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Analysis of a Systematic Review About Blue Light–Filtering Intraocular Lenses for Retinal Protection:

Understanding the Limitations of the Evidence

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Abstract

IMPORTANCE—Cataract surgery, with intraocular lens (IOL) implantation, is the most common ocular surgical procedure worldwide. It has been suggested that IOLs that selectively attenuate short wavelength visible light (blue light-filtering IOLs) may be beneficial for macular health. Whether blue light-filtering IOLs impart retinal photoprotection is of public health relevance, particularly in the context of aging demographics and the increasing global prevalence of age-related macular degeneration. This review analyzes and interprets the key findings, including consideration of the implications for practice and future research, of a 2018 Cochrane systematic

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review that evaluated the efficacy and safety of blue light-filtering IOLs for providing protection to macular health and function.

OBSERVATIONS—The Cochrane systematic review included 51 randomized controlled trials that were performed in 17 countries. The trials involved adults undergoing cataract surgery in which a blue light-filtering IOL was compared with an equivalent non-blue light-filtering IOL. Study follow-up periods ranged from 1 month to 5 years. Together, these studies considered clinical outcomes in more than 5000 eyes. There was limited ability to combine data across trials (to draw overall conclusions) because of the use of different measurement techniques for outcomes, incomplete reporting of data, and/or varied follow-up periods. We identified substantial shortcomings in the internal validity of many of the included studies, particularly regarding trial design, conduct, and reporting. We propose several avenues for improving the rigor of potential future research in the field, including developing a core set of outcome measures, the inclusion of sample size calculations, the masking of trial participants and outcome assessors, and prospective clinical trial registration.

CONCLUSIONS AND RELEVANCE—Using blue light-filtering IOLs to impart benefits to the macula is currently not supported by the best available clinical research evidence, and it is important that clinicians are mindful of this evidence limitation when adopting these devices in clinical practice.

For the past 2 decades, substantial debate has surrounded the clinical application of ophthalmic lenses that attenuate the transmission of short-wavelength visible (blue) light. Blue light filtering, also termed *blue blocking*, lenses reduce ocular exposure to both ultraviolet (UV) radiation (involving wavelengths in the 200-400 nm range), and short-wavelength visible light (including violet, 400-440 nm, and blue, 440-500 nm light). The 2 principal categories of blue light-filtering lens products are eyeglass lenses, which have been considered in detail elsewhere,[1,2] and intraocular lenses (IOLs),[3] which contain, or are coated with, chromophores that absorb a proportion of the selected incident wavelengths and are the focus of this article.

In addition to claims that blue light filters may alleviate eye strain[4] and improve sleep quality,[5] they have been proposed to potentially provide retinal protection from phototoxicity, particularly at the macula. Underpinning this retinal protection hypothesis are experimental data from animal[6] and cell culture[7-9] studies that demonstrate that high-level exposure to short-wavelength visible light can induce retinal cellular damage. Extrapolating these findings to humans, it has been suggested that blue light may contribute to the development and/or progression of age-related macular degeneration (AMD).[10] Age-related macular degeneration is currently the leading cause of adult vision impairment in developed countries, and in the absence of a cure, any intervention that can impart a relative reduction in risk has the potential for individual and public health benefits.

Although sunlight is the predominant source of environmental blue light, concern has been expressed regarding modern light-emitting diode and compact fluorescent lamp sources that emit higher levels of visible short-wavelength light than traditional incandescent sources. Guidelines have been published by the International Commission on Non-ionising Radiation Protection (ICNIRP)[11] to inform safety limits for human ocular exposure to optical

radiation. Notably, the level (weighted radiance) of blue light emission from modern lighting sources, including computer, tablet, and smartphone displays, is estimated to be approximately 100-fold times lower than the ocular hazard level that is specified in the ICNIRP guidelines.[12] The risk of retinal damage attributed to blue light emitted from digital devices and domestic light sources is thus thought to be minimal, even under "extreme long-term viewing conditions." Despite these findings, an increasing number of blue light-filtering ophthalmic lens devices have received regulatory approval for purposes associated with refractive correction (rather than photoprotection per se) and there has been a considerable uptake in clinical practice.

