Journal of Ophthalmology

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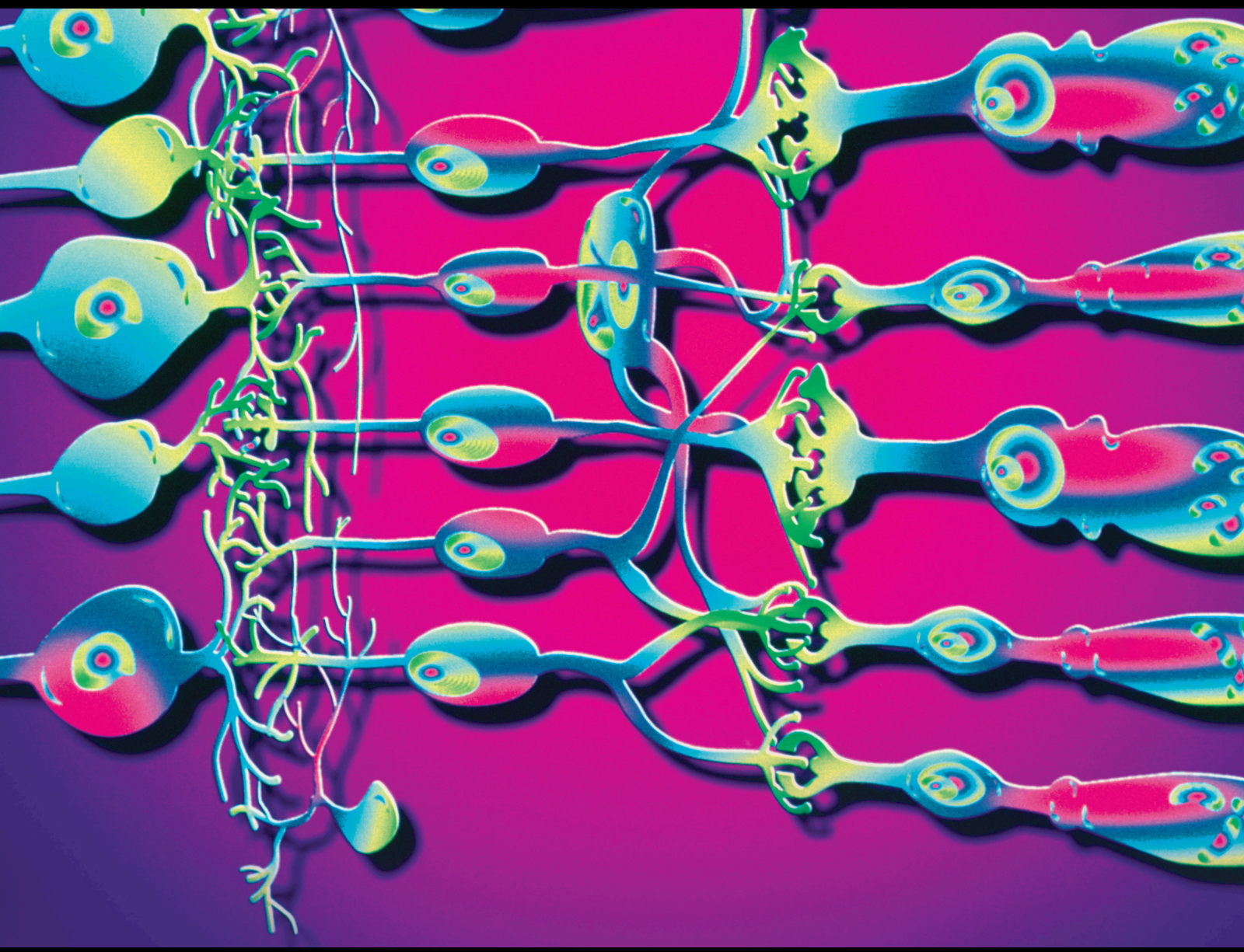

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Editorial

Macular Surgery: Classification, Management and Surgical Techniques

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In recent years, there has been a rapid advance in diagnostic modalities as well as therapeutic interventions for macular diseases. Multimodal imaging enables a highly accurate classification of macular diseases which in turn permits us to follow a rational therapeutic approach. These macular diseases special issue focuses on the diagnostic approach and pathological classification as well as on the medical and surgical treatments available today.

