European Journal of Ophthalmology / Vol. 18 no. 6, 2008 / pp. 972-979

Clinical evaluation of the use of infracyanine green staining for internal limiting membrane peeling in epimacular membrane surgery

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PURPOSE. *To evaluate the use of infracyanine green (IFCG) staining in idiopathic epiretinal membrane (ERM) surgery.*

METHODS. *A retrospective comparative study of 63 consecutive eyes with ERM operated on with internal limiting membrane (ILM) peeling using or not filtered IFCG diluted (5:1) in glucose 5%. Main outcome measures were best-corrected visual acuity, central visual field perimetry, fluorescein angiography with blue light fundus photograph, optical coherence tomography (OCT), and in seven eyes multifocal electroretinogram (mfERG).*

RESULTS. *A total of 44 eyes underwent surgery with ILM staining using IFCG and 19 eyes without. In the IFCG group, the staining showed that the ILM was removed together with the ERM in 39% of eyes; ILM was still present on the macula after ERM removal in 57% of eyes and removed secondarily. The improvement in vision was slightly better in the IFCG group throughout follow-up but the difference was not significant. On the postoperative blue light photograph, defects in the optic nerve fibre layer were less frequent in the group with IFCG than without (p=0.023), suggesting less peroperative trauma. Two eyes in the group operated without IFCG had recurrence of the ERM including one with a macular hole vs none in the group with IFCG. No difference was observed in the groups as regards central visual field testing, mfERG, OCT, or angiographic data.*

CONCLUSIONS. *Using IFCG for ILM peeling in ERM surgery seemed to reduce significantly the trauma to the optic nerve fiber layer and to prevent ERM recurrence. Deleterious effects were not observed in this study. (Eur J Ophthalmol 2008; 18: 972-9)*

KEY WORDS. *Epiretinal membrane, Indocyanine green, Infracyanine green, Optic nerve fiber layer, Vitreomacular surgery*

Accepted: June 2, 2008

INTRODUCTION

Since the 1970s, pars plana vitrectomy has been used for the removal of visually disabling epiretinal membranes (ERM) in patients with blurred vision and metamorphopsia. ERM are called idiopathic in the absence of any known ocular disease. This disorder is more frequent beyond the age of 70 years old with a prevalence of 12%, whereas it occurs in only 2% before the age of 60 (1). In the majority of eyes, ERM surgery results in postoperative visual improvement and in a decrease of metamorphopsia. In a number of eyes, however, symptoms may persist or recur. The physiopathology of the recurrence of the ERM is not elucidated, probably due in some eyes to an incomplete removal of the ERM (2, 3) or to the presence of the internal limiting membrane (ILM) (4). Whereas consensus begins to be reached on ILM peeling in macular hole surgery, it remains a matter of debate in idiopathic ERM surgery. A prospective study showed a better final vision and a lower risk of recurrence with ILM removal (5).

1120-6721/972-08$25.00/0

However, histologic studies have shown that the ILM is often removed with ERM even when it was not intended (6, 7).

ILM staining with indocyanine green (ICG) is commonly used to facilitate ILM peeling and has been suggested to prevent peroperative damage to the optic nerve fibers (8). However, the possible toxic effect of ICG on the retina is controversial. More recently, infracyanine green (IFCG) has been advocated as an alternative vital stain. Its ability to stain the ILM seems similar to that of ICG. However, it differs from ICG because it contains no iodine and can be dissolved directly into a glucose 5% iso-osmotic solution (9).

The aim of this study was to evaluate retrospectively the role of IFCG in the outcome of idiopathic ERM surgery with ILM peeling, by comparing clinical results obtained with and without the use of dye.

METHODS

Consecutive eyes undergoing vitrectomy with ILM peeling for idiopathic epiretinal membrane surgery between October 1998 and April 2004 were studied retrospectively. Patients with chronic macular edema from other cause (diabetic retinopathy, vascular disorders), ERM secondary to retinal detachment (macular pucker), previous vitreoretinal surgery in the studied eye, or any other significant ocular disease that could compromise vision, were not included in this study.

