Blue-Light Filtration: Evidence-Based Assessment

The first blue-light–filtering IOL introduced widely to cataract surgeons in the US was the AcrySof Natural (SN60AT) IOL (Alcon Laboratories, Inc., Fort Worth, TX), which received FDA approval in 2002. Since the time of its approval, more than 6 million IOLs with the AcrySof Natural blue-light–filtering chromophore have been implanted worldwide. A large percentage of these blue-light–filtering IOLs since commercial introduction have included innovative aspheric, multifocal, and most recently toric optic designs, with clinically proven performance.

Despite the initial clinical evidence and more recent clinical data from the expanded portfolio of blue-light–filtering IOL models, they remain a subject of debate among critics. A tremendous amount of research has been conducted in the past several years to demonstrate the value and safety of blue-light–filtering IOLs, including the AcrySof Natural IOLs. The purpose of this monograph—based on presentations given during the 2007 Annual Meeting of the AAO in New Orleans—is to communicate to surgeons the findings and implications of this research: to further establish the rationale, safety, and efficacy of these lenses for use in patients worldwide on a routine basis.

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A n IOL that absorbs short-wavelength blue light has several potential benefits. These include the reduction of exposure to short-wavelength blue light and of the potential blue-light hazard that has been associated with an increased risk of age-related macular degeneration (AMD). An extensive body of peer-reviewed research strongly suggests there is a “blue-light hazard,” with an excitation peak around 440 nm, that may play a role in a complex set of cellular events within the retina (lipid peroxidation, deterioration of lysosome function, and accumulation of lipofuscin) and produce photochemical damage to the retinal pigment epithelium (RPE) through oxidative stresses. There is also a possible beneficial effect on chromatic aberration, which would improve visual function. Potential adverse effects of blue-light filtration on visual function include the reduction of scotopic or dark-adapted sensitivity and of hue discrimination.

Researchers at Columbia University and New York University School of Medicine performed a study to investigate the potential adverse effects of a yellow-tinted IOL on scotopic sensitivity and hue discrimination. The study included nine patients who received a yellow-tinted, blue-light–filtering IOL in one eye and a UV-only–absorbing IOL in the other eye. The study also included nine young phakic subjects with and without clip-on lenses made with the same blue-light–filtering yellow chromophore.

The researchers evaluated hue discrimination in all subjects using the Farnsworth-Munsell 100 hue (FM 100) test. The patients also underwent dark-adapted threshold testing with 440-, 500-, and 650-nm light at 23 locations using a modified Humphrey perimeter (Carl Zeiss Meditec, Inc., Dublin, CA). The dark-adapted threshold to white light was also evaluated at 15° temporal retina.

Figure 1. Polar plots show examples of FM 100 hue test results. Patient A: error score 56, no axis. Patient B: error score 52, no axis. Young phakic subject C: error score 20, no axis. Young phakic subject D: error score 16, no axis.
COLOR TESTING

In the nine patients implanted with IOLs, no significant differences in FM 100 error scores were seen between the eyes with the blue-light–filtering IOLs (the AcrySof Natural SN60AT lens [Alcon Laboratories, Inc., Fort Worth, TX]) and the contralateral eyes with UV-only–blocking IOLs (the AcrySof single-piece SA60AT lens [Alcon Laboratories, Inc.]). In the nine young phakic subjects with and without clip-on lenses with the yellow chromophore, there were also no significant differences in FM 100 error scores (Figure 1).

In the nine IOL patients, there were no significant differences between the two eyes in dark-adapted sensitivities to 440, 500, or 650 nm or to the white-light stimuli.

In the young phakic subjects, there was a slight difference in dark-adapted sensitivities with and without the blue-light–blocking clip-on lenses at the specific wavelengths, but there was no difference in sensitivity to the white-light stimuli. Mean sensitivities were decreased with the clip-ons by 2.7 to 2.8 dB at 440 nm, 0.7 to 1.0 dB at 500 nm, and 0.0 to 1.2 dB at 650 nm.

An important point is that there is a difference between a patient with a lens placed in front of his eye and a pseudophakic patient. When comparing data among studies, one must understand that patients who have an implanted IOL may have a different response in terms of overall visual function compared with test subjects with loose lenses placed in front of their eyes.

