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CLINICAL INVESTIGATION

Surgical removal of idiopathic epiretinal membrane with or without the assistance of indocyanine green: a randomised controlled clinical trial

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Abstract
Purpose To carry out a prospective investigation of the functional and morphological outcome of idiopathic epiretinal membrane (IEM) surgery with or without the assistance of indocyanine green (ICG) in a randomised controlled clinical trial.
Methods Sixty patients who underwent vitrectomy with removal of IEM combined with cataract surgery were randomly allocated to two groups: 27 patients were operated on with ICG 0.1% in glucose 5%, 33 patients without ICG. Functional outcome was assessed 3-4 months postoperatively with improvement of best-corrected visual acuity (BCVA), Amsler grid test, and automated and kinetic perimetry. Postoperative residual or recurrent IEM was assessed with bio-microscopy, and macular oedema with optical coherence tomography (OCT). Improvement in BCVA was the main outcome measure.
Results BCVA improved in 49 patients, remained unchanged in five and decreased in five. Improvement in BCVA and reduction of macular oedema were statistically significant within both groups ($P<0.01$). Improvement in BCVA was not statistically significantly different whether ICG was used or not [0.17 (logarithm of minimum angle of resolution; logMAR) with ICG and 0.24 (logMAR) without ICG] ($P=0.59$). There was no statistically significant difference in preoperative or postoperative BCVA, reduction of macular oedema, postoperative Amsler grid test, or incidence of residual or recurrent IEM between the two groups. Visual field defects were detected in two patients operated on with ICG.
Conclusions Removal of IEM with or without the assistance of ICG equally improved visual function and macular morphology.

Keywords Indocyanine green · Toxicity · Safety · Epiretinal membrane · Visual field defect

This study has been registered with http://www.clinicaltrials.gov, no.: NCT00376857.

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Introduction

Idiopathic epiretinal membrane (IEM) is characterised by the formation of epimacular membranous tissue without any known underlying retinal disease. The prevalence of this entity is 2% in people under the age of 60 years and 12% beyond the age of 70 years [1]. IEM is associated with macular dysfunction, probably related to an impairment of the inner retinal layers [2], which is similar to that found in aphakic cystoid macular oedema [3]. In fact, optical coherence tomography (OCT) studies have demonstrated an increased retinal thickness of the macula [4–6], which decreased significantly after surgical membrane peeling but remained greater than the macular retinal thickness of the normal fellow eye [7].

Indocyanine green (ICG) has been introduced to stain and visualise epiretinal membranes and the internal limiting membrane (ILM) to facilitate the delicate surgical manoeuvre of their removal in epiretinal membrane [8–10] and macular hole surgery [11–13]. In the surgical treatment of IEM the delamination of epiretinal membrane usually leads to a complete removal of all epiretinal tissue, and peeling of the underlying ILM is attempted only when complete removal of the epiretinal membranes cannot be readily achieved. However, histological studies have shown that the ILM is often removed together with fibrocellular epiretinal membranes, even when it was not intended to be [14, 15].

Several authors have reported good functional outcome of ICG-assisted vitrectomy [12, 16–18], whereas some authors have reported less favourable results in visual acuity [8, 19, 20] and significant visual field defects when intraocular ICG was used [8, 19–21]. Because of this controversy, the possible toxic effect of ICG on the inner retina has become the subject of an ongoing debate [22, 23].

In our previous clinical study evaluating the outcome of IEM surgery we found no difference in the investigated functional and morphological parameters, whether ICG was used or not [24]. However, this study has some of the usual limitations of retrospective analyses. The presence of the observed visual field defects prior to surgery cannot be excluded. The relatively large number of surgeons and the fact that examiners were not blinded are possible sources of bias. Comparing non-contemporary groups of patients is a source of bias, as the surgeons may have improved their skills when operating on the second group of patients. Finally, the lens status was not standardised, as some patients underwent concomitant cataract removal and some did not [24]. Other clinical studies investigating the effect of ICG in macular surgery have also been designed as retrospective or prospective but uncontrolled trials [8, 12, 16–21]. Retrospective or uncontrolled patient studies are useful to detect pronounced differences between treatment groups; however, more subtle differences may be missed.

It was the aim of the present study to prospectively compare the functional and morphological outcome of IEM surgery with and without the assistance of ICG. All phakic patients underwent concomitant standard cataract surgery to exclude an unwanted effect on the functional outcome caused by accelerated cataract progression following vitrectomy. The main outcome measure was improvement of best-corrected visual acuity (BCVA). This was treated as an open question, and we had no hypothesis as to which of the two therapies was superior. The influence of the degree of difficulty to remove the epiretinal membrane ("easy" or "difficult" to peel) on the main outcome measure was analysed as a covariate.