The multimodal imaging (MMI) helps in accurate diagnosis and detailed characterization of macular hole, epiretinal membrane, and the vitreomacular interface syndromes [1–3].

The OCT-A has the potential of predicting prognosis of macular pathologies. The foveal avascular zone (FAZ) widening, changes in vessels density (VD), and perfusion density (PD) are altered after macular surgery and membrane peeling. Low values of these data correlate with poor visual and anatomical outcomes [4]. MMI permits close monitoring for spontaneous closure of small-diameter traumatic macular hole. The usual period for this may extend till 3 months. Surgical option may be considered beyond this period [5].

ILM peeling may inadvertently remove ganglion cells. This is generally confirmed by immunohistochemistry (IHC) of excised ILM tissue. The same can be confirmed *in vivo* by noting decreased GCC (ganglion cells complex) thickness on OCT scan [6]. This OCT finding points towards hazards of indiscriminate ILM peeling. Hence, one must gauge the benefit of ILM peeling against the visual risk of the same. In their meta-analysis, Ma et al. highlighted better visual outcomes and reduced complications with 27G ports in comparison to 25G vitrectomy, for the treatment of epiretinal membranes (ERMs) [7].

Furthermore, we can read how limited vitrectomy is a time-efficient and effective surgical procedure for removal of epiretinal membrane with no additional complications [8].

Historically, traumatic macular hole (TMH) was deemed to have poor visual prognosis and conservative management was the norm. It has now been shown that vitrectomy combined with ILM peeling achieves better anatomical closure and improved visual outcomes [5].

In patients with idiopathic full-thickness macular hole (MHI $\leq$0.5), a larger ILM peel of 4 disc diameters (DDs) appears to yield better anatomical outcomes than a limited 2 DD peel [9].

Furthermore, this special issue will focus on anatomical and functional outcomes of idiopathic macular hole revision surgery, after failed primary surgery. The success rate of revision surgery in eyes with unclosed MH was 85% and demonstrated an improvement in VA [10]. The possibilty to use autologous material to improve recovery in refractory MH is very interesting; usually autologous internal limiting

membrane flap [11] appears to be effective in the closure of recurrent idiopathic macular holes. Also, we can see how autologous lens capsular flap transplantation can represent a potential alternative treatment for patients with large persistent macular holes after failure of other surgical techniques [12].

Innovations in macular surgery field also deals with use of various tamponades. The conscious choice of tamponade in each case can offer the best possible outcomes. Based on the OCT images, we can choose tamponade for each case; for MH $\leq 400\,\mu$m, a high closure rate can be achieved by combining just air as a tamponade with prone position. However, for larger macular holes $>400\,\mu$m, the greatest anatomical success can be achieved by using little longer-acting SF6 tamponade in combination with the prone position [13].

This special issue also deals with use of pharmacological agents, like anti-VEGF. In patients with diabetic macular edema associated with vitreomacular interface abnormalities (VMAs), injections of ranibizumab have shown a better anatomical and functional improvement when compared with pars plana vitrectomy [14]. Further evidence shows how antiangiogenic agents, although experimental today, should be considered for persistent and refractory macular oedema [15]. Dexamethasone implant represents an effective treatment for postoperative macular oedema secondary to ERM and post-RD vitrectomy. It showed a significant improvement in anatomical as well as visual outcome. Intravitreal injections may represent a good option in diabetic patients with macular oedema associated with vitreomacular interface abnormalities [16, 17].

