Visual Field Defects After Intravitreous Administration of Indocyanine Green in Macular Hole Surgery

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Objectives: To report the findings on a patient cohort with visual field defects after macular hole surgery with indocyanine green (ICG)-assisted internal limiting membrane peeling and to investigate the correlation between the defects and the use of ICG.

Design: Retrospective, noncomparative interventional case series.

Participants: Thirty-nine eyes of 38 patients having the clinical diagnosis of a macular hole who underwent pars plana vitrectomy between January 1, 2001, and December 31, 2002, were enrolled in this study.

Intervention: Indocyanine green–assisted internal limiting membrane peeling was performed on a series of 22 eyes: 12 eyes using a 0.5% ICG solution and 3-minute exposure to the retina (group 1), 4 eyes using a 0.5% ICG solution and immediate washout (group 2), and 6 eyes using a 0.25% ICG solution and immediate washout (group 3). The remaining 17 eyes underwent vitrectomy without ICG-assisted internal limiting membrane peeling (group 4).

Main Outcome Measures: Visual field, best-corrected visual acuity, and fundus photography were evaluated.

Results: Postoperatively, all patients (100%) in group 1 and 1 (25%) of 4 eyes in group 2 had visual field defects. None of the patients in group 3 had a visual field defect. The visual field defects included 10 eyes (84%) with nasal defects, 1 eye (8%) with an inferotemporal defect, and 1 eye (8%) with an extensive visual field defect. Ophthalmoscopically, mild to moderate optic disc pallor was observed in 8 (62%) of 13 eyes with postoperative visual field defects. Only 1 patient in group 4 had an inferotemporal defect; none of the other patients in group 4 had visual field defects. There was no statistically significant difference in postoperative visual acuity between patients with and without postoperative visual field defects.

Conclusions: Although this study was limited by the few patients enrolled, our experience indicates that visual field defects, specifically nasal defects, can occur after macular hole surgery with ICG-assisted internal limiting membrane peeling, and that the incidence depends on the concentration of the ICG solution and/or the exposure time to the retina. Further studies are needed to clarify the pathomechanism of visual field defects.

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Although indocyanine green (ICG) is a helpful tool in peeling the internal limiting membrane (ILM) in macular surgery, the potential toxic effect of ICG has been recently reported. Previous reports have shown the possible toxic effect of ICG on cultured human retinal pigment epithelial cells. In experimental studies, morphologic and functional damage to the retina was observed using an animal model or human donor eyes. Furthermore, several authors have reported retinal pigment epithelial changes after macular surgery using ICG to facilitate peeling of the ILM. More recently, visual field defects following vitrectomy for macular hole or pucker with ICG-assisted ILM peeling have been observed. We also reported on the development of postoperative visual field defects in 4 patients who underwent vitrectomy for epiretinal membranes using ICG-assisted ILM peeling. Although the application of ICG is thought to be a possible cause of the defects in these reports, the association between the use of ICG and postoperative visual field defects is not fully understood. The dual purpose of this article is to describe patients with visual field defects after macular hole surgery using ICG-assisted ILM peeling and to investigate the relationship between the use of ICG and the occurrence of the defect.
METHODS

This study was an interventional case series in which we performed a noncomparative retrospective review of a consecutive series of patients who had undergone macular hole surgery with or without ICG-assisted ILM peeling. We retrospectively reviewed the medical records of 44 consecutive patients (45 eyes) who had undergone vitrectomy for idiopathic macular holes between January 1, 2001, and December 31, 2002, at Kagoshima City Hospital, Kagoshima, Japan. Six patients were excluded for the following reasons: a history of glaucoma (2 patients), failure to close the macular hole with a single surgical procedure (1 patient), a history of retinitis pigmentosa (1 patient), postoperative dense vitreous hemorrhage (1 patient), or less than 6 months' postsurgical follow-up (1 patient). Therefore, a total of 39 eyes of 38 patients (10 males and 28 females; mean age, 63.5 years) were included in this study. The stage of macular holes included 16 in stage 2 (partial-thickness holes), 14 in stage 3 (full-thickness holes), and 9 in stage 4 (advanced full-thickness holes with vitreous separation from the optic disc and macula). None of these patients had a postoperative retinal detachment. There was no recorded incidence of increased intraocular pressure above 30 mm Hg; there were no sustained increases in intraocular pressure. This study was carried out at a site that has no institutional review board.

