Effects of Cataract Surgery on Melatonin Secretion in Adults 60 Years and Older
A Randomized Clinical Trial

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IMPORTANCE Cataract surgery, which increases perception of light, may increase melatonin secretion. Melatonin secretion has been associated with depression, diabetes, cognitive impairment, and breast cancer. To date, no evidence from a randomized clinical trial exists to support this cataract surgery hypothesis.

OBJECTIVE To determine whether cataract surgery modifies the melatonin secretion at 3 months after cataract surgery in 169 adult patients.

DESIGN, SETTING, AND PARTICIPANTS A parallel-group randomized clinical trial was conducted at a single referral center from July 1, 2014, to June 30, 2017. Data were analyzed from January 1, 2018, to March 31, 2019. Patients were aged 60 years or older, had no history of cataract surgery, and had cataracts with grade 2 or higher nuclear opacifications based on the Lens Opacities Classification System III. Analyses were based on intention to treat.

INTERVENTIONS Patients were randomized 1:1:1:1 to receive cataract surgery using artificial clear intraocular lens (IOL) or yellow IOL. Group 1 received prompt surgery with clear IOL, group 2, prompt surgery with yellow IOL, group 3, delayed surgery with clear IOL, and group 4, delayed surgery with yellow IOL. The intervention group consisted of groups 1 and 2, and the control group consisted of groups 3 and 4.

MAIN OUTCOMES AND MEASURES Urinary melatonin excretion in the intervention group was measured at 3 months after surgery, and urinary melatonin excretion in the control group was measured before delayed surgery.

RESULTS Of the 169 randomized patients, 97 were men (57.4%). The mean (SD) age was 75.7 (6.7) years. Mean urinary melatonin excretion was calculated as standardized urinary concentration, the ratio of urinary concentration to urinary creatinine concentration (nanograms per milligram of creatinine), in the intervention group after cataract surgery. Mean urinary melatonin excretion was significantly higher than in the control group (adjusted mean difference of creatinine concentration, 0.159 log ng/mg, 95% CI, 0.045-0.273; \( P = .007 \)) independent of baseline urinary melatonin excretion and potential confounders. Subgroup analysis comparing group 1 with group 3 revealed that concentration of urinary melatonin excretion in patients who received clear IOLs was higher than the control group by creatinine concentration 0.212 log ng/mg (95% CI of the difference, 0.058-0.365; \( P = .008 \)). However, the difference between patients in group 2 and group 4 was not significant (adjusted mean difference for creatinine excretion, 0.083 log ng/mg, 95% CI, –0.087 to 0.253; \( P = .33 \)). The difference of concentration of mean urinary melatonin excretion between patients in group 1 and those in group 2 was not significant (95% CI of the difference for creatinine concentration, –0.19 to 0.40 log ng/mg; \( P = .48 \)).

CONCLUSIONS AND RELEVANCE The findings in this study support the hypothesis that cataract surgery increases melatonin secretion. The effect of clear IOLs vs yellow IOLs on these outcomes was not shown to be different.

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Melatonin secretion is an important indicator of the human circadian biological rhythm. Circadian biological rhythm misaligned with the external environment is associated with various diseases; epidemiologic studies have reported that night-shift workers are at high risk for depression, insomnia, diabetes, obesity, metabolic syndromes, and cardiovascular diseases. Moreover, low concentration of melatonin secretion has been associated with depression, diabetes, cognitive impairment, and breast cancer. Nonvisual light perception by the human photosensitive retinal ganglion cell plays a substantial role in synchronizing the central clock at the suprachiasmatic nuclei with the external environment. Modifying the circadian rhythm by light exposure was presented in a 2003 study by the phase response curve. The light exposure in the morning advances the phase of melatonin secretion, while evening and night light exposure before light exposure in the morning advances the phase of melatonin secretion.13

Cataract is the most common cause of vision loss worldwide. One-third of visual impairments and approximately half of vision losses worldwide are caused by cataracts. In addition to the decreased visual perception, patients with cataracts may experience decreased transmission of nonvisual light as they age. Cataract surgery involving replacing the opacified lens with an artificial intraocular lens (IOL) is hypothesized to increase the nonvisual light perception and improve the circadian alignment, which also increased the concentrations of melatonin secretion. Although some previous studies have compared melatonin secretion before and after cataract surgery, to our knowledge, no evidence on this topic from randomized clinical trials (RCTs) has been presented.