In conclusion, this special issue has a platter of original research articles and experimental studies, as well as case series on vitreoretinal interface disorders and macular surgery, illustrating and discussing functional and/or anatomical outcomes. This may offer readers a new perspective in dealing with macular pathologies and stimulate further research.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

Matteo Forlini
Stanislao Rizzo
Robert Rejdak
Sundaram Natarajan
Teresio Avitabile
Rodolfo Mastropasqua

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Review Article

Intravitreal Dexamethasone Implant for Postoperative Macular Oedema Secondary to Vitrectomy for Epiretinal Membrane and Retinal Detachment: A Systematic Review and Meta-Analysis

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Purpose. To evaluate the efficacy of intravitreal dexamethasone implant (DEX) for the treatment of macular oedema secondary to vitrectomy for epiretinal membrane (ERM) and retinal detachment (RD) by conducting a systematic review with meta-analysis of published studies. *Methods*. Studies reporting clinical outcomes of DEX use for the treatment of macular oedema secondary to ERM and RD vitrectomy were searched on PubMed and Embase databases. The primary outcome was best-corrected visual acuity (BCVA) change between baseline and post-DEX treatment, reported as mean difference (MD) with 95% confidence interval (CI). Mean central macular thickness (CMT) change was assessed as a secondary outcome. Postimplant adverse events, including intraocular pressure rise and cataract development, were reported as well. *Results*. Five uncontrolled studies, 1 nonrandomized controlled study, and 1 randomized controlled study were included, with a total of 5 cohorts and 3 cohorts in the ERM group and RD group, respectively. Considering the last available follow-up, a significant improvement in postimplant BCVA was found in the overall population, irrespective of the indication for vitrectomy (MD = −0.28, 95% CI = −0.37, −0.20; $p < 0.001$), but with significant heterogeneity. In either group, mean BCVA significantly improved following the implant (in the ERM group, MD = −0.31, 95% CI = −0.40, −0.22; in the RD group, MD = −0.22, 95% CI = −0.41, −0.03), with no difference between the two groups ($p = 0.41$). However, there was significant heterogeneity in both groups. Considering the last available follow-up, a significant CMT reduction was found in the overall population, irrespective of the indication for vitrectomy (MD = −129.75, 95% CI = −157.49, −102.01; $p < 0.001$). In the ERM group, a significant CMT reduction was shown following DEX (MD = −133.41, 95% CI = −155.37, −111.45; $p < 0.001$), with no heterogeneity. In the RD group, mean CMT reduction was borderline significant (MD = −128.37, 95% CI = −253.57, −3.18; $p = 0.040$), with significant heterogeneity. No difference in CMT improvement was found between the two groups ($p = 0.94$). *Conclusion*. This meta-analysis showed that DEX yielded a significant improvement in visual and anatomical outcomes, even if limited by significant heterogeneity. Dexamethasone implant represents an effective treatment for postoperative macular oedema secondary to ERM and RD vitrectomy.

1. Introduction

Postoperative cystoid macular oedema (CMO) represents one of the main causes of postoperative visual impairment, generally occurring between 4 and 12 weeks after surgery [1]. This condition has been also reported following vitrectomy, with an incidence as high as 47% of cases [2]. Its etiology mainly depends on an inflammatory process triggered by the surgery [3, 4].

For such a reason, steroids have been widely used for the treatment of postoperative CME, including the sustained-release dexamethasone intravitreal implant (Ozurdex®, Allergan Inc., Irvine, CA, USA, and Allergan Pharmaceuticals, Ireland) [5].

In particular, several authors reported the use of intravitreal dexamethasone implant (DEX) for macular oedema secondary to vitrectomy for epiretinal membrane (ERM) and rhegmatogenous retinal detachment (RRD), showing promising results [6–13]. However, most of these studies were limited by a small sample size and retrospective design.

To date, no systematic review has been conducted with the purpose of analysing outcomes of DEX for the treatment of postvitrectomy CMO. Such a study would provide a clearer picture of both the potential benefits and drawbacks of this therapeutic option.

Therefore, we systematically reviewed the scientific evidence on the use of DEX for macular oedema secondary to vitrectomy for ERM and RRD and performed meta-analyses on visual and anatomical outcomes.

2. Materials and Methods

2.1. Literature Search. The methodology was based on the statements reported by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14] (Table S1 available online in the Supplementary Material) and the Cochrane Handbook [15].