Surgery was performed by a single surgeon (A.U.). Informed consent was obtained prior to surgical intervention in all patients. A standard 3-port pars plana vitrectomy was performed in all patients using retrobulbar anesthesia. The infusion cannula was placed in the inferotemporal quadrant. The crystalline lens was removed by phacoemulsification followed by intraocular lens implantation before pars plana vitrectomy. The crystalline lens was removed by phacoemulsification followed by intraocular lens implantation before pars plana vitrectomy. The crystalline lens was removed by phacoemulsification followed by intraocular lens implantation before pars plana vitrectomy. The crystalline lens was removed by phacoemulsification followed by intraocular lens implantation before pars plana vitrectomy. The crystalline lens was removed by phacoemulsification followed by intraocular lens implantation before pars plana vitrectomy.

The ICG solution was prepared as follows: 25 mg of ICG dye was reconstituted with 1.0 mL of sterile water. After the ICG was completely dissolved in the sterile water, 4.0 or 9.0 mL of balanced salt solution was added to attain a final ICG concentration of 0.5% or 0.25%. A total of 0.1 to 0.8 mL of ICG solution was then injected into the fluid-filled eye using a 27-gauge blunt needle. After removal of the ICG dye, the green-stained ILM was cut with a microvitreoretinal blade. With Tano forceps, the ILM was lifted and peeled off in a circular fashion. As a result, the ILM was removed from a 2 to 3 disc diameter.

Twenty-two patients who had undergone ICG-assisted ILM peeling were divided into 3 groups according to the concentration of the ICG solution and the ICG staining time. In 12 patients (group 1), 0.6 to 0.8 mL of 0.5% ICG solution was injected into the vitreous cavity. The ICG dye was left in the vitreous cavity for 3 minutes with scleral plugs in place and then washed out. In 4 patients (group 2), less than 0.2 mL of 0.5% ICG solution was injected and removed immediately with active suction. In 6 patients (group 3), less than 0.2 mL of 0.25% ICG solution was used and it was aspirated immediately. A Humphrey static perimeter test was performed preoperatively in all patients. Humphrey static perimeter and Goldmann perimeter were performed between 3 and 6 months after surgery. Visual field, best-corrected visual acuity, and fundus photographs were evaluated. For statistical analysis, best-corrected visual acuity measured at the 1-year follow-up visit was considered. Standard postoperative examinations were performed at 1 week, 2 weeks, 1 month, 2 months, 3 months, and every 3 months thereafter. The mean follow-up period was 17.4 months (range, 12-31 months).

Visual acuity data were converted to the logarithm of the minimal angle of resolution (logMAR) and analyzed using Stat View version 4.3 (Abacus Concepts Inc, Berkeley, Calif). The t test was used to compare preoperative and postoperative visual acuities.

RESULTS

All patients (100%) in group 1 had visual field defects. The defects included 10 eyes (84%) with nasal defects, 1 (8%) with an inferotemporal defect, and 1 (8%) with an extensive visual field defect (Figure 1). In group 2, 1 patient (25%) had a nasal defect. In group 3, there were no postoperative visual field defects. Nasal or extensive defects were noted on both types of perimetry and the visual field changes were similar when present by both methods of testing. There was a statistically significant difference in the presence of postoperative visual field defects between groups 1 and 2 (P<.001) and between groups 1 and 3 (P<.001).