Figure 1. These graphs show the two study groups’ dark-adapted sensitivities to 440, 500, and 650 nm and white light. Graph A shows the nine patients’ mean differences in sensitivity between eyes with the SN60 (AcrySof Natural) and fellow eyes with SA60 IOLs. Graph B shows the nine young phakic subjects’ mean differences in sensitivity with and without yellow clip-on (B).

Figure 2 shows the dark-adapted sensitivities of all study subjects, both pseudophakic (Figure 2A) and young phakic subjects (Figure 2B). The vertical groupings show the distribution of difference at each of the wavelengths and with white light. Note the slight reduction in the individual wavelengths in the phakic patients with the clip-on lens and no difference with white light.

SUMMARY

The results of this study suggest that implantation of a yellow-tinted, blue-light–filtering IOL has no significant effect on scotopic sensitivity or hue discrimination clinically or statistically, and visual performance is equal to that of a traditional UV-only filtration IOL.

In my professional opinion, it is exciting to also have available for my patients a portfolio of blue-light–filtering lenses, such as aspheric, toric, and multifocal optic designs, whose clinical performance is equal or superior to UV-only IOLs. These newest models have advanced the original monofocal platform we tested in our study described herein and are providing cataract surgeons with more innovative IOL technologies for addressing the specific needs of their cataract patients. ■

As an ocular oncologist and pathologist, I want to deliver this message to cataract surgeons: Evidence is mounting that the ability to help prevent ocular melanoma is in your hands. Exposure to blue light has been established as a risk factor for both uveal and skin melanoma, not only through animal models and in vitro studies but also increasingly through clinical and epidemiologic evidence. This article discusses recent studies in our laboratory and elsewhere adding to this evidence.

OVERVIEW

Uveal melanomas are composed of spindle and epithelioid cells, and they are classified histopathologically as either spindle-cell–type or mixed-cell–type tumors. Uveal melanoma is the most common primary ocular tumor in adults and the most deadly. Fully 50% of patients presenting with uveal melanoma will die of liver metastasis, regardless of intraocular treatment.

The only way to decrease mortality rates from uveal melanoma is prevention. Increasingly, evidence suggests that blue-light–filtering IOLs may play a role in the prevention of uveal melanoma.

Uveal melanoma is an area of intersection between cataract surgery and ocular oncology. The highest incidence of uveal melanoma occurs in people between the ages of 50 and 80 years. Similarly, 85% of cataract surgery is performed in patients between the ages of 50 and 80 years. In several reported cases, uveal melanomas have been diagnosed after cataract surgery.

Blue light, with a wavelength of approximately 475 nm, is a component of both natural and artificial light. Work in our laboratory suggests that blue light may trigger the malignant transformation of melanocytes to spindle cells and epithelioid cells in uveal melanoma.

Manning and colleagues reported that rats exposed to blue light long term developed intraocular masses that were pathologically similar to uveal melanoma. Normal melanocytes may transform into nevus cells, the benign counterpart of melanoma, or into spindle-cell or epithelioid-cell melanomas, and blue light can make this transformation faster and more malignant.

RECENT EXPERIMENTAL STUDIES

Our laboratory developed an experimental model of uveal melanoma using human melanoma cells in albino rabbits. In an immunesuppressed albino rabbit, we implant human melanoma cells from our own patients. The duration of the experiment is approximately 12 weeks. After the third week, about 95% of the animals develop intraocular tumors that are very similar to human uveal melanoma. The tumors are 100% metastatic, liver metastasis is present, and circulating malignant cells can be detected.

Recently, we used this animal model of uveal melanoma to evaluate the effect of blue-light exposure on tumor development. An experimental group of 10 rabbits was exposed to blue light, while a control group of 10 rabbits was protected from the blue light using a yellow filter. The exposure to blue light...
led to more proliferation in cell lines derived from intraocular tumors compared with controls. The animals exposed to blue light had larger tumors and more metastasis. Notably, the exposed animals developed intraocular tumors in the first week, while control animals developed them in the third week. If we make an analogy that each week in this experimental model equals 1 year in the human experience of melanoma, this amounts to a 3- to 4-year difference in tumor development.

Subsequently, we evaluated the effects of blue light and blue-light protection in different lines of human melanoma cells from four different patients. We designed a structure that allowed light irradiation simultaneously in 96 well plates with an intensity of approximately 650 fc. Two cutoff filters were used to ensure that the cells were exposed exclusively to blue light in the range of approximately 400- to 550-nm wavelength. The cells were protected with two types of IOLs, one with UV protection only and the other with UV plus blue-light protection. Control cells were covered with aluminum foil.

