CLINICAL STUDY

Outcome of ICG-assisted ILM peel in macular hole surgery

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Abstract

Purpose   To investigate whether indocyanine green (ICG) staining of the internal limiting membrane (ILM) improves surgical outcome.
Methods   A total of 34 patients were identified who underwent macular hole surgery with ILM peeling augmented with ICG. These were matched retrospectively with 34 patients who underwent macular hole surgery without the use of ICG. Closure rates from primary and secondary procedures were compared, as were changes in Snellen and Logmar visual acuity.
Results   There was no significant difference between the two groups with reference to demographic features of age, sex, staging of the macular holes, and the proportion subsequently undergoing cataract surgery. The mean follow-up period was 7.7 months in the ICG group and 6.3 months in the non-ICG group. Closure rates from primary surgery were 91.2% in the ICG group and 73.5% in the non-ICG group ($P = 0.056$), whereas overall closure rates following further surgery were similar in both groups (94.1 and 91.2%, respectively). Logmar visual improvement above baseline was achieved in 53% of the non-ICG group compared to 82% of the ICG group ($P = 0.01$). Where primary hole closure occurred, there was no statistically significant difference in visual outcome between the two groups.
Conclusion   ICG-assisted ILM peel in macular hole surgery is associated with a higher closure rate following a single surgical procedure. This difference was found to approach statistical significance ($P = 0.056$). Overall visual improvement was greater in the ICG group ($P = 0.01$); however, this reflected the higher closure rates. Visual outcomes between the two groups were comparable where primary hole closure occurred.
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Introduction

Macular hole was first described by Gass,[1,2] and is characterised by an anatomical opening or dehiscence in the fovea. The mechanism is uncertain, but is believed to involve tangential or anterior/posterior vitreofoveal traction. The four stages of macular hole formation are stage 1A, flattening of the umbo with loss of foveal depression and a yellow macular spot, stage 1B, loss of the foveal depression with a yellow macular ring, stage 2, a small full thickness retinal hole inside the yellow ring, stage 3, $d < 400\,\mu$m hole without separation of the posterior hyaloid face from the macular, stage 4, $d > 400\,\mu$m hole with separation of the posterior hyaloid from the macular and optic disc. Macular holes at stage 3 or 4 are typically associated with poor acuity and symptoms of distortion that rarely improve spontaneously.

Vitrectomy to close macular holes was first described in 1991.[3] The benefits of surgery for stages 2–4 macular holes have been demonstrated.[4,5] Closure rates vary between 60 and 100% in reported series, and it has been shown that with ILM peeling the rates of anatomical closure are greater and late reopening reduced.[6–11]

Visualisation of the internal limiting membrane (ILM) is difficult and failure to successfully remove the ILM may contribute to failure in hole closure. Indocyanine green (ICG) is used as an adjunct to the surgery enabling visualisation of the ILM.[12,13] Whether ICG toxicity is clinically significant is controversial. Our study attempts to address this issue using a case–control analysis of macular hole surgery at a UK-based teaching hospital.

Methods

In total, 34 consecutive patients were identified with stage 3 and 4 macular holes of less than 12 months duration, who underwent macular hole surgery with ILM peel augmented with ICG. These were matched retrospectively with 34 patients who underwent macular hole surgery and ILM peel without the use of ICG. Closure rates from primary and secondary procedures were compared as were changes in Snellen and Logmar visual acuity.

All surgery was performed by surgeons with at least 12 months experience in vitreoretinal surgery (PR, CKP, DC, NK), each having performed a minimum of 300 vitrectomy procedures. This included a standard three-port pars plana vitrectomy with removal of the posterior hyaloid. ICG was diluted to 5 mg/ml concentration using balanced salt solution (BSS) and a small volume (approximately 0.1 ml) was injected over the macular, inside the macular arcades. The eye remained fluid filled at this stage, but the continuous infusion of BSS was temporarily halted. The ICG was then removed after a contact time of just 10 s. At this concentration, the ILM staining was consistently intense and uniform. ILM peel was undertaken with a microvitreoretinal blade to initiate the flap and intraocular forceps to peel the ILM in a circular fashion around the macular hole. At the end of surgery, 14% C_3F_8 gas was used to provide tamponade. The patients were instructed to posture for 75–80% of the time over a 2-week period.