Ophthalmoscopy revealed optic disc pallor in 8 (62%) of 13 eyes with visual field defects (Figure 2). Fundus examination revealed no detectable changes corresponding to the visual field defects. Fluorescein angiography, which was performed in 3 patients with visual field defects, showed no abnormalities such as retinal vessel damage or alteration in the retinal pigment epithelium. Only 1 patient had an inferotemporal defect; all of the remaining eyes that underwent full macular hole surgery without ICG-assisted ILM peeling had no visual field defects postoperatively.

The mean preoperative visual acuity (Snellen equivalent) was 20/122 for group 1, 20/106 for group 2, and 20/100 for group 3. The mean postoperative visual acuity at 1-year follow-up was 20/36 for group 1, 20/30 for group 2, and 20/27 for group 3. Twenty-one of 22 eyes in which ICG was used had postoperative visual acuity of 20/40 or better (Table). Mean visual acuity was significantly improved after surgery in each group (P<.001). There was no significant difference in postoperative visual acuity between patients with and without visual field defects (Figure 3).

COMMENT

Our study showed that all patients in group 1 had visual field defects postoperatively. Most of the defects occurred in the nasal field. Only 1 patient in group 2 had a nasal visual field defect. None of the patients in group 3 had postoperative visual field defects. Additionally, visual field defects were noted in only 1 of 17 patients who underwent macular hole surgery without ICG-assisted ILM peeling. These data suggest that the occurrence of visual field defects is strongly related to the use of ICG and that the incidence depends on the concentration of
ICG solution or tissue contact time of ICG or both, as proposed by Gandorfer et al.\textsuperscript{12}

Visual field defects after vitrectomy for macular hole or pucker with the use of ICG have been reported. In 1 series by Haritoglou et al,\textsuperscript{9} seven of 20 patients who had undergone macular hole surgery using ICG-assisted ILM peeling had visual field defects postoperatively. They injected 0.2 to 0.5 mL of 0.05\% ICG solution to stain the ILM and then washed this out after about 1 minute. They also reported postoperative visual field defects in 7 of 20 patients who had undergone macular pucker surgery with the use of less than 0.5 mL of 0.05\% ICG solution.\textsuperscript{10} In our series, postoperative visual fields were normal in patients in whom less than 0.2 mL of a 0.25\% ICG solution was used with immediate washout. These data suggest that exposure time to the retina may be critical in the occurrence of visual field defects as well as the dose and concentrations of ICG.

Eleven of the 13 patients with visual field defects after ICG-assisted ILM peeling had nasal defects: one had an extensive defect and the other had an inferotemporal defect. Nasal visual field defects detected in our series are similar to those reported previously.\textsuperscript{9,10} Furthermore, 1 patient had a more severe type of visual field defect that was described in our previous article.\textsuperscript{11} However, the reason why the nasal field is predominantly affected remains unknown.

An inferotemporal visual field defect was detected in 1 of the group 1 patients. From the shape of the defect, we speculated that it was caused by a dehydration injury of the nerve fiber layer during fluid-air exchange,\textsuperscript{13-15} although we cannot eliminate the possibility that it was caused by the use of ICG. Given the fact that a similar defect was seen in a patient in whom ICG had not been used, it is reasonable to suggest that the temporal defect is not correlated with the use of ICG.

Fundus examination of 8 of 14 patients with postoperative visual field defects showed a suggestion of diffuse optic disc pallor at the final follow-up. This is the first description of optic disc pallor in patients in whom ICG has been used. We did not see optic disc pallor in our previous report of visual field defects following vitrectomy for epiretinal membrane.\textsuperscript{11} The degree of optic disc pallor was different in each eye: from slight pallor...
to complete optic disc atrophy. This finding was evident only in eyes with postoperative visual field defects; therefore, optic disc pallor appears to be strongly related to both visual field defects and the use of ICG. No other abnormalities, such as mottling of retinal pigment epithelium or retinochoroidal atrophy seen in patients with air infusion–related visual field defects, were observed in those eyes. Since fundus change may become apparent after years,16 however, long-term follow-up of these eyes is essential.