We performed a parallel-group, assessor-blinded RCT comparing the intervention group at 3 months after surgery with the control group to determine whether cataract surgery modified melatonin secretion.

Methods

Study Design

All cataract surgeries were performed at Nara Medical University Hospital, Nara, Japan. The study protocol was published and registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000014559). The Nara Medical University Ethics Committee approved this study, and written informed consent was obtained from all patients. The present study adhered to the tenets of the Declaration of Helsinki. The trial protocol and statistical analysis plan are available in Supplement 1.

After the baseline measurements were performed, we randomized the participants into 4 groups at a 1:1:1:1 ratio: group 1 received prompt surgery with a clear IOL; group 2, prompt surgery with a yellow IOL; group 3, delayed surgery with a clear IOL; and group 4, delayed surgery with a yellow IOL. Groups 1 and 2 belonged to the intervention group, and groups 3 and 4 to the control group. We assessed the outcomes in the intervention group at 3 months postoperatively. The outcomes in the control group were measured before delayed surgery.

Key Points

**Question** Does cataract surgery affect melatonin secretion in patients aged 60 years and older undergoing their first cataract surgery?

**Findings** In this randomized clinical trial, 169 patients with cataracts were randomized to receive prompt cataract surgery with a clear or yellow artificial intraocular lens or delayed surgery with a clear or yellow intraocular lens. Urinary melatonin excretion values were significantly higher in the cataract surgery group at 3 months after the operation than the control group.

**Meaning** The results of this study suggest that increased light perception by cataract surgery may align the internal biological rhythm with the external environment accompanied by increased melatonin secretion.

**Participants**

The eligibility criteria were as follows: age 60 years or older, no history of cataract surgery, and cataract with grade 2 or higher nuclear opacifications based on the Lens Opacities Classification System III. Conversely, the exclusion criteria were major depression with current medication, severe mental illness or dementia, severe corneal opacities with assessment difficulty in the lens opacity or fundal examination, glaucoma with visual field defect of the least mean deviation of less than −14 dB (Humphrey perimeter; Humphrey Field Analyzer [Carl Zeiss Medical Inc]), vitreous hemorrhage, proliferative diabetic retinopathy, macular edema, age-related macular degeneration, need for immediate cataract surgery, and need for a combined cataract and glaucoma surgery or cataract surgery and vitrectomy. Patients undergoing surgery in one or both eyes were included.

**Intervention**

We used a yellow aspherical IOL (SN60WF; Alcon), a yellow spherical IOL (SN60AT; Alcon), and a clear spherical IOL (SA60AT; Alcon) in a 1:1:2 ratio for cataract surgery. We estimated the appropriate IOL power using the SRK/T formula for each IOL and implanted the selected IOL after phacoemulsification with a small incision.

**Measurements**

Based on the concentration of 6-sulfatoxymelatonin in a spot urine sample in the morning, we assessed the level of urinary melatonin excretion as an indicator of the melatonin secretion. The values for peak concentration of plasma melatonin in the night significantly correlated with the urinary melatonin excretion as determined by the subsequent morning spot urine sample (Spearman rank correlation, r = 0.69). We assessed the urinary concentration of 6-sulfatoxymelatonin at a commercial laboratory (SRL Co Inc) with an enzyme-linked immunosorbent assay kit (RE54031; IBL International) and calculated the standardized urinary concentration as the ratio of urinary concentration to urinary creatinine concentration (nanograms per milligram of creatinine).

We investigated participants’ age, sex, smoking and drinking habits, and the prevalence of hypertension and diabetes.
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Original Investigation Research

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Randomization

A researcher independent of patient enrollment (one of us, K.S) played a role as an allocation center and conducted simple randomization using a computer-generated random sequence. After receiving informed patient consent and patient registration, the physician who enrolled the patient received the intervention assignment via research staff from the allocation center and determined the date of cataract surgery. We masked the intervention assignment from the assessors of the outcomes.

