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Abstract *Background:* Macular hole surgery including vitrectomy and peeling of epiretinal membranes and the internal limiting membrane (ILM) has become a standard procedure in retinal surgery. Poor visualization of the ILM is an obstacle for successful surgery. Recently, indocyanine green (ICG) has been reported to be a helpful intraocular substance in identifying these membranes. *Patients and methods:* Eighteen eyes with macular holes stages 2–4 were included. Intraoperatively, the ILM was stained with three drops of 1:9-diluted ICG. After 1 min incubation, the vitreous cavity was rinsed with Ringer's lactate solution, and the ILM was peeled. Autologous thrombocytes were applied to the macular hole and the eye was endotamponaded with 20% SF-6 gas. Preoperatively, 6 weeks postoperatively, and in 3-month intervals thereafter, visual acuity, fundus photographs, scanning laser ophthalmoscope imaging, and Humphrey 24–2 static perimetry was performed. *Results:* Intraoperatively, the ILM could be nicely visualized by ICG, which allowed easier and less traumatic peeling. At 6 weeks follow-up, visual acuity had improved in 14 of 18 patients, and the macular hole was closed 6 weeks after surgery. Scanning laser imaging revealed a strong signal. During prolonged follow-up, visual acuity declined due to cataract formation. *Conclusion:* ICG as an intraocular tool for staining of the ILM is helpful in macular hole surgery. We observed no negative effects on retinal function, but patients should be followed.

Introduction

Macular holes are neuroretinal lesions affecting the fovea and consequently reduce visual acuity. Clinically traumatic macular holes are differentiated from idiopathic macular holes. Regarding development of idiopathic macular holes, several hypotheses have been formulated. Avila postulates that anterio-posterior traction of the vitreous at the macula is the major pathomechanism [1]. Gass hypothesizes localized constriction of the vitreus cortex and consequent tangential vitreomacular traction as the pathway for macular hole formation [8, 9]. For the development of macular holes, effects of both tangential and anterio-posterior traction seem responsible [2]. With the advent of vitreoretinal surgery, macular holes have become accessible to therapeutic intervention.

Today, macular hole surgery, including vitrectomy and peeling of epiretinal membranes and the internal limiting membrane (ILM) has become a standard procedure in retinal surgery. Successful anatomic closure of macular holes can be achieved in almost 90% of cases [4, 10, 11]. In some cases of macular hole surgery, the induction of a posterior vitreous detachment and the identification of the internal ILM are difficult. These difficulties derive primarily from strong adherence of the posterior vitreous to the retina and low visibility of the vitreous and ILM. Attempts to peel the ILM implies the risk of traumatizing adjacent retinal tissue. Additionally, prolonged surgery duration due to difficulty of ILM

