th order were measured using a Shack-Hartmann aberrometer (KR9000-PW; Topcon, Tokyo, Japan), modified to include a Badal optical system[9] and Maltese cross target. Dilation would have affected the accommodative response of subjects and no subject had pupils < 3 mm, therefore aberrations were interpreted over a standardised 3 mm pupil. Subjects were asked to blink before measurements to minimise potential tear film effects. Movement of the IOL (anterior chamber depth) and pupil size with attempted accommodation was determined with optical coherence tomography (Visante, Zeiss, Oberkochen, Germany).[10] With each instrument, subjects viewed a static 90% contrast Maltese cross located at 0.00, 0.50, 1.00, 2.00, 3.00 and 4.00 D accommodative demand through a Badal optical system.

To allow for individual differences between eyes, Pearson's correlation (r) of accommodative demand compared to Zernike coefficients, pupil size and anterior chamber depth were calculated for each eye and averaged across the 13 eyes. Repeated measure ANOVAs were applied to the 10 repeated aberration Zernike coefficients at each accommodative demand for each eye to determine changes with accommodative effort.

RESULTS

The average time since implantation of the Tetraflex lens in the subjects was 2.2 ± 0.2 years (mean ± standard deviation), range 2.0 – 2.8 years. As accommodative demand increased, pupil size decreased (mean correlation ± standard deviation; r = -0.51 ± 0.55; by 0.62 ± 0.41 mm) and anterior chamber depth increased (r = 0.36 ± 0.68; by 0.02 ± 0.05 mm.). Maximal objective accommodation achieved over the accommodative demand range was 0.2 ± 0.3 D (range 0.0D to 1.0D) as measured with the autorefractor.

The mean correlation across subjects for each of the Zernike coefficients from 2nd to 8th order over a 3mm standard pupil size with increasing accommodative demand is displayed in Table 1. Those aberrations that on average were significantly correlated with accommodative demand were defocus (Z^0_2), vertical trefoil Z^{-3}_3, vertical and horizontal secondary astigmatism (Z^{-2}_4, Z^2_4), vertical pentafoil (Z^{-5}_5), vertical secondary coma (Z^{-1}_5), secondary spherical aberration (Z^0_6), vertical secondary pentafoil (Z^{-5}_7), vertical secondary hexafoil (Z^{-6}_8), vertical tertiary quadrafoil(Z^{-4}_8, tertiary spherical aberration (Z^0_8), and vertical and horizontal quaternary astigmatism (Z^{-2}_8, Z^2_8).

Those aberrations that changed systematically with increased accommodative demand (mean across all subjects r > 0.30) were defocus (Z^0_2 r = -0.42 ± 0.48), vertical astigmatism (Z^2_2 r = -0.38 ± 0.61), horizontal trefoil (Z^{-3}_3 r = -0.48 ± 0.42), vertical secondary astigmatism (Z^2_4 r = 0.35 ± 0.63) and horizontal secondary trefoil (Z^{-3}_5 r = 0.30 ± 0.60). Those aberrations that changed significantly at any level of accommodative effort in over 60% of eyes were vertical astigmatism (Z^2_2), horizontal and vertical trefoil (Z^{-3}_3; Z^3_3), vertical coma (Z^1_3), horizontal and vertical secondary trefoil (Z^{-2}_4 ; Z^2_4) and spherical aberration (Z^0_4).

Table 1: Correlation of the average aberrations with increasing accommodative demand for Zernike polynomial coefficients between 2nd and 8th order in eyes implanted with the Tetraflex 'accommodating' intraocular lens. A negative correlation indicates the Zernike polynomial decreases with accommodative demand. n=13 eyes. A negative Zernike sign indicates vertical direction and a positive Zernike sign indicates horizontal direction. * p<0.05, ** p<0.01.

