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RETINAL DISORDERS

Restoration of macular structure as the determining factor for macular hole surgery outcome

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Abstract
Objective The aim of this work is to evaluate the preoperative and postoperative spectral domain optical coherence tomography (SD-OCT) findings as predictors of visual acuity for macular hole (MH) surgery.
Methods Fifty eyes of 46 patients diagnosed with MH and that had undergone 25-g vitrectomy with internal limiting membrane peeling were included in this retrospective study. A complete clinical examination and SD-OCT were performed before and after surgery. Three groups were considered on the basis of the postoperative integrity of photoreceptor inner and outer segment (IS-OS) junction and the external limiting membrane (ELM): group A (11 eyes, both lines disrupted), group B (ten eyes, disrupted IS/OS line and complete ELM), and group C (29 eyes, both lines restored).
Results LogMAR BCVA improved significantly after surgery from an average 0.60±0.29 to 0.19±0.19 ($p<0.01$). No significant differences had been detected preoperatively among these groups ($p\geq0.18$). Postoperative BCVA was significantly better in group C compared to groups A and B ($p\leq0.01$). A significant correlation was found between ELM restoration and postoperative BCVA ($r=-0.63$, $p<0.01$), as well as between IS/OS line restoration and postoperative BCVA ($r=-0.55$, $p<0.01$).
Conclusions Outer retina restoration seems to be the best determining factor for a good visual rehabilitation after MH surgery.

Keywords Macular hole · Vitrectomy · Optical coherence tomography

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Introduction

The surgical procedure for macular hole (MH) management consists of vitrectomy with internal limiting membrane (ILM) peeling. The removal of ILM improves functional results and anatomical success rates [1–3], but the visual outcome is variable depending on how the MH repair is produced [4, 5].

The correlation between preoperative optical coherence tomography (OCT) findings and the anatomical [6] and functional [7–9] outcomes after MH surgery have been studied. Recently, it has been demonstrated the relevance of the restoration of the outer retina on visual acuity results by using the time domain (TD) [10, 11] and spectral domain

(SD) OCT technology [12–17]. Specifically, the integrity of the photoreceptors' inner segment (IS) and outer segment (OS) junction and the ELM has been identified by most of the authors as critical for the subsequent restoration of visual acuity after surgery.

The objective of our study was to evaluate the SD-OCT preoperative and postoperative findings as predictors of visual acuity for macular hole (MH) surgery.

Patients and methods

We have performed a retrospective study including 50 eyes of 46 patients diagnosed with idiopathic MH grade 2 (seven eyes), grade 3 (16 eyes), and grade 4 (27 eyes) according to Gass [18, 19], operated on at the Alicante Institute of Ophthalmology by the same surgeon (JMR-M) with at least 6 months of follow-up. This study was approved by the local ethics committee of this institution and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained after explaining the nature of the procedure prior to surgery. Data gathering was approved by the local ethics committee.

A 25-g vitrectomy under peribulbar anesthesia was performed in all cases. Detachment of the posterior hyaloid was induced by suction with the vitrectomy probe around the optic disc if necessary. ILM peeling was performed after staining with brilliant blue (Brilliant Peel, Fluoron Co.). A circular area of ILM peeling of about two optic disk diameters was performed in all cases. Air–gas exchange with 14% perfluoropropane was performed and face down position was maintained for 1 week after surgery. If epiretinal membranes (ERM) were present, they were stained and eliminated before ILM peeling.

