·Clinical Research·

Macular hole surgery with or without internal limiting membrane peeling

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Abstract

• AIM: To compare the anatomical and visual outcome in primary idiopathic macular hole surgery with or without indocyanine green (ICG) stained internal limiting membrane (ILM) peeling.

• METHODS: The medical records of the 40 consecutive eyes receiving primary idiopathic macular hole surgery with gas as internal tamponade performed by a single surgeon were retrospectively reviewed and analyzed. All eyes had a follow-up of at least 6 months. In the initial 22 consecutive eyes, no ILM peeling was performed (non-ILM peeling group). The subsequent 18 eyes underwent surgery with ICG stained ILM peeling (ILM peeling group).

• RESULTS: The primary anatomical closure rates were 88.9% and 59.1% in the ILM peeling group and non-ILM peeling group, respectively. The difference was statistically significant (Fisher's exact test, P=0.038). Improvement in visual acuity was more marked in the ILM peeling group than in the non-ILM peeling group, with a mean improvement of 3.6 and 1.3 lines respectively (two-tailed t-test, P=0.036). There were significantly more cases with improvement of two or more lines of visual acuity after surgery, with 66.7% in the ILM peeling group and 31.8% non-ILM peeling group (Chi-square test, P= 0.028). However, there was no significant difference in the final postoperative logMAR best corrected visual acuity(BCVA) between the two groups (two-tailed t-test, P=0.073).

• CONCLUSION: Based on this study, ICG stained ILM peeling seems to improve the anatomical and visual outcome in primary idiopathic macular hole surgery. Further studies in this aspect are warranted.

• KEYWORDS: indocyanine green; internal limiting membrane; macular hole; surgery

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INTRODUCTION

A decade ago Kelly and Wendel[1] first demonstrated the successful closure of macular hole by pars plana vitrectomy and fluid-gas exchange. Since then, this surgery has been proven to be useful in the treatment of Stage 2, 3 and 4 macular holes[2,3]. Various adjuncts like growth factors, as well as surgical refinement such as retinal internal limiting membrane (ILM) peeling, have also been studied in order to improve the closure rate of macular hole surgery. Most studies on the role of ILM peeling in macular hole surgery, with or without the use of indocyanine green staining (ICG), have reported favourable anatomical and visual outcomes [4-10]. In our previous studies, we demonstrated that removal of ICG stained ILM around idiopathic macular hole was confirmed with histology and might contribute to macular hole closure [9-11]. Without an ILM staining technique, it may be difficult for vitreoretinal surgeons to differentiate between complete and partial ILM removal during macular hole surgery [12]. However, ICG stained ILM peeling may risk damaging the retina. Asymptomatic paracentral scotomata detected by microperimetry and potential ICG toxicity in retinal pigment epithelium culture have been reported[13-15]. An alteration of retinal physiology after the removal of ILM in the macular region has also been suggested by the selectiv delay of recovery in focal macular electroretinogram b-wave six months after macular hole surgery; however, no adverse effect on visual acuity was found [16]. Smiddy *et al*[17] have concluded that the peeling of ILM was not essential for both anatomical and visual success in macular hole surgery. It seems that the role of ILM peeling in macular hole surgery is not yet well defined.

The purpose of this study is to determine the anatomical and visual outcome in primary idiopathic macular hole surgery, with or without ICG-assisted ILM peeling, by analyzing the surgical outcomes of consecutive patients operated by a single surgeon with a minimum follow-up of six months.

MATERIALS AND METHODS

Subjects The medical records of the last 40 consecutive eyes that underwent primary idiopathic macular hole surgery with gas as internal tamponade by a single surgeon (AK) was retrospectively reviewed and analyzed. Patients of age are less than 18, with a follow-up less than 6 months, or with myopia more than 6 diopters, or with traumatic or secondary macular holes were excluded. In the initial 22 consecutive eyes, no ILM peeling was performed (non-ILM peeling group). The subsequent 18 eyes all received ICG-assisted ILM peeling (ILM peeling group). Informed consents were obtained from all patients prior to surgery.