The preoperative recorded data were the duration and the type of symptoms: decrease of visual acuity, metamorphopsia, or scotoma. Clinical examination included best-corrected visual acuity (BCVA) measurement (ETDRS chart), a biomicroscopic slit-lamp examination to determine ERM characteristics and lens status, fluorescein angiography, and optical coherence tomography (OCT 2 first and then OCT 3, Carl Zeiss Meditec, Dublin, CA). Microperimetry with macular sensitivity profile test (automatic Humphrey perimeter) was performed in the majority of patients. Multifocal electroretinogram (mfERG, Retiscan, Roland-Consult Instrument, Wiesbaden, Germany) was performed before and after surgery in the consecutive patients operated on between August and December 2002. mfERG was performed with the 61 hexagon program (8 cycles per eye) using a gold foil electrode after pupillary dilation. The surgical technique always performed by the same surgeon included a standard three-port pars plana vitrectomy with removal of the posterior hyaloid in case of no previous spontaneous posterior vitreous detachment. When the ERM was easily visible with clear limit, it was first removed with forceps before IFCG injection. On the contrary, when the ERM was very thin without visible limit, the IFCG was injected first. Infracyanine green solution (IFCG) was prepared as follows: 25 mg infracyanine green (Laboratoire SERB, Paris, France) was first dissolved in 10 mL of glucose 5%, and then diluted in glucose 5% to a 1:5 solution, for a final concentration of 0.5 mg/mL (osmolarity of 295 mOsM). After filtration (20 µm filter), 0.05 mL of the IFCG solution was injected over the macular region in the fluid-filled globe. The endoillumination was turned off during the 30 seconds of presence of IFCG in the eye in order to reduce the risk of phototoxicity. Then, IFCG was rapidly and carefully washed away. The ILM was usually peeled with some leftover ERM on a circular area of 1 to 2 disc diameters around the fovea. An air or gas exchange (10 to 20% SF_6) was sometimes performed. Peroperative data included the appearance of the staining of macular region by IFCG, the approximate evaluation of the surface of the removed ILM, potential complications, and surgery duration.

Patients underwent clinical examination the day after surgery, at 1 week, at 1 month, and then every 6 months with best-corrected visual acuity measurement, visual symptoms (persistence of scotoma or metamorphopsia), lens status, and fundus examination. At the 1-month follow-up visit, blue, red, and red-free light photographs, fluorescein angiography, and OCT were performed, as well as central field testing and mfERG in some patients. The defect in the optic nerve fibre layer was evaluated on the blue light photograph (dark arcuate stria between optic disc and macula) and macular retinal pigment epithelium (RPE) changes on fluorescein angiography.

Statistical analysis was performed using SPSS software (13.0) for Microsoft Windows. Differences between the groups' data were calculated using Fisher exact test for qualitative data and Mann-Whitney nonparametric test for quantitative data.

RESULTS

Among the 139 consecutive patients operated on between October 1998 and April 2004 for ERM surgery, 63 eyes of 63 patients (42 women and 21 men) fulfilled the inclusion criteria and were studied retrospectively. The first 19 eyes underwent surgery without the use of IFCG,

and the 44 following eyes underwent surgery with ILM staining with IFCG. Seven patients were initially pseudophakic.

Both groups were similar at baseline: mean age of patients was 69 years in the group without IFCG and 68 years in the group with IFCG; preoperative visual acuity was 20/63 in both groups. The mean follow-up was longer in the group without IFCG (23 months) than in the group with IFCG (12 months, Tab. I).

TABLE I - CHARACTERISTICS OF PATIENTS OPERATED ON FOR ERM

	Surgery without IFCG, n=19	Surgery with IFCG, n=44
Age, y	69±6.28	68±6.75
Duration of symptoms, mo	14±15	15±18
Preoperative visual acuity	20/63	20/63
Surgery duration, min	59.71±18	57±24
Follow-up, mo	22.7	12.3

Values are mean ± standard deviation.
ERM = Epiretinal membranes; IFCG = Infracyanine green

TABLE II - PEROPERATIVE DATA CONCERNING ILM AND ERM REMOVAL AFTER IFCG STAINING (N=44)

Data	N (%)
Posterior hyaloid still present and adherent upon the macula	5 (11)
ILM totally removed together with the ERM	17 (39)
ERM removed without the ILM, ILM removed secondarily	25 (57)
Spontaneous rip of the ILM possibly secondary to tangential tractions due to the presence of a thick ERM	10 (23)