Pre and postoperative best-corrected visual acuity (BCVA) measured with ETDRS charts and SD-OCT images (cube and raster with proper centering scans in the center of the MH, Topcon 3D-OCT 2000, Topcon Medical Systems, Inc. Japan) were obtained. Two preoperative parameters were measured according to our previous experience [18, 19]: minimal diameter of MH and MH base diameter at the level of retinal pigment epithelium (RPE). Postoperatively, two independent and masked investigators (JMR-M and FL) interpreted the SD-OCT images. When a disagreement between examiners in the interpretation of one specific OCT image occurred, a third investigator (JAM) was consulted for the final decision. Restoration of the integrity of the back-reflection lines from the IS/OS and ELM was determined according to the criteria defined by Wakabayashi et al. [14]. Eyes were divided into three groups on the basis of the postoperative integrity of these lines: group A (disruption of both lines), group B (disruption of the IS/OS line with integrity of the ELM) and group C (restoration of both lines). No cases showing simultaneously a complete IS/OS line and a disrupted ELM were observed in our sample. Phacoemulsification with IOL implantation was performed in the event of cataract occurrence during the follow-up period. In such cases, only the visual outcomes after surgery were reported.

The statistical analysis was performed using the SPSS software version 15.0 for Windows (SPSS, Chicago, IL, USA). Non-parametric statistics were performed (significance level $p<0.05$): Wilcoxon rank-sum test (preop-postop comparisons), Kruskal–Wallis test (comparison of independent groups) using Mann–Whitney test with Bonferroni's adjustment for post-hoc analysis, and Spearman correlation coefficient. Finally, ROC curve analysis was performed to obtain cut-off values of the minimal diameter and base diameter for the prediction of postoperative ELM and/or IS/OS disruption.

Results

A total of 13 patients were females. Mean age was 70.8 ± 8.1 years, ranging from 53 to 87 years. Mean follow-up after MH surgery was 35.3 ± 15.5 months (range, 6 to 48). Primary successful MH closure was achieved in 96% of cases (48/50). A second vitrectomy was performed in the two cases of MH reopening using the same surgical protocol, but with a wider area of ILM peeling: one eye with final LogMAR BCVA of 0.3 (absence of both IS/OS line and ELM; follow-up 57 months), and the other eye with final LogMAR BCVA of 0.2 (restoration of ELM only; follow-up 10 months). Forty-one eyes of the current sample were phakic (82%, 41/50). Cataract surgery was performed in 33 of those eyes (80.5%, 33/41) during the follow-up.

LogMAR BCVA improved significantly after surgery from a mean value of 0.60 ± 0.29 (range, 0.15 to 1.52) to a mean value of 0.19 ± 0.19 (range, 0.00 to 0.82) at the last follow-up visit ($p<0.01$; Wilcoxon rank-sum test). BCVA gain (≥1 ETDRS lines) was observed in 47 eyes, whereas no change was observed in two eyes. Visual acuity decrease was observed only in one eye.

Mean preoperative minimal diameter of MH was 398.8 ± 155.5 µm (range, 157 to 810) and mean base diameter was 738.0 ± 281.3 µm (range, 237 to 1,235). A statistically significant positive correlation was found between the postoperative LogMAR BCVA and MH base diameter ($r=0.51$; $p<0.01$). No significant correlation was detected between postoperative LogMAR BCVA and the minimal diameter of MH ($r=0.28$, $p=0.08$).

The concordance between masked observers was 48/50 for the level of restoration of the ELM and 46/50 for the IS/OS line. Postoperative SD-OCT showed disruption of both ELM and IS/OS lines (Fig. 1) in 11/50 eyes, restoration of both lines (Fig. 2) in 29/50 eyes and normalized ELM with disrupted IS/OS line (Fig. 3) in 10/50 eyes (Table 1).

