Internal limiting membrane removal in macular hole surgery for severely myopic eyes: a case-control study

A K H Kwok, T Y Y Lai

Aims: To determine the surgical outcome of indocyanine green (ICG) assisted retinal internal limiting membrane (ILM) peeling in macular hole surgery for severely myopic eyes and compare the visual and anatomical outcomes with an emmetropic control group.

Methods: 10 severely myopic eyes (≥6.0 D or greater) of 10 patients with macular holes without retinal detachment were recruited prospectively. All eyes received ICG assisted ILM removal of 3–4 disc diameters around the macular holes. Cases were matched with a prospective control group of 10 emmetropic macular hole patients who underwent identical ICG assisted ILM peeling surgery in the same period.

Results: The mean refractive error in the myopic and control group was −11.8 D and +0.3 D, respectively (two tailed t test, p < 0.001). The mean follow up duration for the myopic and control group was 12.1 and 13.3 months, respectively (two tailed t test, p = 0.63). The primary anatomical closure rate in both groups was 90% (Fisher’s exact test, p = 1.0). For both the myopic and control groups, there were significant improvements in the mean log MAR visual acuity after the surgery with improvements from 0.86 to 0.57 for the myopic group (two tailed t test, p = 0.015) and 0.89 to 0.44 for the control group (two tailed t test, p = 0.002). The mean preoperative and postoperative visual acuity, rates of final visual acuity of 20/50 or better, and improvement of two or more lines were not statistically different between the two groups.

Conclusion: ICG assisted ILM peeling in macular hole surgery for severely myopic eyes without retinal detachment gives promising anatomical and visual outcomes, which are comparable to that of non-severely myopic eyes.

Since the early 1990s, pars plana vitrectomy has been widely accepted as the treatment for idiopathic macular holes. In order to facilitate macular hole closure, removal of the internal limiting membrane (ILM) has been used as a surgical adjunct primarily to counter surface traction and promote the closure of the macular hole. Since the ILM is a thin transparent membrane, it is often difficult to have adequate visualisation intraoperatively for its complete removal without risk of damaging other parts of the retina. Indocyanine green (ICG) dye has been used to stain the ILM and facilitate its removal.

One of the risk factors for macular hole development is severe myopia. Macular hole in severely myopic eyes differs from the idiopathic one as the former seems to be more difficult to close with surgery, and is associated with a higher incidence of retinal detachment. Pars plana vitrectomy, epiretinal membrane removal, gas endotamponade with or without endolaser has been successfully used in most cases of retinal detachment associated with a macular hole in severely myopic eyes. The use of ICG assisted ILM peeling has also been demonstrated to be useful in the management of myopic macular holes with retinal detachment in severely myopic eyes. However, macular holes without retinal detachment in severely myopic eyes were less extensively studied. Through a Medline search, three retrospective studies in the English literature were identified which showed that macular hole surgery in severely myopic eyes could result in both anatomical and visual improvements. The risks of posterior retinal detachment could also be decreased after successful closure of the macular holes in severely myopic eyes. However, because of the retrospective nature, these studies involved various surgical adjuncts like platelet concentrate, and transforming growth factor, with or without preretinal membrane dissection.

We have shown that ICG assisted ILM peeling gives promising anatomical and visual outcomes in idiopathic stage 3 or 4 macular hole surgery. This technique may also be useful in the management of more difficult macular holes like chronic ones or those in severely myopic eyes. The purpose of this prospective study was to evaluate the anatomical and visual outcomes of ICG assisted ILM peeling in macular hole surgery of severely myopic eyes and to compare the outcomes with emmetropic control eyes.

PATIENTS AND METHODS

Consecutive patients aged 18 years or older with macular holes due to severe myopia of 6 dioptres or more undergoing ICG assisted ILM peeling surgery were prospectively recruited between June 2000 and March 2002. Patients with concurrent retinal detachment, macular damage from a subfoveal neovascular membrane, or a Fuchs spot were excluded from the study. Institutional ethical approval was not required. Informed consent was obtained from all patients. The staging of macular holes were confirmed intraoperatively and was categorised according to Gass classification. The size of the macular hole was assessed by comparing it to a peripapillary retinal vein of 125 µm in diameter. Myopic macular hole cases were then matched with prospective control cases of idiopathic macular hole with refractive errors within 2.0 dioptres of emmetropia that were operated on with exactly the same protocol by the same surgeon (AK). Each study eye was matched with a control case immediately before or after the myopic eye underwent surgery.