Patients and methods

Study design

The present study was designed as a prospective, controlled, randomised, clinical, intention-to-treat trial in the setting of a tertiary academic eye hospital.

Study protocol

Inclusion criteria

Those patients with IEM and cataract or posterior chamber intraocular lens pseudophakia and complaining of loss of visual acuity and metamorphopsia during the previous 6 months were included in the study.

Exclusion criteria

Not included were those with other retinal diseases, non-idiopathic epiretinal membrane, glaucoma or history of retinal detachment.

Informed consent was obtained. The present study was in adherence to the tenets of the Declaration of Helsinki. Approval was obtained from the Ethics Committee of the University of Regensburg. Patients were examined preoperatively and 3-4 months postoperatively by the same ophthalmologist (P.S.) in a masked fashion. The degree of cataract was classified by slit-lamp bio-microscopy as either "mild" or "dense". Best-corrected decimal visual acuity with a Snellen chart (BCVA) was tested pre- and postoperatively. Visual function was further assessed with the Amsler grid test, 10° and 30° automated perimetry (Heidelberg visual field analyser, HFA), and Goldmann kinetic perimetry pre- and postoperatively. Macular oedema was assessed by OCT measurement of the macular retinal thickness at the point of fixation (OCT 3, Zeiss-Meditec, Jena, Germany) pre- and postoperatively. The incidence of residual epiretinal membrane was assessed postoperatively with stereoscopic bio-microscopy.

Surgical technique

All patients underwent the same surgical procedure either with or without the aid of ICG. All patients were operated on by the same experienced surgeon (V.-P.G.).

Patients with cataract underwent standard small-incision phacoemulsification cataract surgery with implantation of a yellow acrylic intraocular lens (Hoya AF-1 UY, Hoya, Tokyo, Japan) and standard 3-port pars-plana vitrectomy, including the induction of a posterior vitreous detachment. Balanced salt solution (BSS; Alcon, Fort Worth, TX, USA) was used as an irrigation solution. Pseudophakic patients with a posterior chamber lens at the time of surgery underwent an identical procedure without cataract surgery. In the group operated on without ICG the epiretinal membrane was engaged with intraocular forceps to create a flap and then peeled in a capsulorrhexis fashion [25] before routine closure without the use of tamponade agents. In the group operated on with ICG the continuous BSS irrigation was briefly stopped, and less than 0.5 ml of ICG (Pulsion, Munich, Germany) at a 0.1% concentration dissolved in glucose 5% was injected into the BSS-filled globe just above the posterior pole. The osmolarity of this solution was 296 mosmol, as measured with an osmometer (Knauer, Berlin, Germany). After 10 s to 20 s, the irrigation was re-started, and, thus, the dye was quickly washed out of the globe. Usually, the epiretinal membrane was not stained very well, but the underlying ILM was stained a faint green colour at the border of the epiretinal membranous tissue and was clearly visible under illumination from the standard light pipe of the vitrectomy instrument. The stained membrane was engaged with intraocular forceps and peeled in the same manner as in the patients operated on without ICG, before routine closure without the use of tamponade agents. Because ICG stains the ILM better than epiretinal tissue, it may have been removed in some patients together with the epiretinal membrane, although this was not a goal of the operation. The goal of the operation was to remove all epiretinal membranous tissue completely, in all patients in both groups. It was recorded whether the surgeon found the membrane relatively "easy to peel" or relatively "difficult to peel". In cases where the membrane could not be safely removed without the use of ICG in a patient assigned to the "without ICG" group, ICG was used.

Outcome measures

The main outcome measure was improvement of BCVA. Other outcome measures included BCVA pre- and postoperatively, Amsler grid test, macular retinal thickness, reduction of macular retinal thickness, and residual or recurrent macular epiretinal membrane.

Statistical methods

In the statistical analysis of the outcome measures the type I error (alpha) was set at 0.05. Projection of target sample size: under the assumption that the standard deviation is 0.2 and the number of patients per group is 30, a 0.15 mean difference in the main outcome measure (improvement of BCVA) between the two treatment groups can be detected with a power of 80%.

The results were statistically analysed with SPSS 10.0 software (SPSS, Chicago, IL, USA) and Microsoft Excel (Microsoft, Redmond, WA, USA).

