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The Effect of Cataract Surgery on Circadian Photoentrainment

A Randomized Trial of Blue-Blocking versus Neutral Intraocular Lenses

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Purpose: Cataract decreases blue light transmission. Because of the selective blue light sensitivity of the retinal ganglion cells governing circadian photoentrainment, cataract may interfere with normal sleep–wake regulation and cause sleep disturbances. The purpose was to investigate the effect of cataract surgery on circadian photoentrainment and to determine any difference between blue-blocking and neutral intraocular lenses (IOLs).

Design: The study was a single-center, investigator-driven, double-masked, block-randomized clinical trial.

Participants: One eye in 76 patients with bilateral age-related cataract eligible for cataract surgery was included.

Methods: Intervention was cataract surgery by phacoemulsification. Patients were randomized to receive a blue-blocking or neutral IOL.

Main Outcome Measures: Primary outcome was activation of intrinsic photosensitive ganglion cells using post-illumination pupil response (PIPR) to blue light from 10 to 30 seconds after light exposure as a surrogate measure. Secondary outcomes were circadian rhythm analysis using actigraphy and 24-hour salivary melatonin measurements. Finally, objective and subjective sleep quality were determined by actigraphy and the Pittsburgh Sleep Quality Index.

Results: The blue light PIPR increased 2 days (17%) and 3 weeks (24%) after surgery ($P < 0.001$). The majority of circadian and sleep-specific actigraphy parameters did not change after surgery. A forward shift of the circadian rhythm by 22 minutes ($P = 0.004$) for actigraphy and a tendency toward an earlier melatonin onset ($P = 0.095$) were found. Peak salivary melatonin concentration increased after surgery ($P = 0.037$). No difference was detected between blue-blocking and neutral IOLs, whereas low preoperative blue light transmission was inversely associated with an increase in PIPR ($P = 0.021$) and sleep efficiency ($P = 0.048$).

Conclusions: Cataract surgery increases photoreception by the photosensitive retinal ganglion cells. Because of inconsistency between the significant findings and the many parameters that were unchanged, we can conclude that cataract surgery does not adversely affect the circadian rhythm or sleep. Longer follow-up time and fellow eye surgery may reveal the significance of the subtle changes observed. We found no difference between blue-blocking and neutral IOLs, and, because of the minor effect of surgery in itself, an effect of IOL type seems highly unlikely. *Ophthalmology 2015;122:2115-2124 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Sleep is essential for maintaining health. Conversely, sleep disruption and disorders are associated with comorbidities, use of medication, and personal burden,[1,2] and the consequent daytime sleepiness increases the risk of falling and traffic accidents.[3–5] Sleep regulation is maintained by a homeostatic process maintaining sleep wakefulness equilibrium and by the circadian rhythm, generated in the suprachiasmatic nucleus (SCN). The circadian rhythm relies on daily external cues to entrain to the solar 24-hour day, the principal cue being daylight.[6]

Photoentrainment of the circadian rhythm is in the mammalian retina governed by intrinsically photosensitive ganglion cells via axonal projections to the SCN.[7] These cells express melanopsin that absorbs blue light with a peak absorption of approximately 460 to 480 nm[8–10]; therefore, blue light is important to circadian entrainment.[11] In addition, the photosensitive ganglion cells form the afferent part of the pupil light response.[12] Because of the characteristics of the intrinsic response and the absorption spectrum of melanopsin, the intrinsic (melanopsin)

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contribution to the pupil response can be estimated as the post-illumination pupil response (PIPR) to blue light.[9]

Cataract is an opacification of the lens of the eye characterized by light scattering and absorption, predominantly of blue light. Thus, cataract may be associated with a decreased potential for circadian photoentrainment.[13] This assumption is supported by previous nonrandomized, questionnaire-based studies that found a beneficial effect of cataract surgery on sleep quality.[14,15]

During the past decade, blue light–blocking intraocular lenses (IOLs) mimicking the natural coloring of the human crystalline lens have been introduced. It is believed that this may protect the retina from phototoxic blue light, possibly contributing to the development of age-related macular degeneration.[16] Although the visual function is comparable to neutral IOLs,[17] the increased absorption of blue light, vital to circadian photoentrainment, has led to concern that the blue-blocking IOLs may interfere with the circadian rhythm.[18]

The aim of this study was to evaluate the effect of cataract surgery on circadian photoentrainment and sleep. Second, the effect of the blue light transmission characteristics of the implanted IOL was tested in a randomized study. Objective measures for intrinsic photosensitive retinal ganglion cell activation were estimated using pupillometry. Effects on the circadian rhythm were evaluated by actigraphy and salivary melatonin concentration measurements. Sleep quality was determined using sleep quality–specific actigraphy parameters and by validated questionnaires.