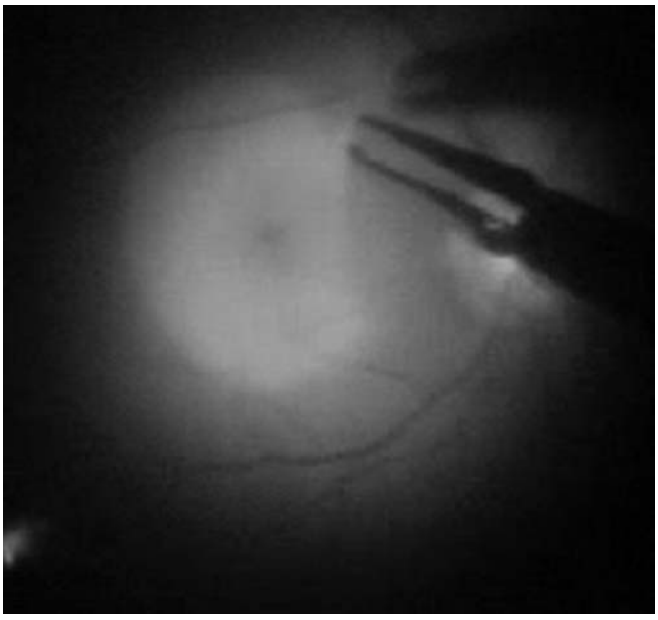


Fig. 1 Intraoperative aspect during internal limiting membrane (ILM) peeling

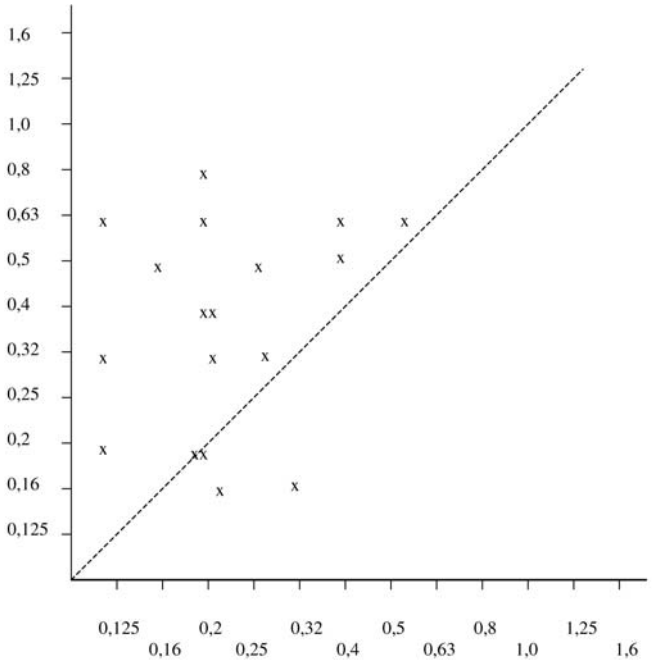


Fig. 2 Scattergram of visual acuity (logarithmic decimal values) at 6 weeks follow-up. Values above the diagonal represent visual increase; below the diagonal, visual loss

identification may be responsible for phototoxic damage to the retinal pigment epithelium, which has been described by some authors [3].

Recently, a number of reports emerged describing the beneficial use of diluted indocyanine green (ICG), a dye usually used for angiography, as an intraocular tool for staining the ILM (Fig. 1) [6, 12, 15]. Histological investigation revealed binding of ICG to laminin and collagen IV within the ILM, which explains the affinity of ICG to the ILM in contrast to its low affinity to epiretinal membranes [13]. We have described previously the detection of ICG traces 6 weeks after intraocular ICG application in macular hole surgery using a scanning laser ophthalmoscope [14]. Here we present clinical results of a series of patients who underwent macular hole surgery with ICG-assisted ILM peeling.

Patients and methods

Eighteen patients with idiopathic macular holes stadium Gass II–IV were consecutively recruited for this study and included if minimal best-corrected visual acuity was at least 0.1 (20/200). Eyes with diabetic retinopathy, glaucoma, or cataract, or with a history of previous retinal surgery, retinal detachment, or blunt trauma, were excluded.

Pre- and postoperative examination included visual acuity testing, fundus photographs, Humphrey 24–2 SITA static perimetry, and imaging with a scanning laser ophthalmoscope (HRA, Heidelberg Engineering) at 790 nm using the mode for ICG angiography without injecting ICG.

In cases where ILM peeling produced larger ILM fragments, the fragments were analyzed histologically by electron microscopy. Surgical procedure included a standard three-port pars plana vitrectomy, followed by a fluid-air exchange. The instillation of 2–4 drops of ICG diluted 1:9 in sodium chloride 0.9% was performed under air, using a 2 μm membrane filter to exclude precipitates. During ICG incubation, the intraocular light source was left within the eye, its light beam directed to the peripheral retina. The ICG was removed after 60 s with a suction cannula.

The eye was consequently filled with balanced salt solution, and the stained internal limiting membrane was peeled about two disc diameters perifoveally with an intraocular forceps. ILM peeling was followed by a second fluid-air exchange and application of 2–4 drops of autologous thrombocyte concentrate to the macular hole. The eye was rinsed with 20% SF-6 gas before closure. On the day of surgery, patients were instructed to lie flat on their backs to achieve pooling of the thrombocyte concentrate in the macular area. The following days, patients were asked to keep a face-down position until the 20% SF-6 gas resolved. Patients were followed up 6 weeks after surgery and in intervals of 3–6 months thereafter.

Results

Initial visual acuity ranged from 0.16 to 0.5. Sixteen eyes were phakic and two had posterior chamber intraocular lenses. At 6 weeks follow-up, visual acuity improved at least one line in 14 eyes, two eyes remained stable, and two decreased by one line and three lines respectively (Fig. 2). Humphrey 24–2 static perimetry was inconsistent: four improved, four worsened, and ten remained stable. We observed intraindividual variation in attention and false-negative and false-positive errors, which made interpretation difficult.

