Evaluating the Biostability of Yellow and Clear Intraocular Lenses with a System Simulating Natural Intraocular Environment

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Received: 1 May 2016
Accepted: 27 September 2016
Published: 1 December 2016

Keywords: intraocular lens; long-term biostability; in vitro culturing

Citation: Hayashi R, Hayashi S, Arai K, Yoshida S, Chikuda M, Machida S. Evaluating the long-term biostability of yellow-tinted IOLs using an in vitro system simulating natural intraocular environment. Trans Vis Sci Tech. 2016; 5(6):11, doi:10.1167/tvst.5.6.11

Purpose: Blue light–filtering intraocular lenses (IOLs) are thought to protect the retina from blue light damage after cataract surgery, and the implantation of yellow-tinted IOLs has been commonly used in cataract surgery. To our knowledge, this is the first investigation measuring the long-term biostability of yellow-tinted IOLs using an in vitro system simulating natural intraocular environment.

Methods: Six hydrophobic acrylic IOLs, three clear IOLs, and three yellow-tinted IOLs were included in the study. Each yellow-tinted IOL was a matching counterpart of a clear IOL, with the only difference being the lens color. The IOLs were kept in conditions replicating the intraocular environment using a perfusion culture system for 7 months. Resolution, light transmittance rate, and the modulation transfer function (MTF) were measured before and after culturing. Surface roughness of the anterior and posterior surfaces was also measured.

Results: After culturing for 7 months, there were no changes in the resolution, the light transmittance rate, and MTF. The surface roughness of the anterior and posterior surfaces increased after culturing; however, this increase was clinically insignificant. There were no differences in surface roughness between the clear and yellow-tinted IOLs, either before or after culturing.

Conclusions: A novel in vitro system replicating intraocular environment was used to investigate the biostability of yellow-tinted IOLs. The surface roughness showed no clinically significant increase after culturing for 7 months.

Translational Relevance: This system is useful for evaluating the biostability of IOLs.

Introduction

Opacity of the crystalline lens known as cataract causes visual impairment and is responsible for 33% of the 285 million world’s blindness, according to the World Health Organization. Removing the lens and implanting an intraocular lens (IOL) is currently the only available treatment. However, light transmittance through the lenses of 41- to 79-year-old humans has a peak at wavelengths 500 to 600 nm,¹ thus the aged lens is considered as a natural filter that decreases the transmittance of short wavelength light (blue light, 400–450 nm) to reduce retinal phototoxicity.² Cataract surgery involving implantation of clear IOLs increases the transmittance of light at approximately 410 nm,³ which causes visible spectrum and short wavelength radiation light to reach the retina. Reactive oxygen species induced by short wavelength blue light causes retinal pigment epithelial cell damage,⁴ which is considered as one of the causes inducing age-related macular degeneration. The findings of the Beaver Dam Eye Study indicated an association of cataract surgery with subsequent risk for age-related macular degeneration.⁵

Yellow-tinted IOLs could minimize this problem. Yellow-tinted IOLs absorb blue light and are thought to protect the retina from damage, thus helping to prevent age-related macular degeneration after cata-
In addition, yellow-tinted IOLs have been reported to lower the incidence of blood-retinal barrier disruption, to inhibit retinal pigment epithelial cell damage from light, and to help prevent age-related macular degeneration. The implantation of yellow-tinted IOLs has therefore become common practice in recent years, so the biostability of these IOLs is an important issue.

We have developed a culturing system that simulates the natural intraocular environment of the eye. This system was originally designed for immersing the anterior surface of the lens in an aqueous humor culture base while immersing the posterior surface of the lens in a vitreous humor culture base. The biostability of IOLs could be tested using this in vitro system. In this study, clear and yellow-tinted IOLs were immersed in the culturing system perfused with artificial aqueous humor. We believe this study to be the first investigation on the surface roughness of the anterior and posterior surfaces of IOLs and also the first comparison of yellow-tinted IOLs and clear IOLs after long-term culturing in conditions similar to the human anterior chamber.

**Materials and Methods**

Six types of hydrophobic acrylic IOLs were included in the study, including three clear IOLs, an AF-1 VA-60BB (Hoya, Tokyo, Japan), an AcrySof SA60AT (Alcon, Ft. Worth, TX), and a Nex-Acri N4-
18B (Nidek, Aichi, Japan), and three yellow-tinted IOLs, an AF-1 YA-60BB (Hoya), an AcrySof SN60AT (Alcon), and a Nex-Acri AA N4-11YB (Nidek). Of IOLs used, yellow-tinted IOLs were compared with matching clear IOLs. For example, a yellow AF-1 YA-60BB IOL was compared with a clear AF-1 VA-60BB, with the only difference being the lens color.