The surgical technique involved standard subtotal pars plana vitrectomy with removal of the posterior hyaloid. The vitreous base was not dissected. Any visible epiretinal membrane (ERM) was removed with an intraocular forceps.
Preparation of the ICG solution has been described previously.\textsuperscript{6,7} A volume of 0.2 ml of the prepared ICG solution (1 mg/ml) was gently injected over the disc and then the macula with the infusion temporarily stopped. Care was taken to avoid direct injection over the macular hole. After 30 seconds, infusion was resumed and ICG in the vitreous cavity was removed. The ILM would then be stained light green in colour. A myringo-vitreoretinal (MVR) blade or an intraocular forceps was used to initiate a flap of ILM at the temporal raphe 1.5–2.0 disc diameters from the macular hole. An intraocular forceps was used to hold the flap and ILM of 3–4 disc diameters was removed in a circular fashion around the macular hole. The ILM in close proximity to the macular hole was removed in a centripetal direction towards the macular hole. At the end of surgery, 12% perfluoropropane gas was injected. Patients were required to maintain a face down posture for 2 weeks postoperatively.

Preoperative data included age and sex of the patient, axial length and refractive error of the eye, duration of symptoms, stage and size of the macular hole, lens status of the patient, and best corrected Snellen visual acuity (BCVA). Intraoperative data, including any concurrent surgical procedures, degree of ILM staining by ICG, presence or absence of ERM and any intraoperative complications, was noted. Postoperative data, including anatomical status of the macular hole, any postoperative complications, and BCVA during follow up, were recorded. Fundus photographs and fluorescein angiography were performed in all patients to determine the possible toxicity as a result of the use of ICG.

Snellen visual acuity was converted to logarithm of minimal angle of resolution (logMAR) visual acuity for analysis. All data were entered into computer software for statistical analysis (SPSS for Windows v 10.0, SPSS Inc, Chicago, IL, USA). A p value of 0.05 or less was considered statistically significant.

**RESULTS**

Ten eyes of 10 consecutive patients with follow up of at least 6 months were recruited in the myopic group (Table 1). Each eye was matched with a control eye within 2 D of emmetropia. The mean spherical equivalent refraction of the myopic group was -11.3 (SD 5.1) D while that of the control group was -0.8 (1.4) D. There was a statistically significant difference (two tailed t test, p < 0.001) (Table 2). The mean axial length in the myopic group was 27.7 (1.8) mm while that of the control group was 23.0 (1.0) mm. The myopic group was statistically significant longer (two tailed t test, p < 0.001). There were four females and six males in the myopic group and three females and seven males in the control group (Fisher’s exact test, p = 1.0). The mean age of the patients in the myopic group and the control group was 48.3 (12.0) years and 58.0 (11.0) years, respectively. This difference was not statistically significant (two tailed t test, p = 0.076). There was also no statistical difference in the number of eyes with stage 2, 3, or 4 macular hole between the myopic and control groups as listed in Table 2.

The mean follow up duration for the myopic and control group was 12.1 and 13.3 months, respectively (two tailed t test, p = 0.63). The mean size of the macular hole in the myopic and control group was 580 (275) µm and 415 (97) µm, respectively (two tailed t test, p = 0.10). The mean duration of symptoms before surgery was 8.1 (7.4) months for the myopic group and 13.0 (7.7) months for the control group (two tailed t test, p = 0.16). There were three (30%) chronic holes of more than 12 months’ duration in the myopic group compared to five (50%) in the control group (Fisher’s exact test, p = 0.63).