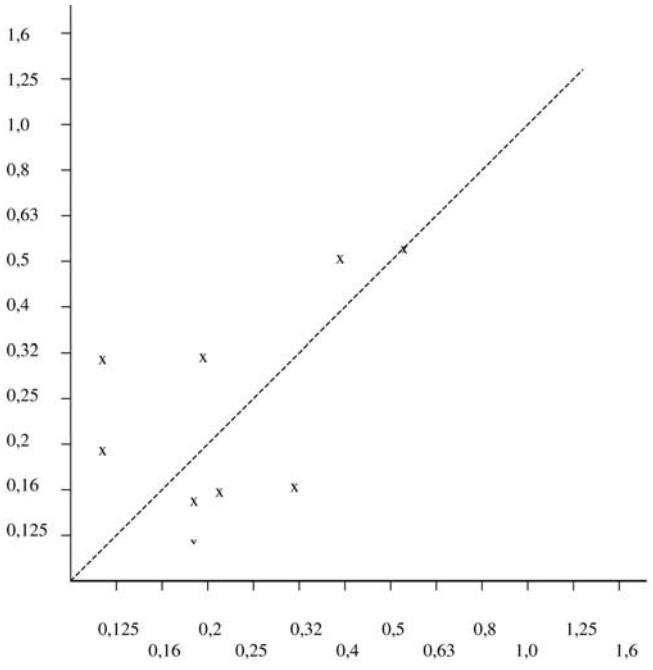
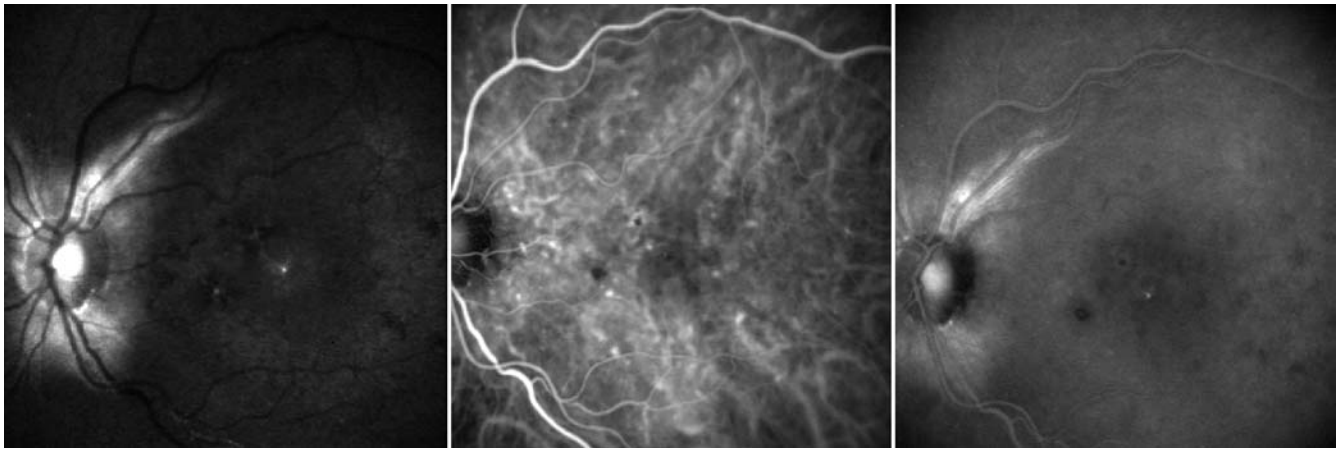


Fig. 3 Scattergram of visual acuity (logarithmic decimal values) at 6 months follow-up. Values above the diagonal represent visual increase; below the diagonal, visual loss

Patients were followed up 4–14 months, with a mean of 8 months (ten patients). During the extended follow-up, all phakic patients developed mild-to-moderate cataracts with a consequent decrease in visual acuity. At mean follow-up of 8 months, five patients had improved visual acuity compared to baseline, one was equal, and four had decreased (Fig. 3).

Imaging with the scanning laser ophthalmoscope revealed a strong signal in all cases at 6 weeks follow-up, probably indicating postoperative intraocular ICG rem-

Fig. 4 Patient 6 weeks after indocyanine green (ICG) peeling. We performed an ICG angiogram due to a small hemorrhage nasal to the fovea. *Left*: Imaging before ICG injection shows a strong signal from the disk and the vascular arcades. *Middle*: Early phase ICG angiogram reveals an atypical signal from the optic disc. *Right*: Late phase ICG angiogram shows the signal from the disc and vascular arcades is already stronger than the background fluorescence of injected ICG