Figure 1 illustrates the results of this study. Cells exposed to blue light showed a statistically significant increase in proliferation. When the blue light was filtered through a standard UV-absorbing IOL, the cells showed less increase in proliferation, although the difference from unfiltered exposure was not statistically significant. The cells exposed through a blue-light–filtering IOL showed no increase in proliferation compared with control in all four cell lines. In fact, some lines had lower proliferation than at baseline. In all cell lines, exposure to blue light led to an increase in proliferation compared with controls. Blue-light–filtering IOLs eliminated those increases in proliferation in all four lines.

**CLINICAL AND EPIDEMIOLOGIC STUDIES**

Shah and colleagues recently performed a meta-analysis of published studies to examine the association between UV light exposure and uveal melanoma. They reviewed 133 published reports and identified 12 studies with sufficient data to calculate odds ratios and standard errors for UV exposure. They found inconsistent results associating UV exposure with uveal melanoma, but there was evidence implicating arc welding as a possible risk factor.

The investigators thought of welding as a source of UV light. In industrial welding, workers are protected only against UV light. Approximately 85% of the exposure they experience is in fact UV. In response to the Shah meta-analysis, Fernandes et al published a letter in *Ophthalmology* noting that our data suggest that welding may be implicated in the oncogenesis of uveal melanoma, not because of UV light but because of blue-light exposure.

Subsequent to this exchange, the discussion of blue light’s relationship to melanoma has moved beyond ophthalmology into dermatology and pediatrics. Matichard and colleagues assessed the role of neonatal blue-light phototherapy, used in the treatment of hyperbilirubinemia, in nevus acquisition in...
The first blue-light–filtering IOL to appear in the new millennium was the AcrySof Natural IOL (Alcon Laboratories, Inc., Fort Worth, TX). Since that lens was approved by the FDA in 2003, more than 6 million IOLs on the AcrySof Natural platform have been implanted worldwide (data on file with Alcon Laboratories, Inc.).

Data submitted to the FDA for approval of the AcrySof Natural showed no clinical differences between the Natural and the AcrySof Single-Piece IOL. Nonetheless, critics of the lens’ blue-light–filtering capabilities expressed concerns that it could affect color vision, functioning in scotopic lighting conditions, responses to glaucoma testing with short-wavelength automated perimetry, and, more recently, circadian functioning.

Peer-reviewed studies have since shown that the blue-light–filtering chromophore in the AcrySof Natural IOL does not affect color vision, scotopic functioning, or short-wavelength perimetry. A recent study by Muftuoglu et al at Ankara University in Turkey found no difference in photopic or scotopic contrast sensitivity or blue-color perception between patients with AcrySof Natural IOLs and patients with UV-only–blocking AcrySof SA60 IOLs. All patients had IOLs implanted with the same technique, including clear corneal incision, phacoemulsification, and in-the-bag lens placement by the same surgeon. Like previous investigators, these researchers concluded that scotopic sensitivity decreases with age, but that a UV-only–blocking IOL does not provide statistically significantly better visual performance in patients in a scotopic environment than a blue-light–filtering IOL.

Critics of blue-light–filtering IOLs have suggested that wearing sunglasses outdoors offers sufficient protection from potentially damaging blue light. Although it is true that sunglasses generally provide some protection from solar blue light, we are being further exposed to blue light when indoors as well, most specifically from fluorescent lighting in offices and other lifestyle environments. Figure 1 illustrates exposure to daily light sources. The irradiance scales shown are relative and meant to illustrate the peak levels of high energy, short-wavelength blue light in sunlight, and various indoor lighting sources. Clearly, the sun...
is the brightest light source with the broadest spectrum of irradiance that we are exposed to, but fluorescent lighting emits a large amount of blue light and even some UV light. So, there is a significant amount of blue light exposure indoors as well as outdoors.10

BLUE-LIGHT TOXICITY: RECENT RESEARCH

Blue light’s toxicity to retinal cells has been shown in animal and in vitro experiments. A recent Medline search using the key words retina and blue light identified 550 articles, many of which contain cautionary statements about the possibility of retinal damage from blue light. A few recent studies are summarized here.

A study by Marshall and colleagues at McGill University evaluated the effect of blue light on four human uveal melanoma cell lines.11 Researchers exposed the cells to blue light with and without filtering it through UV-absorbing or blue-light–filtering IOLs. Exposure to blue light increased cell proliferation compared with unexposed controls, but protection with the blue-light–filtering IOL prevented the increase in proliferation. The investigators recommended the use of UV- and blue-light–filtering IOLs for older patients, those with light-colored irides, or those who experience exposure to natural sunlight.