Zernike Term		Description	Correlation (r)	Significance
2	-2	Astigmatism	-0.027	0.959
	0	Defocus	-0.913	0.011*
	2	Astigmatism	-0.670	0.145
3	-3	Trefoil	-0.954	0.003**
	-1	Coma	0.143	0.788
	1	Coma	-0.308	0.553
	3	Trefoil	0.593	0.215
4	-4	Quadrafoil	0.570	0.237
	-2	Secondary Astigmatism	0.929	0.007**
	0	Spherical Aberration	-0.680	0.138
	2	Secondary Astigmatism	0.881	0.020*
	4	Quadrafoil	0.017	0.975
5	-5	Pentafoil	-0.821	0.045*
	-3	Secondary Trefoil	0.614	0.194
	-1	Secondary Coma	-0.948	0.004**
	1	Secondary Coma	0.200	0.703
	3	Secondary Trefoil	0.678	0.139
	5	Pentafoil	0.121	0.820
6	-6	Hexafoil	0.519	0.291
	-4	Secondary Quadrafoil	0.014	0.979

	-2	Tertiary Astigmatism	-0.449	0.372
	0	Secondary Spherical Aberration	-0.973	0.001**
	2	Tertiary Astigmatism	-0.788	0.063
	4	Secondary Quadrafoil	-0.135	0.799
	6	Hexafoil	0.426	0.399
	-7	Heptafoil	-0.351	0.495
	-5	Secondary Pentafoil	-0.832	0.040*
	-3	Tertiary Trefoil	0.601	0.207
	-1	Tertiary Coma	-0.795	0.059
7	1	Tertiary Coma	0.548	0.260
	3	Tertiary Trefoil	-0.633	0.177
	5	Secondary Pentafoil	-0.703	0.119
	7	Heptafoil	-0.583	0.225
	-8	Septafoil	-0.280	0.591
	-6	Secondary Hexafoil	0.881	0.020*
	-4	Tertiary Quadrafoil	0.969	0.001**
	-2	Quaternary Astigmatism	-0.928	0.008**
8	0	Tertiary Spherical Aberration	-0.973	0.001**
	2	Quaternary Astigmatism	0.886	0.019*
	4	Tertiary Quadrafoil	-0.085	0.872
	6	Secondary Hexafoil	0.700	0.121
	8	Septafoil	-0.244	0.642

DISCUSSION

Determining the mechanism of action of 'accommodating' IOLs when they only provide a small objective benefit in near performance is limited by the resolution of the techniques available to assess optical and biometric changes. It is further complicated by targets within the subjective depth of focus, resulting from the pupil aperture and static optical aberrations, providing no drive to accommodation. Also the accommodative system is principally driven by high frequency, high contrast targets.[11] Therefore, measured accommodation will increase within the range of objective optical change in focus available to the eye (once the depth of focus has been exceeded), but may decrease or become more variable above this level due to the resulting image blur. The analysis performed in this study used objective, sensitive techniques and examined both systematic effects over a range of accommodative demands and significant changes between these demands, regardless of accommodative level at which they occurred, to minimise these limitations.

Previous studies have noted a decrease in objective accommodation with time after implantation.[1,6,12-15] At two years post implantation, the Tetraflex 'accommodating' IOL appears to be relatively fixed in position within the eye, moving backwards on increasing accommodative demand from 3.23 ± 1.31 mm to 3.27 ± 1.33 mm. Pupil size decreased from 4.5 ± 1.7 mm to 3.9 ± 1.6 mm over the same increase in accommodative demand, but the depth of focus of the eye is relatively constant with pupil sizes greater than 2.5 mm.[16,17] The ocular aberrations of the eye changed with increased accommodative demand, but not in a consistent manner between individuals. As well as the defocus Zernike term, which correlated with objective eye focus as determined by the autorefractor (mean across all subjects r = 0.44), those aberrations that appeared to be most commonly affected by the accommodative demand of the stimulus viewed were vertical primary and secondary astigmatism, vertical coma, horizontal and vertical primary and secondary trefoil and spherical aberration. These ocular aberrations may be particularly beneficial to a patient's near vision as vertical astigmatism and coma aberrations in eye implanted with IOLs have previously been found to linked with spectacle independence.[18]

In conclusion, flexure changes to the optics of the Tetraflex ‘accommodating’ IOL do appear to occur with accommodative effort and could be responsible for some of the previously shown near visual benefit of this IOL.

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Figure 1: The Tetraflex intraocular lens.