Assignment

Patients were assigned to two treatment groups: "with ICG" and "without ICG". The allocation sequence was generated by chance and concealed in sealed envelopes until the patient was enrolled. The allocation sequence was generated by J.H. and P.S. J.H. enrolled participants, and P.S. assigned participants to their group. Successful masking was controlled by W.A.H.

Results

Patients' characteristics

A total of 60 patients (29 female, 31 male), 52 to 81 years of age, with a mean age of 69.7±7 years (mean ± SD) were prospectively recruited. Fifty-three patients underwent concomitant cataract surgery. Four patients in the "with ICG" group and three patients in the "without ICG" group were pseudophakic at the time of surgery (Table 1, Figure 1).

Test of main outcome measure

In our intention-to-treat analysis the main outcome measure, improvement of BCVA, was not statistically significantly different between the two treatment groups (Table 1).

In three patients assigned to the "without ICG" group the membrane could not be safely removed without the use of ICG. ICG was used in these patients. Since the results of the statistical analysis may have been influenced by these three patients and by the three patients who had to be re-operated on for postoperative retinal detachment, we repeated the statistical analysis for the main outcome measure, excluding these six patients. Improvement of BCVA was also not statistically significantly different between the two treatment groups after these six patients had been excluded (Table 2).

Test of other outcome measures

Overall, BCVA improved in 49 patients, remained unchanged in five and decreased in five. Improvement in BCVA and reduction of macular oedema was statistically significant within both groups ($P<0.01$).

The following outcome measures and patient characteristics were not statistically significantly different between the two treatment groups: BCVA before and after surgery, Amsler grid test, number of patients with dense cataracts, number of patients with IEM classified as difficult to peel, and number of residual or recurrent epiretinal membrane postoperatively (Table 1).

Macular retinal thickness, as measured by OCT, was significantly greater in the group operated on with ICG

Table 1 Statistical analysis of results comparing the two patient groups (with and without ICG)

Patient group	Age (years)	BCVA preoperatively (logMAR)	BCVA postoperatively (logMAR)	Improvement in BCVA with surgery (logMAR)	Amsler grid test (positive postoperatively)	Macular retinal thickness preoperatively (µm, OCT)	Macular retinal thickness postoperatively (µm, OCT)	Reduction of macular retinal thickness (µm, OCT) with surgery	Cataract grading (number of dense cataracts)	Macular epiretinal membrane difficult to peel	Macular epiretinal membrane postoperatively (number of patients)
With ICG (n=27)	67±7	−0.46 (0.11)	−0.28 (0.38)	−0.17 (0.35)	17 of 27	473 (91)	352 (105)	−115(112)	5 of 27	10 of 27	7 of 27
Without ICG (n=32)	71±6	−0.42 (0.11)	−0.18 (0.17)	−0.24 (0.17)	15 of 32	412 (104)	313 (84)	−106(120)	12 of 32	15 of 32	10 of 32
Statistical analysis	P=0.051 (Mann–Whitney test)	P=0.48 (Mann–Whitney test)	P=0.25 (Mann–Whitney test)	P=0.59 (Mann–Whitney test)	P=0.26 (Fisher's test)	P=0.016 (Mann–Whitney test)	P=0.17 (Mann–Whitney test)	P=0.79 (Mann–Whitney test)	P=0.15 (Fisher's test)	P=0.6 (Fisher's test)	P=0.22 (Fisher's test)

Values given as mean ± SD.