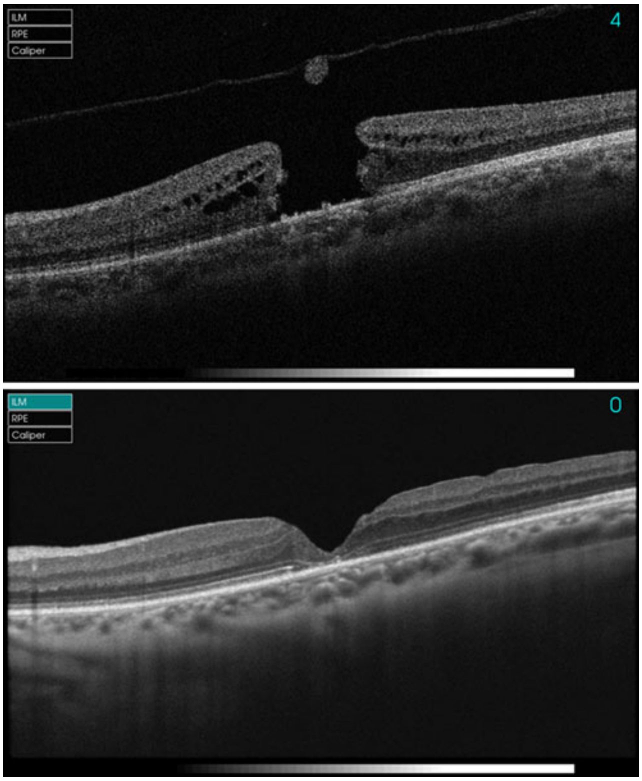

Fig. 1 Pre and postoperative SD-OCT of one patient from group A showing disruption of both ELM and IS/OS lines

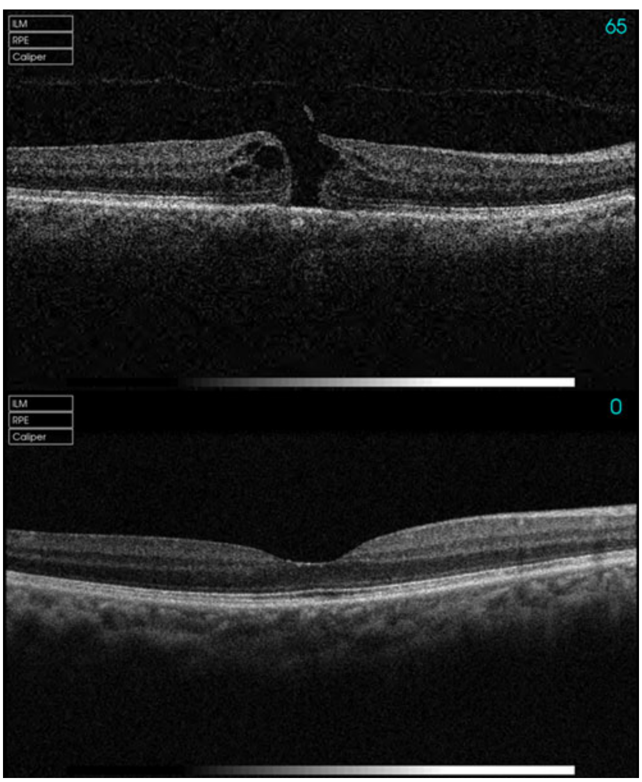

Fig. 2 Pre and postoperative SD-OCT of one patient from group C with restoration of both lines, ELM and IS/OS

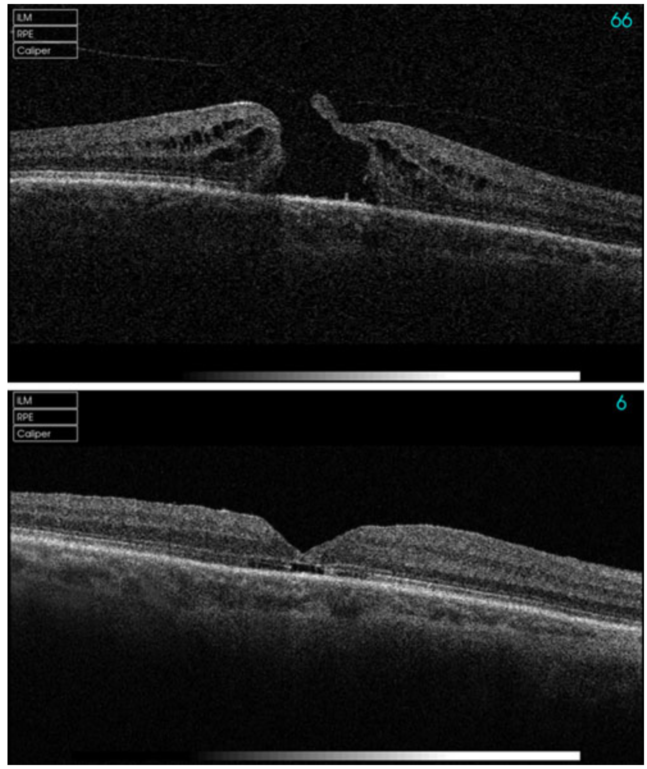

Fig. 3 Pre and postoperative SD-OCT of one patient from group B showing ELM restoration and no IS/OS