It is still controversial whether the use of ICG precludes good visual recovery. Da Mata et al17 reported good visual outcome after ICG-assisted ILM peeling. On the other hand, Kwok et al18 reported less favorable visual outcomes in a series of 10 patients. In our study, visual acuity improved postoperatively despite the use of ICG. Even in patients with visual field defects, most gained 2 Snellen lines or more postoperatively in contrast to the reports by Haritoglou and coworkers,9,10 who reported that there was no statistically significant improvement in postoperative visual acuity after ICG-assisted ILM peeling. Although our results showed that the use of ICG had no adverse effect on postoperative visual improvement, it is likely that it may affect visual results during long-term follow-up.

The mechanism of the induction of visual field defects by ICG is still unclear. An experimental approach using an animal model showed that even low-dose intravitreous ICG induced functional damage of the retina without any apparent morphologic damage.3 The results of previous studies have shown the potential toxic effect of ICG to the retinal pigment epithelium6,19 and the acceleration of the toxic effect by the photodynamic effect of ICG.5,19 In our case series, no obvious changes in the retinal pigment epithelium were detected in patients with visual field defects. Therefore, it cannot be reasonably assumed that the toxic effect on the retinal pigment epithelium is correlated with the occurrence of visual field defects. Haritoglou and coworkers9,10 found that cellular elements were adherent to the retinal side of the ILM in eyes with ICG staining by histologic analysis, but they concluded that the observed visual field defects could not be explained by the findings.

Recent studies have suggested retention of ICG staining, along with some staining of the optic nerve after surgery.20-23 It is possible that the long-lasting staining of the retina and optic nerve with ICG dye may have toxic effects on the retina and optic nerve, leading to visual field defects. Therefore, we should pay attention to the progression of visual field defects during long-term follow-up.

This study has limitations because of the few patients included in the retrospective data analysis. It is clear that the defects occurred after surgery because the preoperative Humphrey static perimetry test was normal in patients with postoperative visual field defects. We use less than 0.2 mL of 0.05% ICG solution in only selected patients with postoperative visual field defects. We have not encountered new patients with visual field defects. It is possible, however, that potential toxic damage to the retina may occur even if we use low concentrations of ICG and remove it immediately after injection. As a result, we have not encountered new patients with visual field defects. It is possible, however, that potential toxic damage to the retina may occur even if we use low concentrations of ICG and remove it immediately. Therefore, we may have to reconsider the use of ICG for macular surgery, and patients who have undergone vitrectomy with ICG should have careful long-term follow-up even if they have no complications during the early postoperative period.

**CONCLUSIONS**

We encountered 13 patients with postoperative visual field defects after the use of ICG in macular hole surgery. The incidence is strongly related to the concentrations of ICG solution or tissue contact time or both. Although lowering the concentration or immediate aspiration of ICG af-

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**Visual Acuity (VA) Data in Patients Using Indocyanine Green-Assisted Internal Limiting Membrane Peeling**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Preoperative VA</th>
<th>Mean Postoperative VA*</th>
<th>Postoperative VA+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LogMAR</td>
<td>Snellen Equivalent</td>
<td>LogMAR</td>
</tr>
<tr>
<td>1 (n = 12)</td>
<td>0.78</td>
<td>20/122</td>
<td>0.26</td>
</tr>
<tr>
<td>2 (n = 4)</td>
<td>0.73</td>
<td>20/106</td>
<td>0.18</td>
</tr>
<tr>
<td>3 (n = 6)</td>
<td>0.70</td>
<td>20/100</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Abbreviation: LogMAR, logarithm of the minimal angle of resolution.

*Indicates visual acuity at the 1-year follow-up visit.
ter injection may reduce the incidence of visual field defects, one should pay attention to the potential toxic effect of ICG even if the dose is minimal. Further studies such as electron microscopic studies in experimental settings in animals or electrophysiologic testing in clinical settings will be needed to better understand the implications of this study. Additionally, longer follow-up of those patients may offer additional information.

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