Yanagi and colleagues12 investigated the protective effect of blue-light–filtering IOLs on retinal pigment epithelial (RPE) cells. They found that the presence of a blue-light–filtering IOL decreased phototoxicity in RPE cells laden with the lipofuscin fluorophore A2E, and it significantly decreased the amount of light-induced upregulation of vascular endothelial growth factor, compared with cells exposed to light without a filtering IOL.

Tanito and colleagues13 at the University of Oklahoma tested the protective effects of blue-light–filtering IOLs in albino rats. Rats with one eye shielded with a yellow filter and one with a clear filter were exposed to blue fluorescent lights with peak wavelengths in the long or short blue portion of the spectrum. Using several measures to assess retinal damage, they found that the yellow material protected the retina against shorter-wavelength light exposure better than the clear material.

CIRCADIAN RHYTHM

Most recently, critics have suggested that blue-light–filtering IOLs may interfere with our circadian rhythms. Humans have evolved through the millennia to have crystalline lenses that filter much of the blue light from reaching the retina.

Full-spectrum white light stimulates melanopsin, a substance localized in human retinal ganglion cells that is key in the regulation of circadian rhythms.14,15 The stimulation of melanopsin initiates a process that results in the release of melatonin by the pineal gland. These processes are part of the circadian rhythms that regulate our wake and sleep cycles, hormonal release, appetite, body temperature, and many other bodily functions.

Figure 2 shows the light transmission curves of a UV-only–blocking IOL, the AcrySof Natural blue-light–blocking IOL, and the crystalline lenses of a 4-year-old and a 53-year-old human. The AcrySof Natural was designed to mimic the light-spectrum transmission characteristics of a young human lens. Between 400 and 450 nm, the blue-light–blocking IOL closely approximates the young human lens. This is important, because this area of the light spectrum is toxic to retinal cells. Above 450 nm, where the peak of melanopsin’s sensitivity is located (480 nm), the AcrySof Natural increases the transmission of light.

Some critics have speculated that blue-light filtration can affect the activity of melanopsin, but this seems speculative given that the AcrySof Natural transmits more light than the adult human lens near the peak of the melanopsin curve. There are no clinical data indicating the minimum level of full-spectrum light needed to reach the retinal ganglion cells to activate melanopsin.

Thus, the Natural lens offers protection in the portion
of the light spectrum that is of greatest risk to retinal cells but at the same time allows greater penetration in the range that stimulates melanopsin.

**CONCLUSION**

Evidence clearly suggests that blue-light–filtering IOLs do not interfere with color vision, scotopic vision, or short-wavelength glaucoma testing. These lenses prevent blue-light–induced damage to retinal cells and also permit the transmission of light necessary for maintaining circadian rhythms. They improve sensitivity and color perception in certain populations, such as diabetics.  

The blue-light filtering of the AcrySof Natural lens more closely approximates the human condition than any other device available. All models of the AcrySof Natural IOL filter blue light in the manner that nature intended, not blocking the blue, as critics tend to imply. The clinical data are clear. Our pledge as physicians is to do no harm, and I believe I am doing my patients only good when using blue-light–filtering IOLs such as the AcrySof Natural family of lenses.  


**Melanoma continued from page 5**

childhood. This is the only medical treatment that exclusively uses blue light. They concluded that intensive neonatal blue-light phototherapy is a strong risk factor for nevus development in childhood and recommended that exposed children should undergo dermatologic preventive measures and surveillance for the development of melanoma.

This suggestion was reiterated recently by Csoma and colleagues in the journal *Pediatrics.* They conclude that, because having clinically atypical nevi is the most important independent phenotypic risk factor for the development of malignant melanoma of the skin, children with a history of neonatal phototherapy should undergo dermatologic screening.

**CONCLUSION**

To return to an earlier point, uveal melanoma is a subject on which cataract surgeons and ocular oncologists share common interest. Ocular oncologists can treat uveal melanoma, but we cannot make our patients survive longer. Cataract surgeons have in their hands a tool that may help to prevent or reduce the incidence of this uncommon but frequently fatal disease. When you implant blue-light–filtering IOLs, you are not only restoring vision to your patients, you are also potentially helping to decrease mortality from uveal melanoma.