Results

We assessed the eligibility of all patients newly diagnosed with cataracts (n = 2309) at the Nara Medical University Hospital from July 1, 2014, to June 30, 2017. Data were analyzed from January 1, 2018, to March 31, 2019. Among the 1499 patients who met the inclusion criteria, 512 required immediate cataract surgery for their cataracts (34.2%), 101 had glaucoma (6.7%), 97 required combined cataract and glaucoma surgery or cataract surgery and vitrectomy (6.5%), 87 had major depression with current smoking, BMI, hypertension, and diabetes, the cataract surgery group showed a higher increase in levels of creatinine concentration in urinary melatonin excretion of 0.159 log ng/mg, 0.047 to 0.272 (P = .006) in the cataract surgery group. After further adjusting for potential confounders such as age, sex, daily drinking, current smoking, BMI, hypertension, and diabetes, the cataract surgery group showed a higher increase in levels of creatinine concentration in urinary melatonin excretion of 0.159 log ng/mg (95% CI, 0.045 to 0.273; P = .007) (Table 2). After further adjustment for day length at the baseline measurement and the follow-up measurement in levels of urinary melatonin excretion, adjusted mean difference of urinary melatonin excretion between the cataract surgery group and the control group remained essentially unchanged (mean difference for creatinine values, 0.159 log ng/mg, 95% CI, 0.045 to 0.272; P = .006).

In a subgroup analysis comparing groups 1 and 3 (n = 83), the cataract surgery group using the clear IOL was associated with a significantly higher increase in urinary melatonin excretion standardized based on the urinary creatinine levels in the cataract surgery group (median [IQR] 6.8 ng/mL [4.0-32.5]) than those who completed follow-up assessment (median [IQR] 14.6 ng/mL [6.7-25.9]), but the difference was not significant (P = .36). The median (IQR) duration from random allocation to the follow-up assessment were 77 days (63-87) in the control group and 176 days (161-189) in the cataract surgery group. No severe adverse events such as endophthalmitis, corneal edema, or IOL malposition occurred after cataract surgery. We did not find any relevant difference in terms of basic characteristics, visual acuity, and intraocular pressure (Table 1).

At 3 months after cataract surgery, urinary melatonin excretion concentration before and after cataract surgery using yellow IOLs. Statistical tests were conducted using SPSS, version 24 (IBM SPSS).

Statistical Analysis

We conducted intention-to-treat analysis. We presented the data as means and SDs for continuous variables with normal distribution and medians and interquartile ranges (IQRs) for variables with skewed distribution. We compared medians of urinary melatonin excretion concentration before and after intervention using Wilcoxon signed rank test. To normalize the distribution, the concentration of urinary melatonin excretion was naturally log-transformed. To estimate the effects of intervention after adjusting for the baseline value, we created a multivariable mixed-effects linear regression model with a random intercept on the participants’ urinary melatonin excretion value at baseline. The model included urinary concentrations of melatonin excretion at baseline and follow-up as the dependent variable and cataract surgery and other covariates as the independent variables. In subgroup analysis, to estimate the effects of cataract surgery using clear IOLs on concentrations of urinary melatonin excretion, we compared group 1 with group 3. Separately, we compared group 2 with group 4 to estimate the effect of cataract surgery using yellow IOLs. Statistical tests with 2-sided P < .05 were considered to be significant. All analysis was conducted using SPSS, version 24 (IBM SPSS).

Using a standardized questionnaire. After weight and height measurements, we calculated the body mass index (BMI). Trained orthoptists measured best-corrected visual acuities, and logMAR values were used for analysis. Intraocular pressure was measured with noncontact tonometry.

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In a subgroup analysis comparing groups 1 and 3 (n = 83), the cataract surgery group using the clear IOL was associated with a significantly higher increase in urinary melatonin ex-
cretion by 0.212 log ng/mg creatinine (95% CI, 0.058 to 0.365; \( P = .008 \)) than the control group after adjusting the baseline value and predefined confounders. Among groups 2 and 4 (n = 86), the increase in concentration of urinary melatonin excretion among the cataract surgery using the yellow IOL was not statistically significantly higher creatinine concentration (0.083 log ng/mg greater in the yellow IOL vs the control group; 95% CI, −0.087 to 0.253; \( P = .33 \)) (Table 3). We also did not identify a statistically significant difference in urinary melatonin excretion concentrations between the cataract surgery group using the clear IOL and those using the yellow IOL group (mean log-urinary melatonin excretion 3.34 vs 3.24 log ng/mg creatinine; difference in creatinine concentration, 0.10 log ng/mg; 95% CI of the difference, −0.19 to 0.40; \( P = .48 \)).