This system (Fig. 1) was originally designed for culturing lenses by immersing the anterior surface of the lens in a composite aqueous humor medium and the posterior surface of the lens in a composite vitreous medium. However, as the IOLs do not usually contact the vitreous humor in vivo, both the anterior and posterior surfaces of the cultured IOLs were immersed in our composite aqueous humor, thus the septum between the composite aqueous humor and the composite vitreous was removed (Fig. 2). The composition of our composite aqueous humor is shown in Table 1. The IOLs were cultured in conditions similar to the natural intraocular environment. The volume of the culture system was equal to that of the human eye, and the composite aqueous humor was perfused at the rate of 2 mL per minute, which is the same rate as that of the human aqueous humor exchange. The IOLs were kept in the culturing chamber at 37°C for 7 months.

The characteristics of each IOL were measured before and after culturing. The resolution and the lens power in air were measured using an IOL meter (LM-7B; Nidek). The light transmittance rate was measured using a spectrophotometer (U-4100; Hitachi, Tokyo, Japan), and the modulation transfer function (MTF) was measured using a MTF tester (NIMO TR0815; Lambda-X, Nivelles, Belgium). Surface roughness of the anterior and posterior surfaces was measured using a white-light interferometer (Confocal, Tokyo, Japan). The results are shown in Table 2.

Table 1. Composition of the Composite Aqueous Humor

| Component          | Concentration   | Description                        |
|--------------------|----------------|------------------------------------|
| K⁺                 | 4.0 mM         | Glutathione (reduced glutathione)  |
| Ca²⁺               | 1.5 mM         | Immunoglobulin G                   |
| Mg²⁺               | 1.0 mM         | High density lipoprotein           |
| Cl⁻                | 134 mM         | Epinephrine                        |
| HCO₃⁻              | 20 mM          | Norepinephrine                     |
| HPO₄²⁻             | 0.62 mM        | Dopamine                           |
| Albumin            | 60 mg/L        | Glutathione peroxidase             |
| Prealbumin         | 3.5 mg/L       | Catalase                           |
| Fibronectin        | 2.5 mg/L       | α-Aminobutyric acid                |
| Hyaluronic acid    | 1.1 mg/L       | Alanine                            |
| Transferrin        | 15 mg/L        | Arginine                           |
| D-glucose          | 499 mg/L       | Asparagine                         |
| Lactic acid        | 4.5 mM         | Aspartic acid                      |
| Citric acid        | 0.1 mM         | Citrulline                         |
| L-ascorbic acid    | 1.1 mM         | Cysteine                           |
| Cu, Zn-SOD         | 12,000 U/L     | Glycine                            |

SOD indicates superoxide dismutase.

Table 2. Changes in the Resolution and Lens Power Measured in Air after Culturing

| IOL    | Power, D | Resolution, lp/mm | Power Measured in Air, D |
|--------|----------|-------------------|--------------------------|
|        | Before Culturing | After Culturing | Before Culturing | After Culturing |
| VA-60BB | +20.0 | 250               | 250                     | 58.00         | 58.00         |
| YA-60BB | +20.0 | 250               | 250                     | 58.00         | 58.00         |
| SA60AT  | +20.0 | 250               | 250                     | 51.50         | 51.50         |
| SN60AT  | +20.0 | 250               | 250                     | 51.25         | 51.25         |
| N4-18B  | +20.0 | 250               | 250                     | 56.75         | 57.00         |
| N4-11YB | +20.0 | 250               | 250                     | 56.75         | 57.00         |

D indicates diopter; lp/mm, frequency measured in line pairs per millimeter.
measured using a three-dimensional imaging surface structure analyzer (New View 7200; Zygo Corp., Middlefield, CT). The differences between clear and yellow-tinted IOLs were investigated before and after culturing.

Another set of same six IOLs was cultured with the same method for 7 months, and the characteristics of each IOL was measured after culturing with the same method.

**Results**

Among the six IOLs, there were no changes in gross appearance, resolution, and power after 7 months of culturing (Fig. 3, Table 2). As the results of second set of IOLs were similar, only one set of results are shown in the figures. The light transmittance rates (Fig. 4) and the MTF (Fig. 5) remained the
same after culturing for both clear and yellow-tinted IOLs. The roughness of the IOL surfaces was assessed using Ra values, which are the arithmetic averages of height deviations from the mean line recorded within the evaluation length. Before culturing, the Ra values of the anterior surfaces of both clear and yellow-tinted Alcon IOLs were higher than those of the other IOLs (Fig. 6). However, the Ra values of the Alcon IOLs remained almost the same after culturing. The Ra value of the Hoya yellow-tinted IOL increased the most after culturing; however, it was still less than 0.5 nm. The Ra values of the posterior surfaces of both clear and yellow-tinted Alcon IOLs were also higher than those of the other IOLs, both before and after culturing (Fig. 7), and the increases in Ra values were also higher than those in the other IOLs. After culturing, there were no significant changes in the Ra values of the Hoya and Nidek IOLs.