Cataract surgery with IOL implantation is the most common ocular surgery, with approximately 10 million procedures performed worldwide annually. In 2011, it was estimated that blue light-filtering IOLs accounted for 1 in 4 implants.[13] As blue light-filtering IOLs more closely mimic the transmission characteristics of the aged human crystalline lens (compared with UV-filtering IOLs), it has been argued that these implants may be clinically justified "until empirical evidence clearly supports a case for doing otherwise"[14] However, according to Mainster and Turner,[13] such practices are best described as hypothesis-based, rather than evidence-based, medical practice.

Cochrane Systematic Review Findings

In the May 2018 edition of the Cochrane Database of Systematic Reviews, a systematic review considered the current, best-available evidence from randomized controlled trials (RCTs) regarding blue light filtering–IOLs for providing protection to macular health.[3] This review included 51 RCTs that were undertaken in 17 countries and involved adults undergoing cataract extraction in which a blue light-filtering IOL was compared with an equivalent non–blue light-filtering IOL. Together, these studies considered the outcomes of IOL implantation in more than 5000 eyes. The primary outcome of the review was a conclusion, with a moderate level of certainty, for no clinically meaningful difference (mean difference, −0.01 logMAR; 95% CI, 0.03 lower to 0.02 higher; $P = .48$) in short-term best-corrected visual acuity (BCVA) between the 2 IOL types.

Analysis of the Findings

Herein, we analyze and interpret the findings of this Cochrane review, including a consideration of the implications for clinical practice and future research. Because of a paucity of high-quality evidence and the short duration (ie, less than 3-month follow-up) of most trials, the association of blue light-filtering IOLs with maintaining macular integrity and/or affecting the clinical course of AMD remain uncertain. The use of blue light-filtering IOLs to impart benefits to macular health is therefore not currently supported by the best available research evidence.

Although 51 eligible RCTs were identified for inclusion in the systematic review, substantially more than are included in most Cochrane Eyes and Vision systematic reviews, these conclusions were based on a meta-analysis (ie, the statistical combination of results from multiple independent studies) of only 2 studies.[15,16] Together, these parallel-arm

clinical trials evaluated clinical outcomes in a total of 131 participants. The study by Caporossi and colleagues[15] that considered 3 different types of blue light-filtering IOLs and a non–blue light-filtering (control) IOL reported BCVA outcomes at up to 2 years of follow-up. Other end points considered in this trial included contrast sensitivity, pupil size, corneal aberrations, and wavefront spherical aberration of the eye. The trial by Vuori and colleagues[16] was a 2-arm trial involving random assignment to either a blue light-filtering or non–blue light-filtering IOL with a 6-month postintervention follow-up period. In addition to BCVA, measured outcomes included color vision and the visibility of the retinal nerve fiber layer from retinal fundus photography results.

The inability to combine data across many trials was due to multiple factors, including the use of different measurement techniques for outcomes, incomplete reporting of outcome data, and varied follow-up periods. A major reason was a lack of appropriate quantitative data in the trial reports. This is a clear example of research waste[17-19] in which most of the included studies could not meaningfully contribute to the conclusions of this systematic review. This problem should be addressed by developing a “core outcome set” for such trials, as recommended by the Core Outcome Measures in Effectiveness Trials initiative,[20] preferably with patient engagement in developing such measures.[21]

In addition, as evident from the Figure, the review highlighted shortcomings in the internal validity of many studies. We propose that developing measures to address these limitations concerning trial design, conduct, and reporting must be a priority for future research in the field. None of the 51 trials referenced a protocol and only 2 (4%) were listed on a clinical trial registry, thus making it difficult to exclude the risk of selective outcome reporting (ie, only a subset of all the outcomes measured and analyzed in a study are potentially fully reported based on the direction, magnitude, or statistical significance of selected outcomes). This is despite all of the trials being published in 2004 or later after implementation of the International Committee of Medical Journal Editors’ statement[22] requiring prospective RCT registration for publication in leading medical journals and the subsequent inclusion of this requirement in the Declaration of Helsinki (2013).

Another finding was a general lack of statistical rigor with respect to trial design and analysis. Only 5 (10%) of the included RCTs reported an a priori power calculation; this is poorer than the reporting of sample size calculations (as determined from systematic reviews) of surgical interventions in other specialties, including oncology (41%), cardiothoracic surgery (28%), and laparoscopic surgery (25%).[23] Inadequately powered RCTs risk the promotion of false-negative and false-positive findings and the drawing of erroneous conclusions that, if inappropriately translated into practice, may lead to the adoption of ineffective and/or harmful interventions. Many RCTs excluded potential participants who experienced intraoperative and/or postoperative complications during the cataract extraction procedure. Transparency in the reporting of adverse events is fundamental to assuring the accuracy of the reported outcomes and for reducing the likelihood of underestimating harms. Finally, none of the included studies reported appropriate methods for considering within-patient correlations when using paired-eye designs (11 studies [22%]) or bilateral eye data (1 study [2%]), which may have resulted in biased estimates of effects.