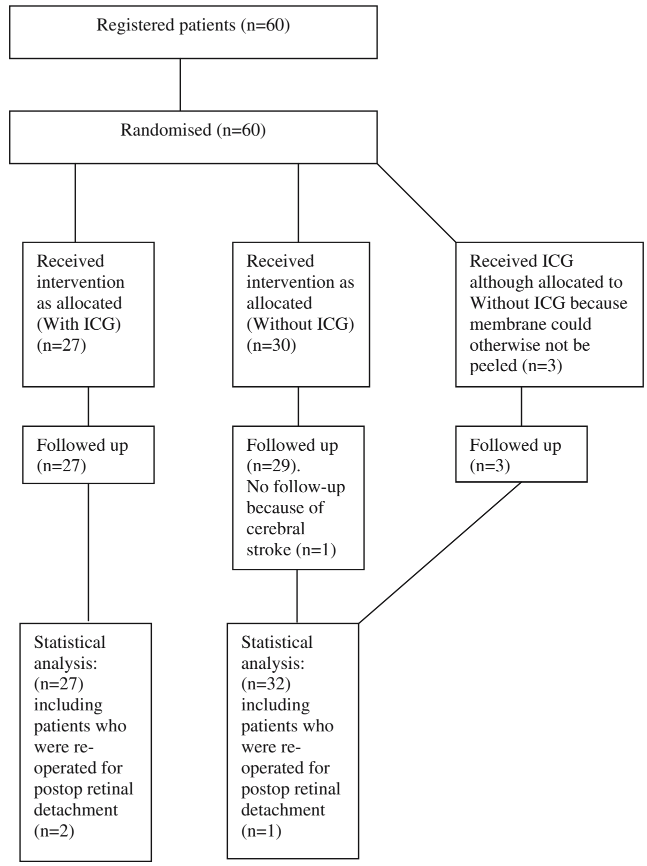

Fig. 1 Flow diagram summarising participant flow including randomisation, assignment, and completeness of follow-up

before surgery; however, postoperative macular thickness and the reduction of macular thickness with surgery were not significantly different between the two groups (Table 1).

Covariate analysis

Intraoperatively, we found considerable morphological variation in IEMs. Some were cellophane-like in appear-

Table 2 Statistical analysis of results comparing the main outcome measure (improvement of BCVA) in the two patient groups (with and without ICG)

Patient group	Improvement of BCVA with surgery (logMAR)
With ICG (n=25)	−0.24 (0.22)
Without ICG (n=28)	−0.25 (0.17)
Statistical analysis	P=0.67 (Mann–Whitney test)

Six patients have been removed: two with retinal detachment in the "with ICG" group, one with retinal detachment in the "without ICG" group and three who received ICG although they had been randomly allocated to the "without ICG" group. All values given as mean ± SD. *logMAR* logarithm of minimum angle of resolution ance and rather "easy to peel" in one piece once an edge of the membrane had been successfully delaminated from the retinal surface. By contrast, other membranes appeared to be multi-layered and could be removed only by the repeated re-grasping of small fragments of a comparatively soft membraneous material. The latter type was classified as "difficult to peel" (Table 1). There was no statistically significant difference in BCVA before or after surgery or in the improvement of BCVA with surgery between patients whose membranes had been classified as "easy to peel" or "difficult to peel" (Table 3).

Complications

Postoperatively, we found paracentral, lower nasal, visual field defects detected by automated and by Goldmann perimetry in two patients operated on with ICG that were not present before the operation. The visual field defects were asymptomatic in both patients.

Two patients in the "with ICG" group and one patient in the "without ICG" group were re-operated on because of retinal detachment after the initial operation. One patient in the "without ICG" group suffered a cerebral stroke several weeks after surgery; however, this event appeared not to be related to the operation. Cataract surgery was performed without complications in all cases.

Discussion

Our results show no statistically significant difference in macular function as assessed by improvement of BCVA or Amsler grid test between the groups operated on with or without the aid of ICG. The projection of sample size was based on the results of our previous retrospective trial [24]. BCVA improved in both groups. In accordance with the findings of others [7], macular oedema improved with surgery. The reduction of macular oedema as assessed by OCT measurement of retinal thickness was not statistically significantly different between the two groups.

Table 3 Statistical analysis of results comparing the main outcome measure, improvement in BCVA before and after surgery between patients whose membranes had been classified as "easy to peel" and patients whose membranes had been classified as "difficult to peel"

Patient group	Improvement in BCVA with surgery (logMAR)
Membranes "difficult to peel" (n=25)	−0.17 (0.35)
Membranes "easy to peel" (n=34)	−0.25 (0.2)
Statistical analysis	P=0.63 (Mann−Whitney test)

All values given as mean ± SD. *logMAR* logarithm of minimum angle of resolution

We found considerable differences in the degree of difficulty of the removal of IEMs between patients. The surgeon (V.-P. G.) therefore classified each operation as either membrane "easy to peel" or membrane "difficult to peel". This parameter was not statistically significantly different between the treatment groups (Table 1). Improvement in BCVA with surgery in patients whose membrane had been classified as "easy to peel" as compared with patients classified as "difficult to peel" was also not significantly different (Table 3). There may have been more difficult cases in the "with ICG" group because three patients had to be operated on with ICG because the membrane was so difficult to remove that the surgeon decided to use ICG although the patient had been assigned to the "without ICG" group.

Our findings of improvement in BCVA are in accordance with our previous retrospective analysis [24] and with those of other authors who described a positive functional outcome of ICG-assisted vitreous surgery [12, 16–18]. Our findings are in contrast with those of authors who described less favourable postoperative visual acuity [8, 19, 20] and visual field defects [8, 19–21] after ICG-assisted vitreous surgery. These reports have contributed to the concern that ICG, when used in macular surgery, may be toxic to the retina.