Methods The surgical technique involved in the two groups was identical except for the ILM peeling. No other adjuvant such as growth factor, laser, serum or platelet concentrate was used. All patients received standard subtotal three-port pars plana vitrectomy with removal of the posterior hyaloid when necessary. Any visible epiretinal membrane was removed with intraocular forceps. At the end of surgery, a two-stage fluid-air exchange followed by 12% perfluoro-propane/air exchange was performed. Patients were required to maintain a facedown posture for two weeks postoperatively.

In the non-ILM peeling group, no attempt was made to remove any invisible membrane. In the group with ILM peeling, an ICG solution of volume 0.2mL and concentration 0.25-1.25g/L was used. Preparation of ICG has been previously described [11]. Briefly, twenty-five milligrams of ICG were reconstituted with the 10mL solution provided. 0.5mL of this solution (2.5g/L) was further diluted with 4.5, 2 and 0.5mL of balanced salt solution respectively, so that the final concentration was 0.25, 0.5 and 1.25g/L, respectively. The corresponding osmolarity was 292, 295 and 299mmol/L, respectively; while that of BSS was 290mmol/L. The prepared ICG solution was then injected gently over the disc and then the macular region with the infusion temporarily stopped. After 30 seconds, infusion was resumed and all excessive ICG in the vitreous cavity was removed. Using a myringo-vitreo-retinal (MVR) blade, a horizontal superficial cut at the temporal raphe was performed to create an ILM edge. A flap could be created by circular movement with the same MVR blade along the direction of nerve fiber layer. The elevated edge and the flap became more conspicuous with a darker saturated green color. The flap was then held by a pair of intraocular forceps and the ILM was removed in a circular fashion about 3-4 disc-diameter centered around the macular hole. ILM close to the macular hole was removed in a direction towards the hole.

Preoperative data including age and sex of the patients, duration of the macular hole, stage of the macular hole, size of the macular hole, lens status of the patients, and the preoperative best corrected visual acuity (BCVA) were recorded. The size of a macular hole was assessed comparing it to a peripapillary retinal vein of 125μm in diameter [3]. Intraoperative data including all concurrent surgical procedures and complications were charted. Postoperative data including anatomical status of the macular hole and BCVA at six months and at the last follow-up were recorded. Anatomical closure of a macular hole is defined as a closed hole without a visible edge or a flat hole without a rim of subretinal fluid. All postoperative complications arising from the surgery were also documented.

Statistical Analysis All Snellen BCVA were converted to logarithm of the minimum angle of resolution (logMAR) BCVA for analysis. Each 0.1 logMAR unit represents one line of Snellen visual acuity [18]. The data were entered into SPSS software (SPSS Inc, Chicago, IL) for statistical analysis. Comparisons of categorical variables in the two groups including stage of the macular hole, number of chronic macular holes, number of macular holes closed after surgery, and number of cases with 2 or more lines of BCVA improvement were performed using Fisher's exact tests or Chi-square tests. Two-tailed t-tests were conducted for analyses of continuous variables between the two groups and these included age, duration of follow-up, preoperative and postoperative logMAR BCVA, and the mean lines of BCVA improvement. P value <0.05 was considered statistically significant.