ILM = Internal limiting membrane; ERM = Epiretinal membranes; IFCG = Infracyanine green

In the group with the use of IFCG, the dye staining revealed interesting data (Tab. II). The ILM was removed together with the ERM in 39% of eyes; on the contrary, ILM was still present on the macula after ERM removal in 57% of eyes, and therefore was removed separately in a second time. In the remaining 4% of eyes, the data could not be accurately specified. The coloration of ILM by IFCG after ERM removal was homogeneous in only 6 eyes (14.6%), and heterogeneous in 35 eyes (85.3%). This heterogeneous staining corresponded to the presence of cellular proliferation onto the ILM that were not stained by IFCG and showed the picture of isolated or multiple non-colored areas at the surface of the colored ILM; this picture was generally associated with ILM folds. In only 11% of eyes, the posterior hyaloid was not detached from the posterior pole, which confirms that in most cases, ERM is the consequence of posterior vitreous detachment. In 23% of eyes, a spontaneous rip of the ILM was observed before the peeling, possibly caused either by the vitrectomy itself or by tangential tractions due to the presence of a thick and retractile ERM. The peeling of the ILM was considered as “large” (two optic disk diameters in average around the fovea) in 10 eyes (53%) in the group without IFCG versus 35 eyes (80%) in the group with IFCG (p=0.026). A large peeling seemed to be correlated with a slightly better BCVA than a small or intermediate peeling, but the difference was not statistically significant. The duration of surgery was not significantly different in both groups (Tab. I).

There was no significant difference in visual acuity between the two groups during follow-up except at 1 year (Fig. 1): 20/80 in the group without IFCG versus 20/50 in the group with IFCG (p=0.033). Cataract extraction was performed at 20 months in average in 10 eyes (59%) in the group without IFCG and in 21 eyes (54%) in the group

TABLE III - POSTOPERATIVE CHANGES AFTER ERM/ILM REMOVAL

	Surgery without IFCG, n=19	Surgery with IFCG, n=44	p
Changes in RPE layer, n (%)	0	2 (4.8)	NS
Changes in central visual field, n (%)	4 (30.8)	4 (12.9)	NS
Lack in the optic nerve fibers layer, n (%)	4 (23.5)	1 (2.4)	0.023
mfERG (nV/deg^2), mean ± SD	250.4±26	278.6±150	NS
Foveal sensibility (central field testing, dB), mean ± SD	29.08±4.53	30.87±2.38	NS

ERM = Epiretinal membranes; ILM = Internal limiting membrane; IFCG = Infracyanine green; RPE = Retinal pigment epithelium; NS = Not significant

with IFCG at 12 months on average. At 1 year, 41% of eyes in the IFCG group were pseudophakic and only 26% in the control group. The mean visual acuity after cataract extraction was 20/40 in the group without IFCG and 20/32 in the group with IFCG; the difference was not statistically significant.

Anatomic results were grossly similar in both groups: 7 eyes (46.7%) in the group without IFCG and 21 eyes (51.2%) in the group with IFCG recovered a normal OCT profile with a foveal depression (Fig. 2). Two patients in the group without IFCG had a persistence of the ERM, none in the group with IFCG. One of those two patients complained of persistent metamorphopsia and was reoperated at 18 months after the first surgery. The other ex-

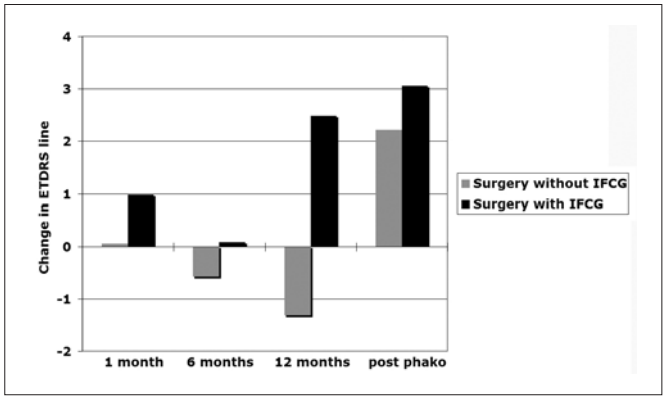

Fig. 1 - *Change in visual acuity after epiretinal membrane/internal limiting membrane removal in both groups.*