Studies reporting clinical outcomes of intravitreal dexamethasone implant for the treatment of postoperative macular oedema after vitrectomy for ERM or RRD were systematically reviewed. An electronic search of PubMed and Embase databases was carried out. The search method included the terms "dexamethasone implant," "vitrectomy," "retinal detachment," "epiretinal membrane," "pucker," and "macular oedema," connected in various combinations by "and/or." The last search was done on November 30, 2020. Studies published in peer-reviewed journals and in the English language were assessed for eligibility, regardless of publication date or status. If clarifications were needed, we contacted the authors by e-mail.

2.2. Eligibility Criteria. The following inclusion criteria were considered (1) to include patients with macular oedema secondary to vitrectomy for ERM and/or RRD, (2) to report clinical outcome of treatment with intravitreal dexamethasone implant, and (3) to present a follow-up ≥3 months.

The following exclusion criteria were adopted: (1) cohorts including patients receiving vitrectomy for diseases different from ERM or RRD; (2) cohorts receiving DEX for the prevention of macular oedema; and (3) a case report design.

The primary outcome measures were mean best-corrected visual acuity (BCVA) change and mean central macular thickness (CMT) change following dexamethasone implant administration.

2.3. Data Extraction and Quality Assessment. The eligibility of the studies was independently assessed by two investigators (G.P. and P.M.), who also carried out data extraction in an independent fashion. A third investigator (M.R.) was involved in case of disagreement. From each included article, the following data were extracted: year; location; first author; study design; number of patients; mean age; follow-up; indication for vitrectomy; type of surgery; time between surgery and macular oedema onset; time between surgery and DEX; type of treatment prior to dexamethasone; amount of intravitreal dexamethasone implant administered; and CMT-, BCVA-, DEX-related adverse events, including intraocular pressure (IOP) rise, cataract, infection. Extracted data on BCVA and CMT included pre-DEX, baseline values, and post-DEX values recorded throughout the follow-up of each study. In particular, post-DEX data included 1-month, 3-month, 6-month, and 12-month follow-up, if available.

The risk of bias of randomized studies was evaluated by using the Cochrane Handbook tool [15], while nonrandomized studies were assessed by using the methodological item for nonrandomized studies, as previously reported [16, 17].

2.4. Statistical Analysis. Best-corrected visual acuity was reported as logarithm of the minimum angle of resolution (logMAR). For both BCVA and CMT, the mean difference (MD) between baseline and post-DEX treatment values (i.e., last available follow-up and specific time-points such as 1-month, 3-month, 6-month, and 12-month follow-up) was calculated along with 95% confidence interval (95% CI). The Q-statistics and the I^2 index were used to assess heterogeneity across studies. When significant heterogeneity was found (I^2> 50% and Q-statistics <0.1), meta-analysis was based on a random effect approach, by applying the DerSimonian–Laird method. Otherwise, a fixed-effect model was used. Publication bias was evaluated by visual inspection of funnel plots along with Egger's test. Statistical analyses were conducted on STATA software (version 16). A p value <0.05 was considered significant for all analyses.

3. Results

3.1. Selection of Studies. Figure 1 illustrates the study selection process. The electronic search allowed to identify a total of 390 articles, of which 114 were duplicates. Abstracts and titles of the remaining 276 articles were screened, and 27 potentially eligible studies were selected for full-text review. Of these, 20 studies were excluded. A total of 7 studies were included in this systematic review and were pooled together for meta-analyses.