The staging of the macular holes was confirmed intraoperatively. The anatomical end points of the macular hole surgery were categorized as 'elevated/open', 'flat/open' and 'flat/closed'.[14] Those classified as 'flat/open' and 'flat/closed' were considered 'closed' in this study. Primary hole closure was also studied as a means of comparing visual outcomes between the two groups without the introduction of confounding factors such as phototoxicity that may accompany multiple procedures.

Statistical analysis of the data was performed using χ^2, Fisher's exact and student's *t*-test.

Results

There were no significant differences between the two groups with reference to demographic features of age ($P = 0.13$), sex ($P = 1.0$), staging of the macular holes ($P = 1.0$) and the proportion subsequently undergoing cataract surgery ($P = 1.0$) (Table 1). The mean follow-up period was 7.7 months (CI 95% 1.5) in the ICG group and 6.3 months (CI 95% 2.7) in the non-ICG group. Closure rates from primary surgery were 91.2% in the ICG group and 73.5% in the non-ICG group ($P = 0.056$), whereas

Table 1 Demographic data and outcomes for all 68 cases studied

	Non-ICG	*ICG*	P-*value*
Number	34	34	
Male	10	10	
Female	24	24	
Age	67.5	69.9	$P = 0.13$
Stage 3	27 (79.4%)	27 (79.4%)	
Stage 4	7 (20.6%)	7 (20.6%)	
F/U period	6.3 months	7.6 months	
Pseudophakic at final F/U	12 (35.3%)	13 (38.2%)	
Residual significant LO	5 (14.7%)	10 (29.4%)	
Preop VA ≥6/24	11 (32.4%)	10 (29.4%)	
Preop VA <6/60	8 (23.5%)	8 (23.5%)	
Number of ops	41	36	
Primary closure	25 (73.5%)	31 (91.2%)	$P = 0.056$
Secondary closure	6/7	1/2	
Overall closure	31 (91.2%)	32 (94.1%)	
Snellen line change	1.00	1.21	$P = 0.62$
≥2 Snellen line improvement	13 (38.2%)	13 (38.2%)	
Postop VA ≥6/24	18 (52.9%)	20 (58.8%)	
Postop VA <6/60	4 (11.8%)	1 (2.9%)	

overall closure rates following further surgery were similar in both groups (94.1 and 91.2%, respectively).

Logmar visual improvement above baseline occurred in 18 patients (53%) in the non-ICG group (Figure 1) compared to 28 patients (82%) in the ICG group (Figure 2) ($P = 0.01$). Amongst those patients where primary hole closure occurred, this difference narrowed to 20/25 patients (80%) in the non-ICG group compared to 27/31 patients (87%) in the ICG group. This difference did not achieve statistical significance ($P = 0.5$). At the end of the follow-up period, both groups contained five patients with a final reduction in VA (Figures 1 and 2) resulting from secondary lens opacity. In addition, the non-ICG group contained one patient with an epiretinal membrane, one patient with cystoid macular oedema, and a single patient with untreated posterior capsular opacification, all causing a reduction in VA.