RESULTS

Preoperative Demographics Forty eyes of 39 patients with follow-up of at least six months were included in the study. There were 28 (70.0%) females and 12 (30.0%) males. The mean±standard deviation (SD) age of all patients was 61.6±12.1 (range, 35-78) years. There were two patients aged 40 years or less and were classified as idiopathic macular hole after excluding trauma or high myopia as the causes of macular holes. The mean ±SD follow-up duration was 19.6±14.3 (range, 6-51) months. All 40 eyes were phakic prior to surgery. Four (10.0%), 20(50.0%) and 16 (40.0%) eyes had Stage 2, 3 and 4 macular holes respectively. There were 83.3% eyes and 95.5% eyes with Stage 3 or 4 idiopathic macular holes in the ILM peeling and non-ILM peeling group respectively. The median size of macular holes was 500 (range,150-750)μm. There were 18 (45.0%) chronic macular holes with duration of symptoms longer than 12 months with 9 in either of the ILM and non-ILM groups (Chi-square test, P=0.57). The mean ±SD preoperative BCVA for the 40 eyes was 0.99±0.26, which was a Snellen equivalent of 20/197 (range, 20/50 to 20/400). The mean ± SD preoperative logMAR BCVA for the ILM peeling and non-ILM peeling group was 1.00 ±0.29 and 0.98 ±0.23 respectively(two-tailed t-test, P=0.80). The major characteristics for the two groups were similar except for the duration of follow-up.

Intraoperative Data Macular hole surgery was performed in 22 right eyes and 18 left eyes. Eighteen (45.0%) eyes had ICG-assisted ILM peeling compared with 22 (55.0%) eyes without ILM peeling. Combined macular hole surgery together with phacoemulsification and implantation of intraocular lens was performed in 10 (25%) eyes. More eyes in the non-ILM peeling group had combined surgery (8 out of 22 eyes) but the difference was not statistically significant (Fisher's exact test, P=0.069). No intraoperative complication was observed in either group.

Anatomical and Visual Outcomes Twenty-nine (72.5%) of the 40 eyes had successful primary anatomical closure of the macular hole at the last follow-up. Sixteen (88.9%) of the 18 eyes had anatomical closure of the macular hole in the ILM peeling group, comparing to 13(59.1%) eyes in the non-ILM peeling group. The difference in anatomical closure rate between the two groups was statistically significant (Fisher's exact test, P=0.038). Re-operation was performed in one of the two open macular holes in the ILM peeling group and five of the nine open macular holes in the non-ILM peeling group. The re-operated macular hole in the ILM peeling group remained open after the second operation, whereas three of the five macular holes in the non-ILM peeing group closed after the second operation.

Eleven (61.1%) of the 18 chronic macular holes with duration longer than 12 months had anatomical closure compared to 18 (81.8%) of the 22 non-chronic macular holes. This difference was not statistically significant (Fisher's exact test, P=0.14). The closure rates of chronic macular hole were 77.8% and 44.4% in the ILM peeling group and the non-ILM peeling group respectively. This difference was not statistically significant (Fisher's exact test, P=0.14).

For all 40 eyes, 19 (47.5%) eyes had visual acuity improvement of two or more lines after surgery at the last follow-up. Seventeen (42.5%) eyes had a final visual acuity within one line of the preoperative visual acuity. The mean ± SD postoperative logMAR BCVA at the last follow-up was 0.76±0.37, which is a Snellen equivalent of 20/117 (range, 20/25 to 20/400). The improvement in logMAR BCVA after macular hole surgery was significantly more marked (two-tailed t-test, P<0.001). The mean improvement in Snellen BCVA was 2.3(range: -3 to 10) lines.

The mean postoperative logMAR BCVA at the last follow-up for the ILM peeling group was better than that for the non-ILM peeling group, with a mean postoperative logMAR BCVA of 0.64 and 0.85 respectively. However, the difference was not statistically significant (two-tailed t-test, P=0.073). Improvement in BCVA was significantly more marked in the ILM peeling group than in the non-ILM peeling group, with mean improvement of 3.6 and 1.3 lines respectively (two-tailed t-test, P=0.036). After excluding eyes with open macular holes after primary surgery, the 16 eyes with closed holes in the ILM peeling group improved by a mean of 4.3 lines whereas the 13 eyes with closed holes in the non-ILM peeling group improved by 2.4 lines. The difference was not statistically significant (two-tailed t-test, P=0.151).