ICG stained the ILM in all cases of both groups that enabled the surgeon to visualise the ILM for removal. Generally, the ILM staining was less saturated in the myopic group, especially in those with extreme degree of myopia. The ILM

**Table 1** Patient details of the 10 myopic and 10 control macular holes

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Eye</th>
<th>Stage of hole</th>
<th>Size (mm)</th>
<th>Axial length (mm)</th>
<th>Duration of symptoms (months)</th>
<th>Follow up (months)</th>
<th>Preop VA</th>
<th>Postop VA</th>
<th>Preop logMAR</th>
<th>Postop logMAR</th>
<th>Final VA</th>
<th>Final logMAR</th>
<th>Hole status after surgery</th>
<th>Complications</th>
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<tr>
<td>1</td>
<td>F</td>
<td>40</td>
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<td>2</td>
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<td>22.64</td>
<td>6</td>
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<td>2.00</td>
<td>2.00</td>
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<tr>
<td>2</td>
<td>M</td>
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<td>L</td>
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<td>0.10</td>
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<td>F</td>
<td>40</td>
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<td>23.17</td>
<td>4</td>
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<td>49</td>
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<td>22.64</td>
<td>24</td>
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<tr>
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<td>F</td>
<td>65</td>
<td>L</td>
<td>4</td>
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<td>14</td>
<td>6</td>
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<td>0.10</td>
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<td>7</td>
<td>F</td>
<td>65</td>
<td>L</td>
<td>3</td>
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<td>27.94</td>
<td>14</td>
<td>9</td>
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<td>1.00</td>
<td>1.00</td>
<td>0.10</td>
<td>0.10</td>
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<tr>
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<td>50</td>
<td>R</td>
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<td>24</td>
<td>7</td>
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<td>0.00</td>
<td>2.00</td>
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<td>0.10</td>
<td>0.10</td>
<td>Open</td>
<td>No</td>
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<tr>
<td>9</td>
<td>M</td>
<td>38</td>
<td>L</td>
<td>3</td>
<td>6.50</td>
<td>25.98</td>
<td>2</td>
<td>16</td>
<td>0.10</td>
<td>0.00</td>
<td>6.50</td>
<td>6.50</td>
<td>0.10</td>
<td>0.10</td>
<td>Closed</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>66</td>
<td>L</td>
<td>3</td>
<td>1.50</td>
<td>21.55</td>
<td>7</td>
<td>8</td>
<td>0.10</td>
<td>0.00</td>
<td>1.50</td>
<td>1.50</td>
<td>0.10</td>
<td>0.10</td>
<td>Closed</td>
<td>Yes</td>
</tr>
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</table>
was also thinner and more friable in the myopic group, so that the ILM was removed in pieces rather than one or two pieces as in the control group. All 20 patients were phakic at the time of surgery. Combined macular hole surgery together with phacoemulsification and implantation of intraocular lens was performed in one eye (10%) for the myopic group and two eyes (20%) for the control group. None of the eyes in the myopic and control groups developed any intraoperative complications.

The mean preoperative logMAR visual acuity for the myopic and control groups was 0.86 (0.29) and 0.89 (0.29), respectively (two tailed t test, p = 0.81). At the time of last follow up, the final mean logMAR visual acuity for the myopic group was 0.57 (0.36). The improvement in vision after myopic macular hole surgery was statistically significant (two tailed t test, p = 0.015). The improvement in Snellen equivalent was from 20/145 to 20/74. For the control group, there was also a significant improvement in visual acuity with a final mean logMAR visual acuity of 0.44 (0.36) (two tailed t test, p = 0.002). The improvement in Snellen equivalent was from 20/155 to 20/55. The difference in final logMAR visual acuity between the myopic and control group was not statistically different (two tailed t test, p = 0.41) (Table 3).

A final visual acuity of 20/50 or better was achieved in five (50%) eyes in the myopic group versus seven (70%) eyes for the control group. This difference was not statistically different (Fisher's exact test, p = 0.65). Six (60%) of the myopic eyes improved by two or more lines after macular hole surgery compared to nine (90%) in the control group (Fisher's exact test, p = 0.30). One eye in the myopic group had a decrease in three lines of vision due to development of nuclear sclerotic cataract and is awaiting cataract operation. None of the control group had a decrease in vision after surgery.