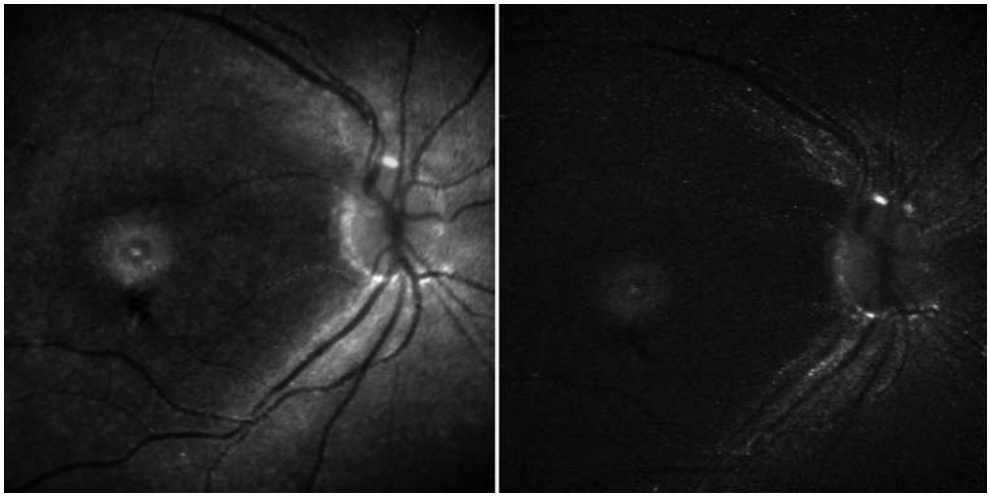


Fig. 5 Imaging with the scanning laser ophthalmoscope reveals a strong indocyanine green (ICG) signal after internal limiting membrane (ILM) peeling with ICG. The signal is strongest perifoveally along the vascular arcades and at the optic disc. *Left*: 6 weeks after surgery. *Right*: same eye, 6 months after surgery

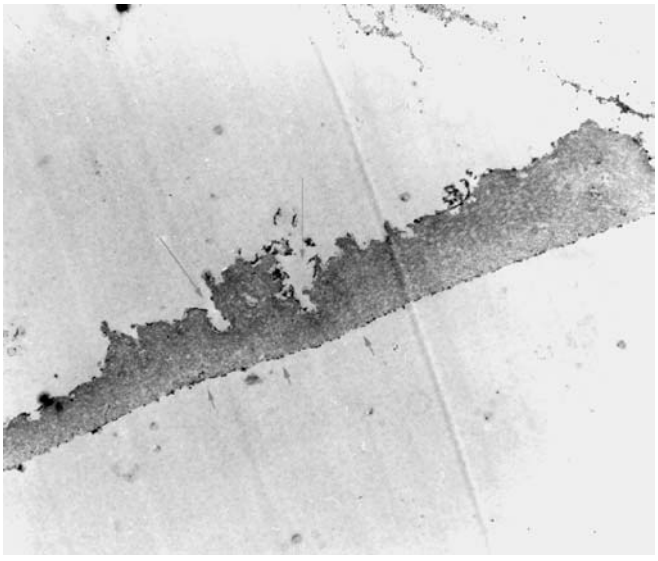


Fig. 6 Electron microscopic image of excised internal limiting membrane (ILM) after intraoperative staining with indocyanine green (ICG). The upper face was adherent to the retina, the *large arrows* indicate sinuation where processes of Müller cells were located. The lower vitreous face is smooth and shows small granular deposition of ICG (*small arrows*)

nants. The signals derived typically from retinal areas along the vascular arcades, the perifoveal region, and the optic disc. During extended follow-up, the signals weakened but were faintly visible, even at 14 months (Figs. 4 and 5). It appears the ICG signals remain stronger at the optic disk.

The histologic analysis of excised ILM material showed a clean separation of the ILM and retinal tissue. The sinuated retinal face of the ILM contained no remnants of Müller cells, and the vitreal face showed fine granular ICG deposition (Fig. 6).

Conclusion

Macular hole surgery with ILM peeling using ICG alleviates the identification of ILM, resulting in shorter surgery duration and less retinal trauma [6]. Functional results at our clinic are satisfactory, with improved visual acuity in most patients. The decreasing visual acuity during extended follow-up caused by cataract formation is a side-effect of endotamponades used after vitreoretinal surgery and in our opinion do not correlate with the use of ICG. Visual field testing using the Humphrey 24–2 static perimetry appeared inconclusive, since we saw both improved and worsened results as well as fluctuation in attention during testing. With the small patient number given, we cannot give a sound interpretation of the results. The electron microscopic analysis of excised membranes revealed a clear separation of ILM and retinal cells by the peeling procedure indicating this technique does not lead to substantial damage to the retina. This has also been reported by other groups [5]. The most interesting aspect to us is the long period of persistence of ICG in the retina and at the disc, visualized with the scanning laser ophthalmoscope. Since ICG binds to collagen IV alpha chain and laminin located within the ILM [13], the persistent signal can be explained by this binding; however, the optic disc is not covered with ILM, so the staining observed there is less clear. The decrease of the ICG signal over time might be due to a washout effect, or, as animal experiments indicate, to a axonal transport mechanism. ICG is a substance that has been in clinical use for decades and has proven to be well tolerated and safe. Our results could not substantiate any adverse effect that could be contributed to ICG. Other groups describe a similar beneficial outcome, but cases of possible toxic effects of ICG to the retinal pigment epithelium (RPE), eventually caused by the photodynamic properties of ICG, have been described [7]. Similar changes to the RPE have been described in macular hole surgery without the use of ICG, and have been attributed to a phototoxic effect during surgery [3]. This risk might be controllable by limited light exposure during surgery. In our experience, the use of ICG decreases the time needed for ILM peeling and therefore light exposure focused to the macula.