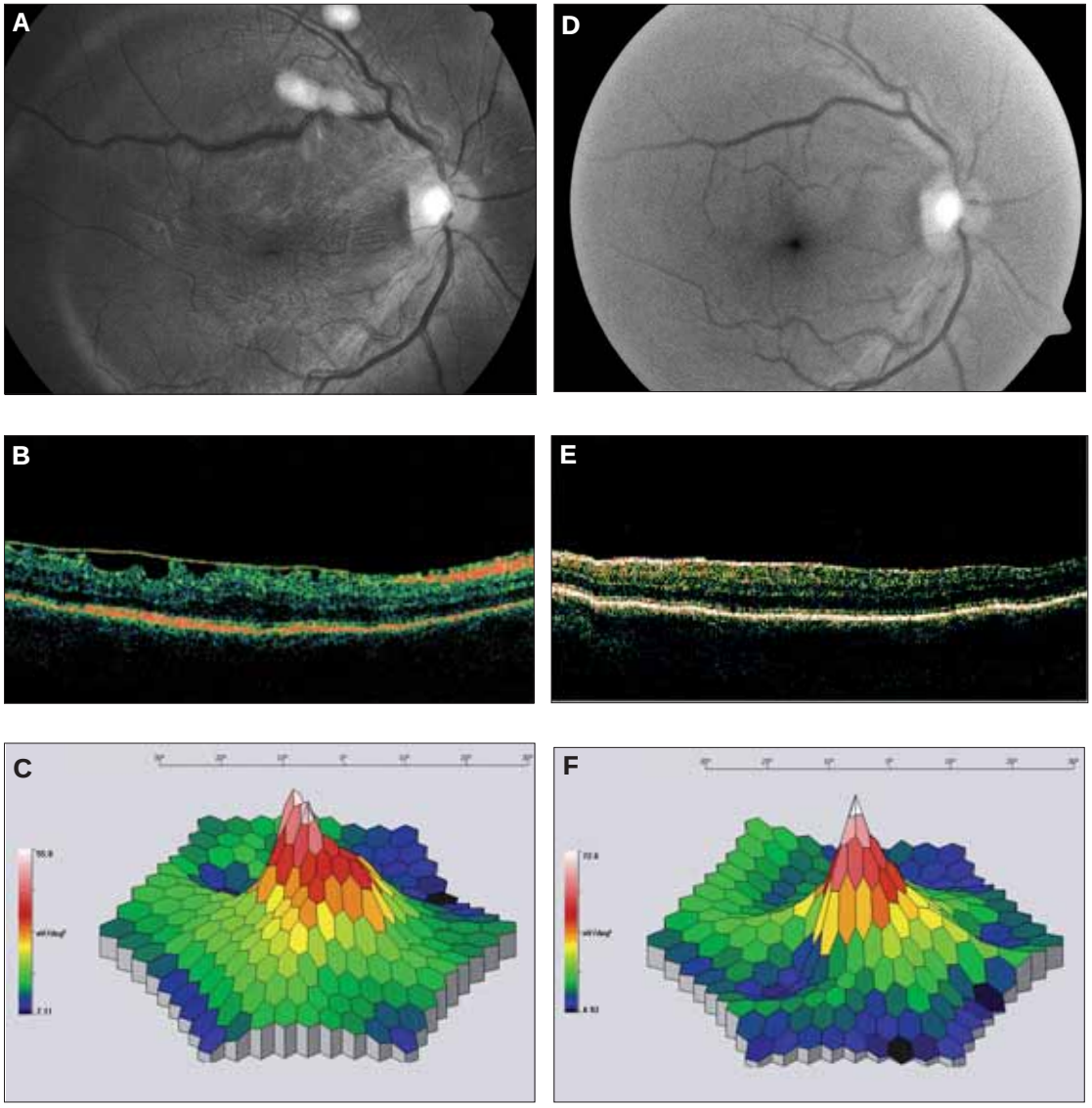

Fig. 2 - *A 46-year-old woman operated on for idiopathic epiretinal membrane (ERM) with the use of infracyanine green (IFCG). Preoperative visual acuity was 20/40.* **(A)** *Preoperative blue light fundus photograph showing the ERM.* **(B)** *The optical coherence tomography of the fovea shows the tight ERM partly detached from the retina that displays superficial folds.* **(C)** *Preoperative multifocal electroretinogram showing the peculiar irregularity of macular sensitivity and reduced peak (55.8).* **(D)** *Postoperative blue light fundus photograph showing the disappearance of the ERM without defect in the optic fiber layer.* **(E)** *Postoperative optical coherence tomography showing the disappearance of the ERM and the decrease in the central retinal thickness.* **(F)** *Postoperative multifocal electroretinogram at 1 month. The foveal peak is partly restored (72.6). Postoperative visual acuity at 1 month was 20/25.*