The anatomical success rates were identical for both the myopic and control groups with nine (90%) eyes in each group achieving successful closure of the macular hole after one operation (Fisher's exact test, p = 1.0). Neither of the two patients with open holes agreed to receive another operation.

Five (55.6%) of the nine phakic patients in the myopic group developed nuclear sclerotic cataract with one patient undergoing phacoemulsification and implantation of intraocular lens and another two patients awaiting cataract operation. Seven (87.5%) of the eight phakic eyes in the control group developed nuclear sclerotic cataract with five eyes undergoing subsequent phacoemulsification and implantation of the intraocular lens.

Besides the development of cataract, there were two cases of macula on rhegmatogenous retinal detachment related to peripheral horseshoe tears in the myopic group postoperatively. One of the cases developed retinal detachment 4 weeks after operation and the other 2 months postoperatively. Both cases underwent scleral buckling and retinal cryopexy and both retinas reattached successfully with a final visual acuity of 20/50. The difference in the number of postoperative retinal detachments was not statistically significant between the two groups (Fisher's exact test, p = 0.47). There was no direct intraoperative or postoperative complication related to ICG assisted ILM peeling. No ICG related toxicity was detected on fluorescein angiograms. During the follow up period, no clinical toxicity like retinal oedema or retinal pigment epithelial (RPE) change was identified.

**DISCUSSION**

Previous retrospective studies on severely myopic eyes with macular holes have demonstrated that vitreous surgery can lead to anatomical and visual improvements (Table 4). Various types of adjuncts including transforming growth factor β2, platelet growth factor, and autologous platelet concentrate have been used in these studies. The mean primary anatomical closure rate for these studies was 75% with a range of 60% to 87.5%. We achieved a primary anatomical closure rate of 90% in our prospective study, despite the mean spherical equivalent refraction was the most myopic in our series. This rate seems superior to the closure rates of 60% and 77% for macular hole surgery in high myopes reported by Patel et al.

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**Table 2** Comparison of preoperative characteristics between myopic and control group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Myopic group</th>
<th>Control group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eyes</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>6 (60%)</td>
<td>7 (70%)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.3 (12.0)</td>
<td>58.0 (11.0)</td>
<td>0.076†</td>
</tr>
<tr>
<td>Mean refractive error (dipteres)</td>
<td>−11.8 (5.1)</td>
<td>+0.3 (1.4)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Mean axial length (mm)</td>
<td>27.7 (1.8)</td>
<td>23.0 (1.0)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Mean preoperative logMAR VA</td>
<td>0.86 (0.29)</td>
<td>0.89 (0.29)</td>
<td>0.81†</td>
</tr>
<tr>
<td>Stage of macular hole</td>
<td>Stage 2</td>
<td>Stage 2</td>
<td>1.0*</td>
</tr>
<tr>
<td></td>
<td>Stage 3</td>
<td>Stage 3</td>
<td>0.35*</td>
</tr>
<tr>
<td></td>
<td>Stage 4</td>
<td>Stage 4</td>
<td>0.66*</td>
</tr>
<tr>
<td>Mean duration of symptoms (months)</td>
<td>8.1 (7.4)</td>
<td>13.0 (7.7)</td>
<td>0.16†</td>
</tr>
<tr>
<td>Mean follow up duration (months)</td>
<td>12.1 (5.6)</td>
<td>13.3 (5.4)</td>
<td>0.63†</td>
</tr>
</tbody>
</table>

*Fisher’s exact test.  †Two tailed t test.