No statistically significant differences were detected in age, BCVA, MH base diameter or MH minimal diameter preoperatively ($p \geq 0.18$; Kruskal–Wallis test). Postoperative LogMAR BCVA was significantly better in group C ($p \leq 0.01$; Mann–Whitney test with Bonferroni's adjustment). In addition, LogMAR BCVA improved significantly in the three groups (Group A, $p<0.01$; Group B, $p=0.01$; Group C, $p=0.03$; Wilcoxon rank-sum test).

A significant correlation was found between ELM restoration and postoperative LogMAR BCVA ($r=-0.63$, $p<0.01$), as well as between IS/OS line restoration and postoperative LogMAR BCVA ($r=-0.55$, $p<0.01$). No significant correlations of ELM or IS/OS line restoration with minimal (ELM, $r=-0.18$, $p=0.25$; IS/OS line, $r=-0.09$, $p=0.56$; both, $r=-0.09$, $p=0.56$) and base diameters of the MH (ELM, $r=-0.29$, $p=0.07$; IS/OS line, $r=-0.15$, $p=0.36$; both, $r=-0.15$, $p=0.36$) were found.

The area under the ROC curve was≥0.5 for the prediction of the disruption of both ELM and IS/OS after surgery from the MH size (base diameter, area: 0.70, $p=0.06$; minimal diameter, area: 0.63, $p=0.24$), with an associated p value close to statistical significance for the base diameter (Fig. 4). For this specific parameter, the cut-off value obtained was 877.50 µm, with an associated sensitivity and specificity of 77.8 and 71.9%, respectively.

MH re-opening during the follow-up was observed in only two cases: in one eye 7 years after the first vitrectomy

Table 1 Comparative table showing the preoperative and postoperative conditions of patients included in the three groups of eyes defined according to the OCT findings: eyes showing disruption of both MLE and IS/OS lines (group A, 11 eyes), eyes showing intact ELM and disruption of IS/OS line (group B, ten eyes), and eyes showing restoration of both lines (Group C, 29 eyes). The corresponding *p* values for the comparison between groups are shown for each parameter evaluated

Mean (SD) range	Group A	Group B	Group C	*p* value	Post hoc comparison
Age (years)	69.8 (9.5) 53 to 87	71.1 (7.8) 53 to 84	70.7 (8.6) 53 to 84	0.65	A-B p=0.99 A-C p=0.99 B-C p=0.78
Preoperative LogMAR BCVA	0.74 (0.36) 0.30 to 1.52	0.56 (0.26) 0.15 to 1.52	0.54 (0.29) 0.15 to 1.52	0.28	A-B p=0.99 A-C p=0.36 B-C p=0.99
MH minimal diameter (μm)	439.0 (136.8) 287 to 711	387.5 (160.5) 157 to 810	385.0 (157.5) 157 to 810	0.50	A-B p=0.99 A-C p=0.99 B-C p=0.78
MH base diameter (μm)	895.6 (241.1) 472 to 1,185	693.7 (279.0) 237 to 1,235	697.1 (282.3) 237 to 1,147	0.18	A-B p=0.99 A-C p=0.27 B-C p=0.48
Postoperative LogMAR BCVA	0.43 (0.19) 0.22 to 0.82	0.12 (0.12) 0.00 to 0.52	0.10 (0.11) 0.00 to 0.36	<0.01	A-B p=0.36 A-C p<0.01 B-C p=0.01
MH stage	2: 1 eye 3: 0 eyes 4: 10 eyes	2: 4 eyes 3: 0 eyes 4: 6 eyes	2: 7 eyes 3: 10 eyes 4: 12 eyes	–	–