Biostaining of the ILM using ICG is a technique still in evolution; therefore, surgical procedures vary between retina centers. We dilute ICG with sodium chloride and administer it into an air-filled eye. Some surgeons administer undiluted ICG into an eye filled with balanced salt solution. Others dilute ICG with glucose 5% as a buffer. It is possible that modifications in administration of ICG have an influence on the persistence of ICG signals, which we detected using a scanning laser ophthalmoscope. Despite good clinical results with ICG-assisted ILM peeling in macular hole surgery, patients should be followed to rule out long-term deleterious effects.

References

1. Avila MP, Jahlk AE, Murakami E (1983) Biomicroscopic study of the vitreous in macular breaks. Ophthalmology 90:1277–1283
2. Azzolini C, Patelli F, Brancato R (2001) Correlation between optical coherence tomography data and biomicroscopic interpretation of idiopathic macular hole. Am J Ophthalmol 132:348–355
3. Banker AS, Freeman, WR, Kim JW, Munguia D, Azen SP (1997) Vision-threatening complications of surgery for full-thickness macular holes. Vitrectomy for macular hole study group. Ophthalmology 104:1442–1452

4. Bresgen M, Heimann K (1995) Idiopathic macular foramen: new aspects of staging and possible therapeutic concepts. Klin Monatsbl Augenheilkd 206:2–12
5. Burk SE, Da Mata AP, Snyder ME, Rosa RHJ, Foster RE (2001) Indocyanine green assisted peeling of the retinal internal limiting membrane. Ophthalmology 107:2010–2014
6. Da Mata AP, Burk SE, Riemann CD, Rosa RHJ, Snyder ME, Petersen ME, Foster RE (2001) Indocyanine green-assisted peeling of the retinal internal limiting membrane during vitrectomy surgery for macular hole repair. Ophthalmology 108:1187–1192
7. Freeman JY, Engelbrecht NE, Aaberg TMJ, Aaberg TMS, Sternberg PJ (2001) Retinal and RPE changes after ICG-assisted ILM peeling in Macular Hole Surgery. Invest Opthalmol Vis Sci 42: S 729
8. Gass JDM (1988) Idiopathic senile macular hole: its early stages and pathogenesis. Arch Ophthalmol 110:629–639
9. Gass JDM (1995) Reappraisal of biomicroscopic classification of stages of development of a macular hole. Am J Ophthalmol 119:752–759
10. Mester V, Kuhn F (2000) Internal limiting membrane removal in the management of full-thickness macular holes. Am J Ophthalmol 129:769–777
11. Ryan EH, Gilbert HD (1994) Results of surgical treatment of recent-onset full-thickness idiopathic macular holes. Arch Ophthalmol 112:1545–1553
12. Stalmans P, Parys-Vanginderdeuren R, De Vos R, Feron EJ (2001) ICG staining of the inner limiting membrane faciliates its removal during surgery for macular holes and puckers. Bull Soc Belge Ophthalmol 21–26
13. Szurmann P, Grisanti S, Schraermeyer U, Schmitz-Valckenberg P, Bartz-Schmidt KU (2001) Indocyanine green staining of internal limiting membrane in vitreoretinal surgery. Invest Ophthalmol Vis Sci 42:S 688
14. Weinberger AWA, Kirchhof B, Mazinani B, Schrage NF (2001) Persistent indocyanine green (ICG)-fluorescence six weeks after intraocular ICG-application for macular hole surgery. Graefe's Arch Clin Exp Ophthalmol 239:388–390
15. Yamaji H, Shiraga J, Endo Y, Yamamoto S, Yumiyama T, Okanouchi H, Ohtsuki H (2001) Adverse effects of the ICG use as an aid for macular hole surgery. Invest Ophthalmol Vis Sci 42:S 691