Methods

Design

The study was a double-masked, block-randomized clinical trial designed to investigate the effect of cataract and the effect of blue-blocking versus neutral IOLs on circadian photoentrainment.

Participants

Participants were recruited from among patients who were referred for cataract surgery to the Department of Ophthalmology, Rigshospitalet–Glostrup, Denmark. Inclusion criteria were all patients who were referred for bilateral senile cataract eligible for cataract surgery and informed written consent. Only the first eye was included in the study, that is, the eye with the lowest visual acuity according to the department's guidelines. Exclusion criteria were any ophthalmological disease with an expected effect on the retina, optic disc, or cornea, including advanced age-related macular degeneration, glaucoma, diabetic retinopathy, corneal dystrophy, ocular trauma, and recurrent uveitis. Furthermore, patients with severe systemic disease, including diabetes, cancer of any kind, and known sleep disturbances, were excluded. Preoperative and postoperative complications with an impact on visual acuity, including ruptured capsule, nucleus drop, and postoperative corneal edema, led to exclusion. Informed written consent was obtained, and the study was approved by the Committee on Health Research Ethics, the Capital Region of Denmark (H-4-2011-121), registered at clinicaltrials.gov (NCT01686308), and was conducted in accordance with the Declaration of Helsinki.

Randomization and Masking

Randomization was performed on the day of the surgery using automated, computerized block-randomization lists with a 1:1 allocation ratio and a block size of 9. The participants were masked to IOL type. Because of the different colors of the blue-blocking and neutral IOLs, it was not possible to keep the investigator masked to IOL type. Instead, statistical analyses were performed after a complete re-masking of the data post hoc. Masking was not broken before all statistical analyses had been performed.

Intervention

Intervention was standard minimal incision phacoemulsification with topical anesthesia without retrobulbar anesthesia. A posterior chamber IOL was placed "in the bag." The implanted IOL was a neutral ultraviolet-only blocking IOL (AMO ZCB00; Abbott Medical Optics, Santa Ana, CA) transmitting approximately 95% at 480 nm[19] or a blue-blocking IOL (Acrysof SN60WF; Alcon, Fort Worth, TX) transmitting approximately 80% at 480 nm.[20,21] The chosen yellow IOL is popular worldwide, and although more absorbent IOLs exist, it has a transmission spectrum representative of the most common blue-blocking IOLs.[22] The fellow eye was operated after the visit at 3 weeks postoperatively. All surgeries were performed around spring and fall equinoxes by 2 highly experienced surgeons (B.H. and Gøril Boberg-Ans).

Ophthalmological Examinations

Snellen best-corrected distance visual acuity with subsequent logarithm of the minimum angle of resolution (logMAR) conversion and refraction followed by slit-lamp biomicroscopy, fundoscopy, and Goldmann applanation tonometry were performed at all visits. The retina was scanned with spectral domain optical coherence tomography (Heidelberg SD-OCT; Heidelberg Engineering, Heidelberg, Germany), and infrared fundus photographs were taken at baseline and after 3 weeks. All subjects were examined by the same physician (A.E.B.).

Circadian Type

Circadian type was determined before surgery using the Danish version of the Morningness-Eveningness Questionnaire, and the sum score was evaluated. Higher values represent morning circadian type, and lower values represent evening type.[23]

Blue Light Transmission and Cataract Grading

The degree and type of cataract were determined before surgery using the Age-Related Eye Disease Study (AREDS) 2008 clinical lens grading protocol.[24] Blue light lens transmission was measured objectively with a lens autofluorescence–based method estimating the lens transmission at 480 nm.[25]

Main Outcome Measures

Intrinsic Photosensitive Retinal Ganglion Cell Activation by Blue Light

Photosensitive retinal ganglion cell activation by blue light was estimated using the PIPR as a surrogate measure.[9,26] Pupil responses to red light were recorded as a control of classic photoreceptor-driven pupil response.[27] Participants were examined with pupillometry 1 to 4 weeks before surgery and 2 days and 3 weeks after surgery.