The histological examination of peeled membranes showed cellular elements that led to the hypothesis that ICG caused retinal damage by altering the vitreoretinal interface [19], whereas another histological study revealed similar cellular elements on membranes that were peeled without the aid of ICG [25]. A possible photosensitising effect after intraoperative illumination of the stained retina with light of wavelengths between 380 nm and 760 nm as emitted by commonly used vitrectomy light pipes, leading to morphological damage of the inner retina, has been reported [26, 27]. This finding was not confirmed by other investigations [28, 29]. A possible cytotoxic effect of ICG has been investigated in experimental studies. Enaida et al. found direct dose-dependent functional and morphological damage of the retina after intravitreous application of ICG in an in vivo rat model [30]. The doses used in this study were within or below the range (0.05–5.0 mg per eye) of clinical application, but, in contrast to clinical practice, where the ICG solution is removed within seconds up to a minute, the authors left the ICG in the eye for 10 days before examination of the exposed retinas [30]. The clinical relevance of the results is therefore questionable.

We found visual field defects in two patients operated on with ICG. In one of these patients the peeling manoeuvre was described as difficult, and the defect might have been caused by mechanical damage to the nerve fibre layer. Overall, visual field defect after vitrectomy is a well-known postoperative complication, which has also been attributed to dehydration injury of the retina during fluid–air exchange [31–33]. This mechanism is unlikely to have played a role in our patients, since we did not perform a fluid–air exchange. Visual field defect after vitrectomy has also been attributed to traction during cortical vitreous peeling [34], to intraoperative fluctuations of intraocular pressure, to optic nerve damage from retrobulbar injection or to direct intraoperative mechanical trauma to the optic nerve [35]. Kim et al. reported a visual field defect after uneventful surgical removal of epiretinal membrane. Electron microscopy of the removed membrane showed adhesion between the epiretinal membrane and axons of the nerve fibre layer in an area of internal limiting lamina defect [36]. We cannot conclude which of several possible mechanisms caused the visual field defects in our patients, and ICG cannot be excluded as a possible cause. However, in view of the low number of patients with visual field defects in the present study, the hypothesis that ICG is a cause seems unlikely.

As cited above, there is principal experimental evidence of a direct dose-dependent cytotoxic effect of ICG [30]. Also, phototoxicity of ICG irradiated with a diode laser emitting light at a wavelength of 805 nm has been studied in vitro. As the result, the photodynamic effect of ICG was related to the amount of ICG and the energy density of the illumination [37, 38]. The comparison of the emission spectrum of the light source used in the present study and the absorption spectrum of ICG showed an overlap [24], and a phototoxic effect, therefore, cannot be excluded. However, the studies mentioned [37, 38] do not necessarily reflect the actual intraoperative situation in macular surgery.

In principle, retinal toxicity of ICG in macular surgery can be expected to depend on the concentration of the ICG solution [39, 40], the osmolarity of the solution [40, 41], the length of time before ICG is removed from the eye [39, 42], whether ICG is injected into an air-filled or a fluid-filled eye (with less toxicity in fluid-filled eyes) [42], and the emission spectrum and the energy density of the illumination [37, 38]. The question of a specific toxicity threshold of the retina for ICG remains unanswered, but the safety margin is narrow, as has been found in in vitro studies [39, 40]. Our results suggest that ICG-assisted macular surgery for IEM in the setting described in the present study did not cause retinal toxicity detectable with the diagnostic tests applied. Less favourable results in visual acuity and visual field defects in some other studies may have been caused by a higher ICG concentration [20, 21] and/or hypo-osmolarity of the solvent [8, 19–21]. An experimental study showed retinal toxicity after subretinal, but not after epiretinal, application of ICG in rabbits [43]. Therefore, retinal toxicity may also depend on the type of macular surgery, possibly because the full-thickness retinal hole allows direct contact of a greater amount of ICG with deeper retinal layers and the retinal pigment epithelium in macular hole surgery [19, 20] than in IEM surgery.

In summary, the results of the present study add relevant clinical data to the current debate on the safety of ICG. The removal of epiretinal tissue with or without assistance of ICG improves visual function and reduces macular oedema in most patients. However, since the safety margin is narrow, ICG should be used cautiously. Future work should investigate other vital stains with less or no toxic potential, as recently initiated by Jackson et al. [44] and Haritoglou et al. [45].

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