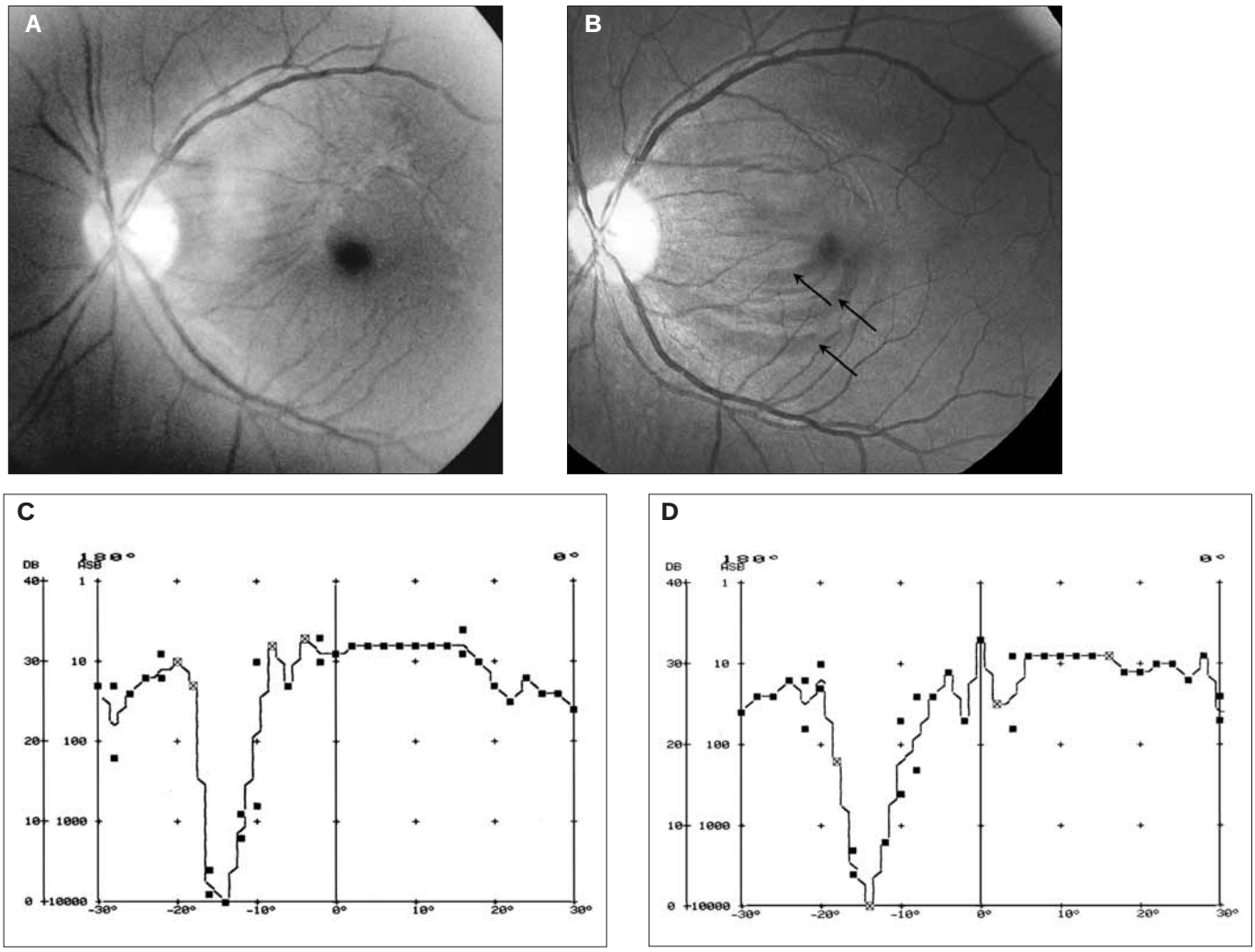

Fig. 3 - *A 67-year-old woman operated on without infracyanine green. Preoperative visual acuity was 20/63.* **(A)** *Preoperative blue light fundus photograph showing the epiretinal membrane.* **(B)** *Postoperative blue light fundus photograph showing the defect in the optic fiber layer as several inferior dark arcuate striae (arrows).* **(C)** *Preoperative visual field showing the curve of macular sensitivity. On the left, the decreased sensitivity corresponds to the disc (blind spot); in the middle of the curve, the foveal peak is reduced.* **(D)** *Postoperative macular sensitivity at 1 month. The foveal peak is partly restored but mild paracentral scotomas have appeared around the peak. Postoperative visual acuity was 20/80.*

perienced a macular hole 42 months after the first ERM surgery, and was reoperated on for ILM peeling with IFCG staining and gas tamponade.

Postoperative side effects are shown in Table III. There was no significant difference in central RPE changes between the two groups. A defect in the optic fiber layer was noted on the blue light photograph in five eyes, and was more frequent in the group without IFCG (23.5%) than in the group with IFCG (2.4%) with a statistically significant difference (p=0.023, Fig. 3). Changes in the central visual field with decrease of the foveal sensibility at 1 month were noted in four eyes in the group without IFCG and in four eyes in the group with IFCG (nonsignificant difference). Multifocal ERG was performed in three patients in the group without IFCG and in four patients in the group with IFCG. The mfERG N1 and P1 response amplitudes and peak latencies of various ring eccentricities were assessed and compared with baseline to determine any serial changes. In one eye without the dye and in one eye with IFCG, the postoperative mfERG response was altered, whereas in three eyes with IFCG, postoperative mfERG was improved. There was no significant difference on the ERG between the two groups as regards to the value of the mean peak latencies 1 month postoperatively.