SD standard deviation; *BCVA* best-corrected visual acuity; *MH* macular hole

and 4 years after the cataract surgery (final LogMAR BSCVA: 0.00; presence of IS/OS line and ELM on OCT exam postoperatively), and in the other eye 5 years after the first vitrectomy and 3 years after the cataract surgery (final LogMAR BSCVA: 0.80; absence of both IS/OS line and ELM on OCT exam postoperatively). A second vitrectomy was performed in these cases using the same surgical protocol, but with a wider area of ILM peeling.

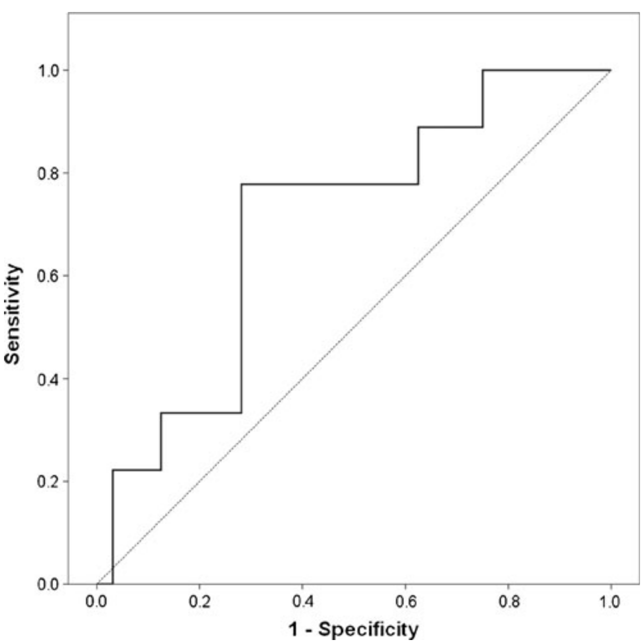

Fig. 4 ROC curve obtained for the base diameter as predictor of the disruption of both ELM and IS/OS after surgery (area: 0.70, p=0.06). The cut-off value obtained was 877.50 μm, with an associated sensitivity and specificity of 77.8 and 71.9%, respectively

Discussion

The anatomical closure of the MH is not always associated with a good visual outcome [7]. Several studies have evaluated the preoperative geometry of the MH and attempted to correlate it with the postoperative visual outcome [6–9, 20]. In the current series, we have found a statistically significant positive correlation between the postoperative LogMAR BCVA and the MH base diameter.

Clinical studies using TD OCT [10, 11] and especially SD-OCT [15, 17, 21–23] have suggested the role of anatomical changes in the outer retina determining the postoperative functional result. It has been demonstrated that macular thickness and morphology are not strongly correlated with postoperative BCVA [11, 24, 25], although some limited statistically significant correlations have been described. On the other hand, a statistically significant correlation has been reported between postoperative BCVA and the integrity of the junction line of the IS/OS. An initial study using TD-OCT and additional studies using SD-OCT have established and confirmed this correlation [11, 15, 17, 21, 22, 24, 25], finding that patients showing OCT restoration of the IS/OS line presented a good postoperative BCVA, while the functional outcome was poorer in those cases without IS/OS line. However, other authors disagreed with this finding [16], stating that the integrity of the IS/OS line only confirms the status of the photoreceptor at the moment of the examination, but it does not provide information about the cell survival that is more critical for the prediction of the visual outcome [16].