The mean Snellen line change was +1.21 (CI 95% 0.5) in the ICG group and +1.00 (CI 95% 0.8) in the non-ICG group. Where primary hole closure occurred, there was a significant improvement in Logmar VA in both groups, 0.38 in the ICG group ($P < 0.00l$) and 0.45 in the non-ICG group ($P < 0.005$) (Table 2). These differences in visual outcome between the groups were not statistically significant ($P = 0.64$ and 0.46). Amongst those patients with primary hole closure, the mean Snellen line change
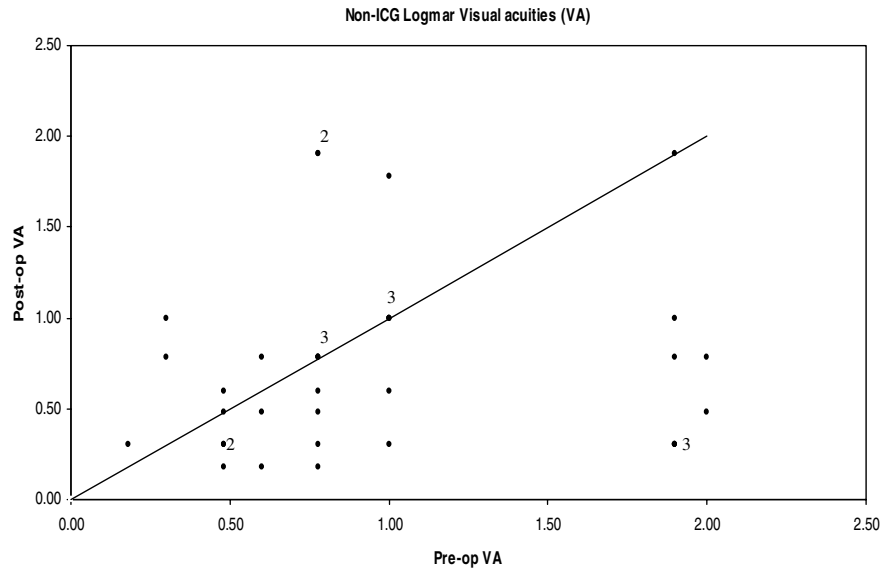
Figure 1 Non-ICG Logmar visual acuities pre- and postoperatively. Those cases represented below the diagonal line demonstrated an improvement in postoperative visual acuity.

Figure 2 ICG Logmar visual acuities pre- and postoperatively. Those cases represented below the diagonal line demonstrated an improvement in postoperative visual acuity.
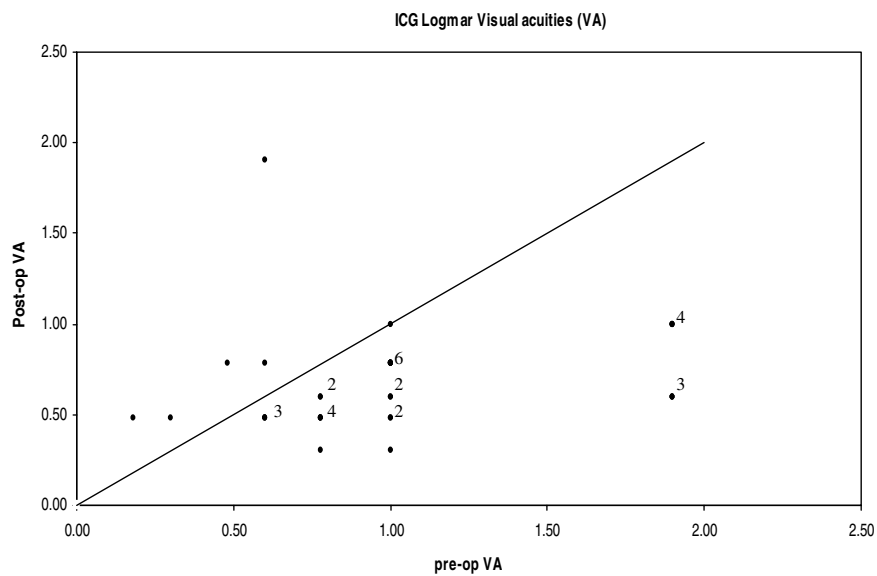
Table 2 Visual outcomes for 56 cases with successful primary hole closure

	Non-ICG (n = 25)	*ICG* (n = 31)	P-*value*
Preop Logmar	0.99	1.00	0.93
Final Logmar	0.55 ($P < 0.005$)	0.65 ($P < 0.001$)	0.26
Mean Logmar change	0.45	0.38	0.64
Snellen line change	1.64	1.26	0.46
$\geq$2 lines of improvement	13/25 (52%)	12/31 (39%)	0.32

was 1.26 in the ICG group and 1.64 in the non-ICG group ($P = 0.46$). In the primary closure groups, if visual improvement is defined as a gain of $\geq$2 lines of Snellen acuity then this was achieved by 39% of the ICG group compared with 52% of the non-ICG group. This difference failed to achieve significance ($P = 0.32$).

Immediate postoperative complications included one retinal detachment, one iris prolapse, two vitreous haemorrhages, and five patients with transient elevated IOP. All these complications were treated successfully and without any adverse visual consequences. There were no episodes of late reopening of any macular holes.