Two peroperative retinal tears (one in each group) and two retinal detachments (one in each group) were observed.

DISCUSSION

Infracyanine green has been used in epiretinal membrane surgery to facilitate ILM peeling. Our results showed no significant difference between the groups in macular function measured by means of BCVA, central field testing, and mfERG. Visual function was slightly better in the group operated on with IFCG, but it was not statistically significant, except at 1 year. The average time between ERM surgery and cataract extraction was slightly shorter in the group operated on with IFCG, which could account for this difference in visual acuity at 1 year. At the end of follow-up, BCVA was grossly similar in both groups. These results suggested that IFCG was at least not toxic for the retina in our series.

This retrospective study carries the drawback of a non-randomized study; the patients operated without IFCG were operated first, and the benefit observed in the IFCG group could account for a learning curve, which is observed in any surgery. Nevertheless, the single surgeon was experienced at the beginning of the study; a learning curve had been suggested in an early study published in 2002 comparing macular hole surgery with or without ILM peeling performed between 1993 and 2000 without staining (10). The same objection cannot be raised more than 5 years later.

Our findings in postoperative visual acuity confirmed those of other authors who described a positive functional outcome with the use of ICG in macular surgery (8, 11-15). Yet these results are in contrast with other previous studies that revealed a decrease in postoperative visual acuity (16-18) after ICG assisted ILM peeling, especially after macular hole surgery. However, very few studies in the literature report the result of ERM surgery.