The yellow-tinted IOLs had a lower light transmittance than did the clear IOLs at 400 to 500 nm (Fig. 8), and these differences did not change after culturing. The MTF was the same between the clear
and yellow-tinted IOLs before or after culturing (Fig. 9). For the Hoya and Nidek IOLs, there were no significant differences in anterior surface Ra values between the clear and yellow-tinted IOLs before and after culturing (Fig. 10). For the Alcon IOLs, the anterior surface Ra value of the clear IOL was higher than that of the yellow-tinted IOL, indicating that the anterior surface of the clear Alcon IOL was rougher than that of the yellow-tinted IOL. For the Hoya and Nidek IOLs, there were no significant differences in posterior surface Ra values between the clear and yellow-tinted IOLs before and after culturing (Fig. 11). For the Alcon IOLs, the posterior surface Ra value of the yellow-tinted IOL was higher than that of the clear IOL before and after culturing, indicating that the posterior surface of the yellow-tinted Alcon IOL was rougher than that of the clear IOL.

Figure 6. Before culturing, the Ra values of the anterior surfaces of both clear and yellow-tinted Alcon IOLs were higher than those of other IOLs. However, the Ra value of the Alcon IOLs remained the same after culturing. The Ra of the Hoya yellow-tinted IOL increased the most after culturing, however it is still <0.5 nm. (a) Clear IOLs, (b) yellow-tinted IOLs, (c) the differences after culturing of each IOL. Surface Ra values of the first set of IOLs are shown in the figures. Surface Ra values of second set of IOLs after culturing are VA-60BB: 0.782 nm; SA-60AT: 2.564 nm; N4-18B: 0.617 nm; YA-60BB: 1.104 nm; SN-60AT: 1.703 nm; N4-11YB: 0.541 nm.
After culturing for 7 months, there were no changes in the resolution, lens power, light transmittance rates, and MTFs of the IOLs. There were no significant changes in surface roughness of the anterior and posterior surfaces after culturing, except for the Alcon IOLs, which significantly increased posterior surface roughness after culturing. There were no differences in resolution, lens power, or MTF between the clear and yellow-tinted IOLs, either before or after culturing. The only significant difference in surface roughness was measured when comparing the clear and yellow-tinted Alcon IOLs both before and after culturing.

The transmittance rates of the three clear IOLs were >60% at 410 nm and up to 90% at 450 nm. However, those of two yellow-tinted IOLs, YA-60BB and SN-60AT, were <15% at 410 nm and 90% at 500 nm, and that of the yellow-tinted N4-11YB IOL was higher than the other two yellow-tinted IOLs, but was still 40% at 410 nm. The results suggested that
filtering of blue light by all three yellow-tinted IOLs was comparable to that of a natural-aged crystalline lens. In addition, the transmittance rates did not change after 7 months of culture, indicating good biostability.

In this study, the MTF of IOLs was also measured. Resolution and modulation are the two factors defining the MTF. Resolution is the ability of an imaging system to distinguish object detail. High resolution images are those that exhibit a large amount of detail and minimal blurring. Modulation of an optical system is defined as how faithfully the object contrast is transferred through an optical system. The MTF of an optical system is a measurement of its ability to transfer the object contrast at a particular resolution. An MTF graph plots the percentage of transferred modulation versus the frequency and is one of the best parameters to quantify the overall imaging performance of an optical system. All MTFs of the six IOLs included in this study changed very little after 7 months of culture, indicating the stability of imaging performance for these IOLs.

The inflammatory reaction and the posterior capsule opacity are two major postoperative complications of visual impairment. Removing the opacity of the crystalline lens and implanting an IOL significantly improves vision. However, deposits on the IOL surface, which are considered a result of the inflammatory reaction in the anterior chamber, are one of the major factors causing visual impairment. Postoperative posterior capsule opacification, caused by the migration and adhesion of lens endothelial cells (LECs), is another major factor causing visual impairment. Thus, the foreign body reaction of monocytic and macrophage cells, considered as uveal biocompatibility, and the wound-healing reaction of LECs, considered as capsular biocompatibility, are two factors that determine the surface biocompatibility of IOLs.