Discussion

Macular holes can cause significant visual disability and visual loss. In all, 15% of patients develop a second macular hole in the opposite eye.[15] Vitrectomy surgery has been shown to be effective in the closure of stage 2–4 macular holes.[4,5] ILM contains myofibroblasts that contract and are thought to contribute to macular hole enlargement.[16] Removal of the ILM around the hole has improved success in idiopathic hole closure.[8]

It is often difficult to assess completeness of the ILM peel. ICG stains ILM green, which contrasts with the underlying pink retina enabling the surgeon to ensure complete maculorhexis.

Differing closure rates are reported in the literature, depending on several factors such as the stage and duration of the macular hole and the use of ILM peeling.[5,17] A prospective randomised controlled trial of 129 eyes reported anatomical closure in 69% of patients with just vitrectomy and gas tamponade.[4] With additional ILM peeling, rates of closure have been reported at between 56 and 100%.[6–11] With additional use of ICG-assisted ILM peeling, success rates of 87.8 and 88% have been reported.[12,13] No published series of cases with ILM peeling, with or without ICG, has contained a control group. Our series, although retrospective, has attempted to provide control data. Our data suggest higher primary closure rates where ICG was used (91.2%) compared to those cases where ICG was not used (73.5%). This difference in closure rates approached statistical significance ($P = 0.056$).

There was a significant difference between the two groups amongst those patients achieving Logmar visual improvement above baseline: 53% in the non-ICG group compared to 82% in the ICG group ($P = 0.01$). This simply reflects, however, the higher closure rates in the ICG group. This study demonstrated no statistically significant difference in visual outcomes between the two groups where primary hole closure occurred. Complications relating to ILM peeling include macular oedema, retinal pigment epithelial (RPE) changes, and small, mostly asymtomatic scotomas.[18] Concerns have been expressed over possible RPE atrophy and poor visual outcomes linked to usage of ICG.[19] Retinal pigment epitheliopathy is, however, a well-recognized complication of this surgery in the absence of ICG.[18,20] Intraretinal accumulation of ICG has also been described

and persistent staining observed, however, as yet there have been no conclusive reports of immediate or long-term ICG toxicity.[21,22] *In vitro* experiments with brief exposure of cultured human retinal pigment epithelial cells to indocyanine green show decreased mitochondrial enzyme activity but without any changes to cell morphology or ultrastructure.[23] A more recent study has suggested that human RPE cell exposure to ICG in the presence of acute illumination can illicit cell cycle arrest and apoptosis. A safety level of 0.25 mg/ml of ICG was recommended.[24]

In this study, the concentration used was 5 mg/ml; however, based on these recent reports in the literature we now routinely use a concentration of 0.25–0.5 mg/ml. Previous studies have used different concentrations of ICG, with varying exposure times and volumes. These include an unspecified volume of 5 mg/ml ICG for 3–5 min,[12] concentrations of 0.25, 0.5 and 1.25 mg/ml,[13] 1 mg/ml,[19] 0.5 mg/ml for 1 min,[22] 1 mg/ml for 20 min,[23] and 0.2–1.0 ml of 5 mg/ml ICG for an unspecified time.[25]

Other concerns have been raised about whether the underlying retina is damaged during the peel. It has been reported that ICG only stains the ILM and not the underlying retina, but a recent report on the histological findings in a case series of 10 patients showed that cleavage was not exactly below the ILM but may include inner retinal structures.[25] However, successive attempts at peeling without staining can be equally adverse and time consuming.[9] Other factors that may influence outcome are variations in the concentration, pH, and contact time of ICG with the retina.[25]

A recent animal model has suggested toxic histological changes at intravitreal doses of ICG above 2.5 mg/ml and transient functional ERG changes recordable at lower doses.[26] However, there was a prolonged exposure time of 2 weeks in this model.

ICG can provide a standardised approach with more easily recognised end points and reduced operating time. Our results show that ICG-assisted ILM peel was associated with higher closure rates following a single surgical procedure and overall higher rates of visual improvement. However, where primary hole closure occurred, the visual outcomes between the two groups were comparable.

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