The mechanism of presumed ICG toxicity is not clear. Many experimental studies have been performed to highlight ICG toxicity to the RPE (19-22). All these in vitro studies were performed with high concentration of indocyanine green. In the current study, we used diluted (1:5) and filtrated infracyanine green, dissolved in glucose 5% (final concentration, 0.5 mg/mL), during 30 seconds in the dark. Stalmans et al suggested that the toxicity of ICG to RPE cells could probably be related to the hypo-osmolarity induced by the physiologic saline solution solvent, and did not exist with IFCG diluted in glucose 5% (9). Jackson et al showed that the in vitro RPE cell viability after exposure to 5 mg/mL IFCG and illumination was not reduced (23) whereas Kodjikian et al found increased acute and chronic in vitro toxicities with ICG and IFCG at a concentration above 0.5 mg/mL (24). In clinical practice, they suggested that better IFCG concentration to obtain a good staining and to limit the retinal toxicity seems to be 0.5 mg/mL. Contrary to what could happen in macular hole surgery, the possible toxicity of ICG to the RPE can be ruled out in ERM surgery because the dye is not in contact with the RPE.

In the current study, mfERG was performed before and at 1 month postoperatively in seven patients. The improvement of the mfERG values was more important in the group with IFCG but the difference was not significant. Recently, Lai et al reported mfERG measurement before ERM surgery with ICG and at 3 and 6 months postoperatively. There was no deterioration between the mfERG before and after surgery for low ICG concentrations (0.5 mg/mL, as in our study using IFCG). For elevated ICG concentration (1.25 mg/mL), mfERG was transitorily altered (25). One month postoperatively is probably a too early period to evaluate the benefit of the surgery (in the current study, we performed at that time the postoperative evaluation with central visual field testing, mfERG, OCT, and fluorescein angiography). According to other studies, a transitory worsening was shown at 1 month, and then an improvement, 6 to 12 months postoperatively (25-27).

Moreover, using IFCG carried obvious advantages. Optic nerve fiber layer has not yet been particularly studied in the literature on macular surgery. A defect in the inner layer of the optic nerve fibers on the postoperative blue light photograph was observed in the current series in 24% of patients in the group without IFCG and in 2% of patients in the group with IFCG. This difference was statistically significant ($p=0.023$). These defects seemed to be related to the surgical injury to the optic nerve fibers during the ILM removal, due either to focal adherence between the ERM itself and the inner retina, or to the attempt to grip the limit of the ERM/ILM with micropic or micro forceps. With IFCG, the visibility of the epiretinal tissue is enhanced and its removal is safer and more precise, which can prevent injuries to the optic nerve fiber layer. Similar results have been reported by our team using IFCG in macular hole surgery (8). The ILM peeling is facilitated with the dye (28) permitting a shortening of light exposure

duration. But, contrary to the macular hole surgery, the duration of the ERM surgery with staining was not significantly reduced in the current study. Our results were in contrast with authors who described visual field defects after using ICG to peel the ILM (29, 30). Some authors showed that these visual field defects seemed to be a complication after vitrectomy attributed to a dehydration injury of the retina during fluid-air exchange (31, 32). In our study, there was no significant difference between the patients who experienced a fluid–air exchange and those who did not, concerning postoperative defect of the optic nerve fibers.

In two eyes without IFCG, ILM persisted partially and was responsible for persistence of metamorphopsia in one eye and of macular hole formation in the other. Systematic ILM peeling seems to prevent persistent metamorphopsia and macular hole formation as suggested by Yoshida and Kishi (33). Peroperative IFCG staining revealed that ILM was removed in the same time as ERM in 39% of cases, and that in the majority of eyes (57%), it remained on the posterior retina after ERM removal. The ILM staining after ERM removal was heterogeneous in 56% of eyes, suggesting that cellular proliferation and tangential tractions can remain at the surface of the ILM after simple EMR removal. The remaining ILM seemed also to be associated with the presence of metamorphopsia.

In conclusion, our results showed that using IFCG for ILM peeling seemed to reduce significantly the trauma to the optic nerve fiber layer and to prevent ERM recurrence. Deleterious effects clearly attributable to the use of IFCG were not observed in this study. At the time when high-resolution imaging tools like OCT influence the surgical decision by detecting ERM or vitreomacular traction that were not seen by clinical examination only (34), the surgeon can be faced with very thin membranes without visible limit. The use of IFCG staining appeared to be a way to perform safely the removal of these thin membranes and of the ILM in order to improve the patient's vision recovery and to reduce the risk of recurrence. Further studies are needed to confirm these conclusions.

The authors report no financial interest or grant support.

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