In a study conducted by Wakabayashi et al. [14], three groups of eyes were differentiated according to the OCT findings after MH surgery: complete ELM and IS/OS line (group A), complete ELM but no integrity of the IS/OS line (group B), and no integrity of both ELM and IS/OS line (group C). These authors did not find statistically significant differences in the preoperative BCVA among these groups ($p=0.137$); however, 3 months after surgery BCVA was significantly better in groups A and B. Postoperative differences between groups A and B were not statistically significant. These authors suggest that the integrity of the ELM at the macular area may be a better predictive factor than the integrity of the IS/OS line [14]. Other authors such as Landa [26] and Shimozono [27] agree on the role of the ELM, even though the latter found the strongest correlation between IS/OS and BCVA restoration. In their paper, Landa et al. report that IS/OS restoration at 6 months was observed in 50% of the eyes that presented ELM integrity 6 weeks after surgery, whereas only 5% of the eyes with disrupted ELM at 6 weeks showed IS/OS integrity at 6 months. This finding seems to support the role of ELM integrity in the restoration of IS/OS and BCVA.

In the current series, BCVA improved significantly in the three groups. Postoperative BCVA was significantly better in group C vs. groups A and B. Therefore, the restoration of the IS/OS line seems to be the key factor for a better postoperative visual outcome. According to histological studies, the ELM is formed by the junctional complexes of cell membranes of the major glial cells, Müller cells and photoreceptors inner segments, and the IS/OS line is the result of the reflection of an extremely narrow cylindrical stalk containing a modified cilium that joins the inner and outer segments of photoreceptors. In our opinion, the integrity of this line may be a better indicative factor of the integrity of the photoreceptor cell than the study of the ELM. However, ELM integrity may facilitate IS/OS restoration and subsequent BCVA improvement.

MH reparation starts at the level of the internal retina in the early postoperative period showing an image of foveal detachment that progressively disappears [28], as occurs in the spontaneous closure of some traumatic MH [29]. According to Wakabayashi et al. [14] and to our own results, IS/OS line restoration does not occur unless it is associated with ELM restoration, confirming that the integrity of the ELM is followed by the integrity of the IS/OS line, in a restoration process from the internal to the outer retina. A recent study by Landa et al. [26] has demonstrated that BCVA was poorer in eyes with disrupted IS/OS and ELM than in eyes with only IS/OS disruption, suggesting that ELM may play a critical role for the restoration of the photoreceptor layer and BCVA restoration. The correlation between IS/OS line and poor visual acuity has been shown recently in several papers and in different conditions [30, 31]. Decreased visual acuity in patients with ELM damage seems to be associated to IS/OS damage.

A recent paper by Spaide and Curzio [32] has re-evaluated the histological correspondence of the outer retinal anatomy as seen in SD OCT. These authors confirms the location of the first (innermost) and the forth (outermost) bands as the external limiting membrane and the retinal pigment epithelium. However, the second band that had previously been attributed to the IS/OS line, histologically seems to correspond with the ellipsoid portion of the inner segments, containing the mitochondria responsible for the energy supply of the cell, and the third band corresponds to an ensheathment of the cone outer segments by apical processes of the retinal pigment epithelium. If this new histological correlation is confirmed by other authors, it would add new evidence to the clinical role of this band previously considered as IS/OS.

The main drawback of the current series is the sample size, especially when the sample was divided in three subgroups. This may have influenced on the lack of statistical significance of the result of some tests, as for example the baseline differences in MH base diameter (clearly larger in group A). In any case, it should be considered that the aim of the current study was to detect trends and correlations to be confirmed with future larger samples.

Even though at present we are still unable to precisely predict final BCVA in MH-operated patients, there is a reasonable chance of expecting a better visual outcome in patients with IS/OS and ELM restoration, and explain poor visual results in patients with damaged IS/OS despite anatomically successful surgery. We still ignore what factors may lay behind these histological changes and are unable to modify them, but a deeper understanding of the changes occurring in MH reparation may help us improving BCVA outcomes.

In conclusion, according to our results and to the published data to date, the reconstruction of the outer retina, especially the IS/OS line, seems to be the better prognostic factor for a good postoperative visual rehabilitation. Studies using the SD-OCT technology with larger samples of eyes are necessary in order to confirm these preliminary findings, since it is still unclear whether it is the integrity of the ELM or the IS/OS line, which determines better the functional visual outcome after MH surgery.

Conflict of interest The authors have no financial or proprietary interest in a product, method, or material described herein.

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