The potential for bias was another methodological concern (Figure). Fewer than 8 studies (20%) were judged as having a low risk of bias in domains regarding selection bias, outcome reporting, and performance bias. Moreover, almost two-thirds of RCTs were considered to have a high risk of bias with respect to “masking of participants and personnel” and “masking of outcome assessment.” Given that the masking of study participants and outcome assessors is highly achievable within an IOL intervention trial, we propose that it should be a study design consideration in future studies.

Finally, despite that the findings from these RCTs have probable commercial implications, the funding sources were not reported in 36 publications (71%) and 17 (33%) did not include an author “declaration of interest” statement. The presence of such omissions is surprising given that including this information is a requirement of the Consolidated Standards of Reporting Trials statement,[24] which provides explicit guidelines for RCT reporting. The importance of transparency in reporting author conflicts of interest in medical research is well established, with recent attention specifically given to the potential influence of financial incentives and commercial contributions on the outcomes of ophthalmic research.[25]

Conclusions

To rigorously assess whether blue light-filtering IOLs have an association with macular health and/or visual function, including photoreception, would require sufficiently powered, robust long-term trials. Studies conducted over several years, potentially targeting populations at a high risk of late-stage AMD (eg, individuals with large-sized drusen and/or AMD pigmentary abnormalities[26]) would be necessary to detect any potential long-term protection from light-related retinal damage. Given that these devices currently hold marketing authorization for their intended use (as IOLs) in various regulatory jurisdictions, there is arguably minimal commercial incentive for what would be lengthy, and therefore costly, clinical trials. Thus, on a pragmatic level there seems little prospect that 1, or more, well-designed adequately-powered RCTs will be performed to assess the blue light–blocking effects of these devices on retinal health. An alternative approach could involve a registry-based study[27,28] with the caveat of the potential limitations of such designs compared with traditional RCTs, such as a less standardized outcome assessment.

Based on the current, best available clinical evidence, the effects of blue light-filtering IOLs on retinal health and function remain unclear. In the absence of future trials that consider the design limitations noted in previous research (eg, power calculations, standardized outcome measures, masking, and appropriate statistical methods), these IOLs will likely continue to be used as approved medical devices, but with any potential blue light–blocking benefits unresolved.

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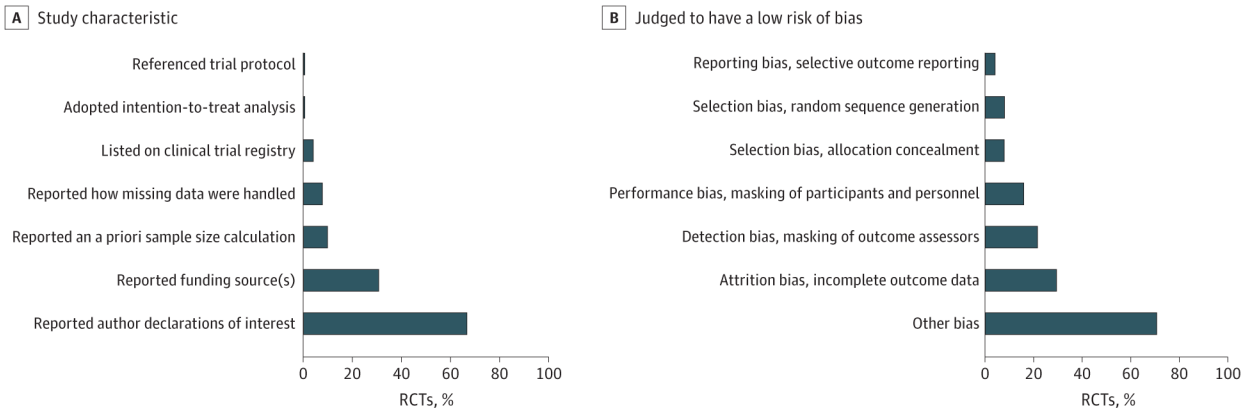

Figure. Features of the Included Randomized Controlled Trials (RCTs)