**Table 3** Comparison of outcomes between myopic and control group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Myopic group</th>
<th>Control group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean final logMAR VA</td>
<td>0.57 (0.36)</td>
<td>0.44 (0.36)</td>
<td>0.41†</td>
</tr>
<tr>
<td>Final VA of 20/50 or better</td>
<td>5 (50%)</td>
<td>7 (70%)</td>
<td>0.65*</td>
</tr>
<tr>
<td>Improved VA of 2 or more lines</td>
<td>6 (60%)</td>
<td>9 (90%)</td>
<td>0.30*</td>
</tr>
<tr>
<td>Anatomical closure</td>
<td>9 (90%)</td>
<td>9 (90%)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Formation of cataract</td>
<td>3 (33.3%)</td>
<td>7 (87.5%)</td>
<td>0.29*</td>
</tr>
<tr>
<td>Postoperative cataract surgery</td>
<td>1 (20.0%)</td>
<td>5 (71.4%)</td>
<td>0.24*</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>2 (20.0%)</td>
<td>0 (0.0%)</td>
<td>0.47*</td>
</tr>
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</table>

*Fisher’s exact test.  †Two tailed t test.
and Sulkes et al., respectively.26,27 In these two series, transforming growth factor β2 and/or platelet growth factor were used without ILM peeling. In the series performed by Gracia-Arumi et al., in which only thickened ILM were removed, a primary closure rate of 87.5% was achieved.28 All three open cases in that series were cases in which ILM removal was not performed. Therefore, ILM peeling may have a role in macular hole surgery of severely myopic eyes by increasing the anatomical success rate. Additionally, our anatomical success rate is similar to other studies in which ILM peeling, with or without ICG staining, was performed as a surgical adjunct for non-myopic macular hole surgery.29

A final visual acuity of 20/50 or better was achieved in 39% and 50% in two of the previous myopic macular hole studies.26,27 With the use of ICG assisted ILM removal, 50% of eyes in our series were able to achieve this level of visual acuity at the last follow up. Additionally, our result was similar to rates of 37.5% to 56% reported in other series in which ILM peeling was performed for macular holes in non-myopic eyes.4,5 This suggests that the encouraging visual outcome of our severely myopic eyes was comparable to those non-myopic ones previously reported. Similarly, the final Snellen equivalent for the myopic and control groups in our study was 20/63 and 20/70, respectively while the corresponding logMAR visual acuity was 0.57 and 0.44, respectively. The difference was not statistically significant (p=0.41). In the retrospective case-control study by Sulkes et al., the final Snellen equivalent was 20/100+2 and 20/200 in their myopic and control group, respectively.5 The difference was marginally statistically significant (p=0.048).

The development of nuclear sclerotic cataract was the commonest postoperative complication in both the myopic and control groups in our study, as previously reported.26 Combined phacoemulsification and vitrectomy therefore may have a role in macular hole surgery.26 Postoperative retinal detachment was another complication that encountered in this study. Both cases occurred in the myopic group and were due to peripheral horseshoe tears. Garcia-Arumi et al. also reported a case of peripheral retinal detachment due to a horseshoe tear 4 months postoperatively in their myopic macular hole series.27 Postoperative retinal detachment in vitrectomy for macular hole is a well known complication. Several large scale studies have demonstrated that postoperative retinal detachment occurred in 11% to 14% of cases.25–29 In view of this potential complication, additional prophylactic scleral buckle or indirect ophthalmoscopic laser cerclage from the ora serrata to the equator on top of standard vitrectomy have been used to prevent retinal detachment after macular hole surgery.28–30

Potential retinal and RPE damages related to the use of ICG for ILM peeling have been reported previously in some studies.31–34 Similar to our past experience using this technique in managing idiopathic macular holes, we did not detect any RPE atrophy related to ICG toxicity in both clinical and angiographic examinations in this series.35 This may be related to the relatively low concentration of ICG employed with a short intravitreal duration. We have demonstrated an upregulation of apoptosis related genes, p53 and bax, and cell cycle arrest protein, p21, in RPE cells treated with illumination and high doses of ICG.36

There were several limitations in our study. The relatively small sample size in our study would lower the power of statistical analysis and might result in type II errors. The number of eyes requiring subsequent cataract extraction also differed between the myopic and control groups.

In conclusion, ICG assisted ILM removal of highly myopic macular hole without retinal detachment appears to give a promising anatomical closure rate and visual outcome when compared to non-myopic macular holes.

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