Baseline urinary melatonin excretion in the cataract surgery group (median [IQR]: 23.2 [17.0–35.6] ng/mL creatinine) appeared to be higher than that in the control group (median [IQR] 17.7 [12.3–27.7] ng/mL creatinine). In the cataract surgery group, as compared with the baseline (23.2 ng/mL), median urinary melatonin excretion at 3 months after cataract surgery was higher by 2.71 ng/mL creatinine (\( P = .02 \)). In the control group, we did not find a significant difference between median urinary melatonin excretion at baseline and 3 months of follow-up (difference, 1.53 ng/mL creatinine; \( P = .74 \)).

Discussion

This RCT compared melatonin secretion between cataract surgery and control groups. Melatonin secretion was significantly higher in patients who underwent cataract surgery as compared with those in the control group at 3 months after surgery, independent of baseline melatonin secretion and potential confounding factors such as age, sex, daily drinking, current smoking, BMI, hypertension, and diabetes.

The results of the present RCT were consistent with those of previous studies comparing melatonin levels before and after cataract surgery. Brøndsted et al\(^7\) evaluated salivary melatonin concentrations before and after cataract surgery in an RCT, in which 65 patients were randomized to the cataract
surgery group using blue-blocking IOLs (n = 34) and to the cataract surgery group using clear IOLs (n = 31). The peak concentration of salivary melatonin measured at 3 weeks postoperatively was significantly higher than the preoperative concentration (11.51 vs 9.37 pg/mL; P < .05) (to convert to picomoles per liter, multiply by 4.305). Shenshen et al26 measured salivary melatonin levels in 30 patients who received clear IOLs. They found significantly higher melatonin concentrations postoperatively than preoperatively (5.51 vs 3.79 pg/mL; P < .001).

Previous studies that investigated the association between higher daylight exposure and higher nocturnal melatonin secretion concentrations explained that higher melatonin secretion values in the cataract surgery group occurred because of increased nonvisual light perception in the daytime. Cataract surgery involving replacing clouded lenses with IOLs increased the light perception in the daytime. Mishima et al25 found significantly higher concentrations of melatonin secretion in 10 patients aged 66 to 82 years with insomnia after bright-light intervention with 2500 lux every 4 hours for 4 weeks compared with the baseline secretion concentration before the intervention (23.9 vs 13.91 pg/mL/h; P < .05). In addition, a population-based observational study showed that higher daylight exposure was cross-sectionally associated with higher level of melatonin secretion.26

The results of subgroup analysis in the present study might be explained by the characteristics of sensitivity to nonvisual light perception by spectrum. As compared with the control group, we found an increase in concentrations of urinary melatonin excretion among the surgery group who received clear IOLs but not so among the surgery group who received yellow IOLs. This inconsistent outcome might be explained by wavelength-specific sensitivity to nonvisual light information. It is known that the sensitivity of nonvisual light perception peaks in the blue portion of the spectrum.27 The effects of cataract surgery using blue-blocking IOLs might therefore be weaker than that of cataract surgery using clear IOLs on levels of melatonin secretion because of reduced nonvisual light perception. The findings from the subgroup analysis in the present RCT by IOL color comparing melatonin secretion concentration between the cataract surgery group and the control group were consistent with results from a previous RCT comparing melatonin secretion between patients who received clear IOLs and those receiving blue-blocking IOL implantation.28 However, we did not find any significant difference in melatonin secretion levels between patients receiving clear IOL implantation and those receiving yellow IOL implantation. Thus, further research is required to better compare the effects of clear and yellow IOLs. Further, although we report a beneficial effect of cataract surgery in the short-term, more investigation into the association between the risk of age-related macular degeneration between cataract surgery performed with blue-blocking IOLs and clear IOLs is warranted. Blue-blocking IOLs have been suggested to mitigate age-related macular degeneration by protecting against retinal phototoxic adverse effects triggered by short-wavelength light,29 but to date there is inadequate evidence from RCTs about the effects of blue-blocking IOLs on longer-term macular health.31

Some observational studies32-33 have suggested the clinical importance of higher melatonin secretion. Higher melatonin secretion was associated with higher muscle strength32 and decreased atherosclerosis.33 The antioxidative and anti-inflammatory functions of melatonin might explain the mechanisms.34,35 Elsewhere, lower concentrations of melatonin excretion in increments of 1.0-unit log-urinary melatonin in morning spot urine was associated with a 48% higher risk of diabetes31 and a 40% higher risk of myocardial infarction36 in the Nurses’ Health Study. The increase of levels of urinary melatonin excretion by 0.159 log ng/mg creatinine in the present study (Table 2) corresponded with finding of 7.6% decreased risk for diabetes and 6.4% decreased risk for myocardial infarction.