In the ILM peeling group and non-ILM peeling group, there was respectively 66.7% and 31.8% patients with improvement of two or more lines of BCVA with significant difference (Chi-square test, P=0.028); there were respectively 27.8% (five out of 18 eyes) and 18.2% (four out of 22 eyes) eyes with final BCVA of 20/50 or better without significant difference (Fisher's exact test, P = 0.364). After excluding eyes with open macular holes, there were 31.3% eyes (5 out of 16 eyes) with final BCVA of 20/50 or better in the ILM group, compared with 30.8% (4 of 13 eyes) in the non-ILM peeling group. This difference was not statistically different (Fisher's exact test, P=0.647).

The mean improvement for eyes with non-chronic macular holes was 3.4 lines compared with 1.0 line for chronic macular holes. The difference was statistically significant (two-tailed t-test, P=0.032). The mean loss of BCVA for open macular hole was 0.5 line compared to improvement of 3.2 lines for holes with anatomical success. There was statistically significant difference in the lines of BCVA improvement between the open and closed groups (two-tailed *t*-test, $P< 0.001$).

In terms of complications, there was one case of postoperative vitreous hemorrhage in the ILM peeling group. It was managed with external gas/fluid exchange six weeks postoperatively. The final BCVA of the patient was 20/100 with 6 lines of improvement and a closed macular hole.

DISCUSSION

ILM forms the innermost layer of retina and the outer boundary of vitreous. It contains collagen fibrils, proteoglycans, the basement membrane, the plasma membrane of the Müller cells and possibly other glial cells of the retina[19]. In our previous histological study, actin staining-positive cells, scattered or layers of presumably myofibrocytes and clinically invisible ERMs were found among specimens of ICG stained ILM[9]. Yooh *et al* [20] also reported similar findings and suggested enlargement of macular hole was due to the contraction of myofibroblasts on the inner surface of ILM. Removal of ILM and adherent ERM around a macular hole seems to be a reasonable surgical approach, considering the mechanical mechanisms of idiopathic macular hole formation.

The anatomical closure rate of Stage 3 or 4 macular holes reported in various randomized clinical trials without any adjunct varies from 53% to 81%[3,21-23]. The mean anatomical closure rate of these four series was 66%. In our study, the primary anatomical closure rates were 88.9% in the ILM peeling group and 59.1% in the non-ILM peeling group and the difference was statistically significant(P=0.038). In view of the high rate of Stage 3 and 4 macular holes in our studied eyes, the anatomical closure rate in the ILM peeling group was encouraging while that of the non-ILM peeling group was comparable to the results of the above four randomized clinical trials [3,21-23]. Although some surgeons reported very high anatomical success rate in their own series without any adjunct, a recent series reported a primary closure rate of 56% in Stage 3 or 4 macular hole surgery[24].

Several studies have reported on the role of ILM peeling in macular hole surgery, with or without the use of ICG staining[4-11,17,25]. Although there were variations of methods among different series, our anatomical success rate was similar to these reports. Anatomical success rate of 91% -100% has been reported in previous series of macular hole surgery with ILM peeling without the use of ICG [4-6,17,25]. With the use of ICG staining, similar anatomical success rate of 88%-100% was reported[7-10]. However, all these series were quite heterogeneous and included macular holes of various stages, traumatic macular holes, myopic macular holes, reoperative cases, as well as cases in which autologus serum was used [4-10,17]. In the series of ICG-assisted ILM peeling, Kadonosono *et al* [7] stained the ILM with ICG using a specially designed cannula with viscomaterial as the carrying medium. In the other three series of ICG-assisted ILM peeling, ICG diluted in balanced salt solution was gently injected over the macula with the infusion temporarily stopped[8-10].