The inflammatory reaction after IOL implantation is initiated by the interruption of the blood–aqueous barrier, followed by the adhesion of cells on the IOL surface. Cell adhesion on the IOL surface is assumed to be due to the adsorption of ligands of cell adhesive proteins. It has been reported that the degree of roughness affects the number of cells adhering to the IOL surface, and the adhesion significantly decreased when the Ra values decreased to 0.7 nm on acrylic IOLs. It is possible that the larger area allows more cells to contact the IOL. In the present study, the roughness of the IOL surface increased after culturing. However, the Ra values of the anterior surface increased less than 0.5 nm after culturing for all IOLs included in the study. Although the Ra values of the anterior surface of the Hoya yellow-tinted IOLs doubled after culturing, the values were still <0.7 nm, which is clinically insignificant. Before culturing, the Ra values of the anterior surfaces of the Alcon lenses were >1.5 nm; however, there was little change after culturing. Although the inflammatory reaction and behavior of LECs were not included in this study, the results described above indicate that one of the most important factors, surface roughness, changed little and may not increase the adhesion of inflammatory cells on the anterior surface of IOLs.

On the other hand, the surface roughness acts differently on the posterior surface of IOLs. It has been reported that adhesion of LECs and the collagen membrane on the optic surface prevent posterior capsule opacity and anterior capsule constriction. In the normal crystalline lens, LECs attach to the anterior capsule in a contact-inhibited manner. Following cataract surgery, residual LECs proliferate and migrate into the space between the posterior capsule and the IOL. These processes have been suggested to be modulated by the design, material, and surface properties of the IOLs. A sharp posterior IOL edge has been reported to prevent posterior capsule opacification by inhibiting LECs migration along the lens capsule. Acrylic IOLs have been reported to be associated with less posterior capsule opacification than polymethyl methacrylate IOLs because the sticky nature of the hydrophobic acrylic IOL possibly inhibits the migration of residual LECs. The Ra values of the posterior surface of the Hoya and Nidek IOLs only changed a little, while those of the Alcon IOLs increased. The Alcon Acrylof IOLs had a

![Figure 6. Continued.](image-url)
greater surface roughness, which may increase adhesion of proteins, such as fibronectin, to the optic surface,\textsuperscript{18} resulting in an increase in the sticky nature and inducing adhesion of LECs\textsuperscript{19} and collage membranes,\textsuperscript{20} further leading to the prevention of posterior capsule opacification.

In conclusion, when using an in vitro culture system simulating the natural intraocular environment for 7 months, there were no changes in the resolution, light transmittance rate, and lens power in air of the yellow-tinted IOLs. The surface roughness of the anterior and posterior surfaces increased after culturing; however, it was clinically insignificant, and the biostability of the yellow-tinted IOLs was the same as the clear IOLs. This system is useful for evaluating the biostability of IOLs.

Figure 7. The Ra values of posterior surfaces of both clear and yellow-tinted Alcon IOLs were also higher than those of other IOLs both before and after culturing. The increases in Ra values were also higher than those of other IOLs. After culturing, there were no significant increases among Hoya and Nidek IOLs. (a) Clear IOLs, (b) yellow-tinted IOLs, (c) the differences after culturing of each IOL. Surface Ra values of the first set of IOLs are shown in the figures. Surface Ra values of second set of IOLs after culturing are: VA-60BB: 0.672 nm; SA-60AT: 2.372 nm; N4-18B: 0.897 nm; YA-60BB: 0.810 nm; SN-60AT: 2.845 nm; N4-11YB: 0.532 nm.
Figure 7. Continued.
Figure 8. The yellow-tinted IOLs had lower light transmittance rates than clear IOLs, at 400 to 500 nm, and the differences did not change after culturing. (a–c) Before culturing, (d–f) after culturing.
Figure 9. The MTF was the same between clear and yellow-tinted IOLs before or after culturing. (a–c) Before culturing, (d–f) after culturing.
For Hoya and Nidek IOLs, there were no significant differences in anterior surface Ra values between clear and yellow-tinted IOLs before and after culturing. For the Alcon IOLs, the anterior surface Ra value of the clear IOL was higher than that of the yellow-tinted IOL, indicating that the anterior surface of the clear Alcon IOL was rougher than that of the yellow-tinted IOL.

For Hoya and Nidek IOLs, there were no significant differences of posterior surface Ra values between clear and yellow-tinted IOLs before and after culturing. For the Alcon IOLs, the posterior surface Ra value of the yellow-tinted IOL was higher than that of the clear IOL before and after culturing, indicating that the posterior surface of yellow-tinted Alcon IOL was rougher than that of the clear IOL.
Acknowledgments

Disclosure: R. Hayashi, None; S. Hayashi, None; K. Arai, None; S. Yoshida, None; M. Chikuda, None; S. Machida, None

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