Strengths and Limitations

The strengths of the present study are its study design that compared 2 randomized groups and its larger sample size as compared with previous non-RCTs. We tried to account for the effects of known and unknown confounding factors by random allocation and by controlling for differences in selected relevant characteristics of patients assigned to each group.

This study had several limitations. First, the sample size was small, and random allocation of the small sample size could

### Table 2. Difference in the Increase of Melatonin Secretion Between Cataract Surgery and Control Groups During 3 Months Adjusted for Baseline Value

<table>
<thead>
<tr>
<th>Cataract Surgery Group</th>
<th>Difference of Urinary Melatonin Excretion (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariable model a</td>
<td>0.162 (0.047 to 0.277)</td>
<td>.006</td>
</tr>
<tr>
<td>Further adjusted effect for age, sex</td>
<td>0.160 (0.046 to 0.274)</td>
<td>.006</td>
</tr>
<tr>
<td>Fully adjusted model c</td>
<td>0.159 (0.045 to 0.273)</td>
<td>.007</td>
</tr>
</tbody>
</table>

a Log-transformed 6-sulfatoxymelatonin concentration standardized for creatinine was included in the regression model.

b Adjusted for baseline value of urinary melatonin excretion using a mixed-effects model with random intercept.

c Adjusted for baseline value of urinary melatonin and age, sex, drinking and smoking habit, body mass index, hypertension, and diabetes.

### Table 3. Subgroup Analysis by the Color of IOLs About the Difference in Increase of Melatonin Secretion Between Cataract Surgery and Control Groups During 3 Months Adjusted for Baseline Value

<table>
<thead>
<tr>
<th>Cataract Surgery Group</th>
<th>Difference of Urinary Melatonin Excretion (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear IOL group, n = 83 (groups 1 and 3) univariate model a</td>
<td>0.216 (0.062 to 0.370)</td>
<td>.007</td>
</tr>
<tr>
<td>Fully adjusted model b</td>
<td>0.212 (0.058 to 0.365)</td>
<td>.008</td>
</tr>
<tr>
<td>Yellow IOL group, n = 86 (groups 2 and 4) univariate model a</td>
<td>0.096 (−0.075 to 0.270)</td>
<td>.26</td>
</tr>
<tr>
<td>Fully adjusted model c</td>
<td>0.083 (−0.087 to 0.253)</td>
<td>.33</td>
</tr>
</tbody>
</table>

Abbreviation: IOL, intraocular lens.
a Log-transformed 6-sulfatoxymelatonin concentration standardized for creatinine was included in the regression model.
b Adjusted for baseline value of urinary melatonin excretion using a mixed-effects model with random intercept.
c Adjusted for baseline value of urinary melatonin and age, sex, drinking and smoking habit, body mass index, hypertension, and diabetes.
not completely remove the effects of confounding factors. Also, some baseline characteristics appeared imbalanced among groups despite randomization. We adjusted the measured potential confounding factors using a statistical model; however, residual confounding effects of unmeasured factors such as light exposure might have remained. Increased light transmission induced by cataract surgery would increase nonvisual light perception at night that suppressed melatonin secretion and might cause circadian misalignment. Second, selection bias might occur from the low proportion of participants who met the eligibility criteria. Therefore, the external validity of these findings might be reduced. Third, we failed to follow up on outcome at 3 months postoperatively among 11 participants (8 in the cataract surgery group, and 3 in the control group). These individuals presented lower urinary melatonin excretion measurements at baseline than others. Fourth, there was a longer period of time between random allocation and follow-up measurement of urinary melatonin excretion in the cataract surgery group than in the control group. Owing to the difference of observational duration, the results may have been influenced by the seasonal change in concentrations of melatonin secretion. The adjustment for day length at the measurement of urinary melatonin excretion did not change the effect of cataract surgery on urinary the concentrations of melatonin excretion. Additionally, outcomes were measured at a short while after the surgery, so the long-term sustained effects remain unknown, and only a minority of patients screened ended up in the RCT. However, conducting a RCT comparing the longer-term effects of cataract surgery with a control group is not readily feasible recognizing the established benefits of cataract surgery on visual acuity.

**Conclusions**

The findings of the present study appear to support the hypothesis that cataract surgery increases melatonin secretion at 3 months postoperatively. The evidence from this study, though, does not support the hypothesis that yellow IOLs affect levels of melatonin secretion differently than clear IOLs.