Improvement in visual acuity was more marked in the ILM peeling group than in the non-ILM peeling group, with a mean improvement of 3.6 and 1.3 lines respectively. The difference was statistically significant(P= 0.036). In terms of improvement of two or more lines of visual acuity after surgery, it was 66.7% and 31.8% in the ILM peeling group and non-ILM peeling group respectively. This difference was also statistically significant (P=0.028). Our results are similar to those of other studies involving ILM peeling. Park *et al* [4] and Smiddy *et al* [17] demonstrated an improvement of two or more lines after surgery in 62% and 72% respectively. Similar data were not available from the series of Brooks [6], and information regarding the chronicity of holes was not mentioned in either series by Mester *et al* [5] or Kadonosono *et al* [7]. The visual results in our study may seem less favorable when compared to the series by Da Mata *et al* [8] in which they reported a 96% visual improvement with a mean of five lines. In their series, visual improvement was defined as gain of one or more lines, rather than the commonly used definition of gain of at least two lines. They also used a conversion scale of 20 lines instead of the logMAR scale as used in our study. Additionally, chronic macular holes with duration longer than 12 months were present in 45% cases in our study compared to only 25% in theirs.

After excluding eyes with open macular holes following primary surgery, the mean lines of improvement was 4.3 lines and 2.4 lines for the ILM and non-ILM peeling group respectively. However, the difference was not statistically significant (P=0.151). This could be due to the small sample size or due to the fact that once the macular hole has been closed, the improvement in visual acuity would be comparable between the two groups. In terms of final BCVA of 20/50 or better, it was 27.8% and 18.2% in the ILM peeling group and non-ILM peeling group respectively. This difference was not statistically significan (P=0.364). This seems to be less favorable compared to the rate of 42% reported by one randomized clinical trial without any adjunct [21]. In those series with ILM peeling, with or without ICG staining, a rate of 41.7% to 56% was reported [4,7,8,17]. The difference between the rates in our study and other series may be due to the different duration and stages of macular hole included as well as a high rate of chronic macular hole (45%) in our series. Visual outcome of macular holes closed after ICG-assisted ILM peeling has been suggested to be less favorable than those receiving macular hole surgery without the use of ICG staining[26]. Haritoglou *et al*[27] also suggested that ICG use in ILM peeling may result in less improvement of visual acuity as there may be potential retinal damage due to ICG by altering the cleavage plane to the innermost retinal layers. These findings were not confirmed in our study, in which no statistically significant difference was shown between the visual outcome of primarily closed macular holes in the two groups. ICG-assisted ILM peeling seems not to jeopardize the visual outcome after surgery. Recently, significant retinal pigment epithelial changes after ICG-assisted ILM peeling in macular hole surgery were reported [28]. We did not find such potential problems in our cases.

In our study, the closure rate of chronic macular hole was 77.8% and 44.4% in the ILM peeling group and the non-ILM peeling group respectively. Although the difference was not statistically significant (P=0.167), the anatomical closure rate in the ILM peeling group was comparable to the reported rates of 62.7%, 81.8% and 70.8% in chronic macular hole surgery with or without other adjuncts [29-31]. Further study of the role of ILM peeling in chronic macular hole surgery is needed.

There were inherent limitations in our study. In addition to its retrospective nature, there was variation in the concentration of ICG used, though all of them were on the low side and the volume used was small compared to the vitreous volume. In addition, not all patients uniformly received combined vitreous and cataract surgery. Patients without combined surgery performed may develop cataract postoperatively and this may result in decreased final visual acuity in these patients. Although the only difference in the surgical technique between the two groups was ILM peeling, there might still be an 'experience cumulative effect' in the ILM group that was operated on in the second part of the study period. On the other hand, all ILM peeling cases including those initial ones in the 'learning curve' were included. It seems that the two opposite effects may counterbalance each other.

Based on this study, ICG stained ILM peeling seems to improve the anatomical and visual outcome in primary idiopathic macular hole surgery. Further studies in this aspect are warranted.

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