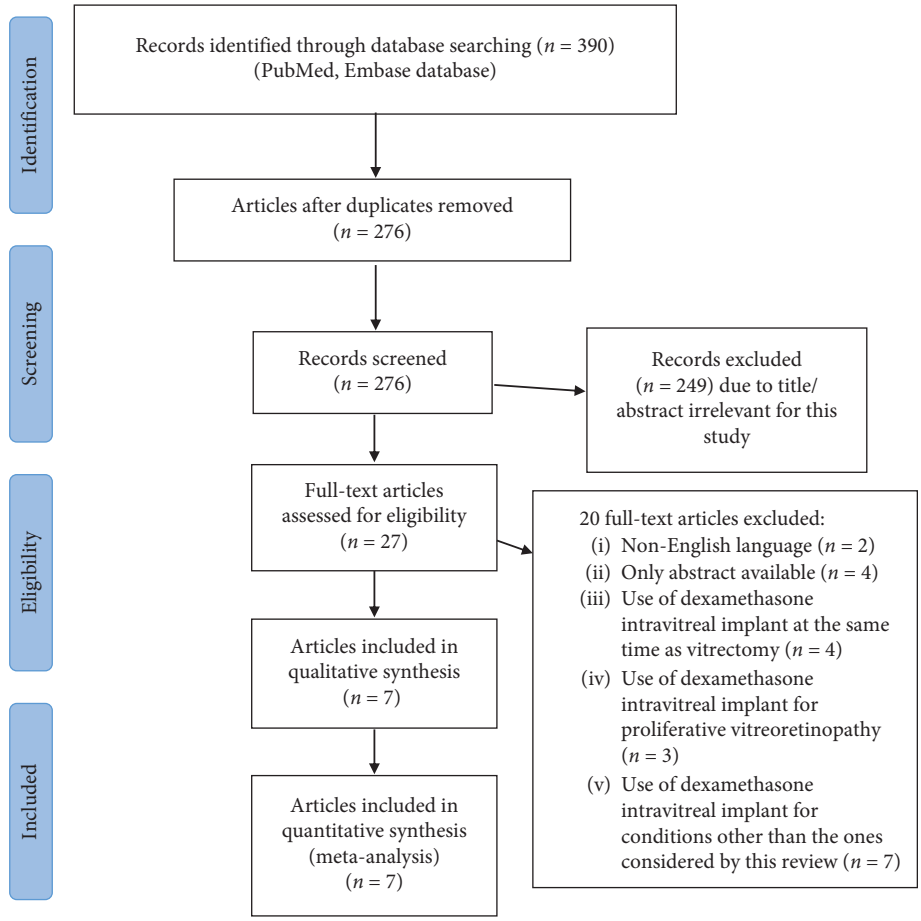


Figure 1: Flow diagram of the study selection process.

3.2. Study Characteristics. Overall, 7 studies were included in this systematic review, of which 5 were uncontrolled retrospective reports [8–10, 12, 13]; one was a non-randomized, retrospective, controlled study [11]; and one was a randomized controlled study [6]. All the included studies were published in years between 2014 and 2020. Overall, a total of 174 eyes were included, of which 46 eyes underwent vitrectomy for retinal detachment and 128 eyes for epiretinal membrane. The main characteristics of included studies are shown in Table 1. Freissinger et al. [9] reported outcomes of two cohorts: one including eyes with macular oedema secondary to ERM vitrectomy and the other including eyes with macular oedema secondary to RRD vitrectomy.

The nonrandomized retrospective controlled study included 40 eyes with long-term macular oedema after vitrectomy for ERM, of which 20 eyes received a single DEX implant and 20 eyes were untreated controls [11]. The results showed better BCVA and macular thickness in the DEX group compared to the control group. These improvements were maintained throughout the 6-month follow-up, even if macular thickness tended to increase at 6 months [11]. Only data from the DEX group were used for our pooled analyses.

The randomized controlled trial enrolled eyes diagnosed with macular oedema secondary to vitrectomy for ERM, which were randomized into two groups: a group receiving DEX implant (15 eyes) and a control, untreated group (12 eyes) [6]. Eyes treated with DEX had a significant improvement in both BCVA and macular thickness compared with the control group at 1-, 6-, and 12-month follow-up. A mean of 1.2 DEX injections was administered during the 12-month study period [6]. Only data from the DEX group were used for our pooled analyses.

No case of endophthalmitis was reported by included studies. The lens status of enrolled patients is shown in Table 1. With regard to IOP rise following DEX, this was recorded in 3 cases out of 39 by Hattenbach et al. [8], in 3 cases out of 20 by Chang et al. [11], in 3 cases out of 15 by Chatziralli et al. [6], in 11 cases out of 61 by Freissinger et al. [9], in 2 cases out of 14 by Chatziralli et al. [13], and in 3 cases out of 17 by Thanos et al. [10]. Furino et al. [12] reported no case of increased IOP. In all studies, IOP rise was successfully managed with IOP lowering drops, with no need for glaucoma surgery.

3.3. Quality Assessment. Table S2 (available online in Supplementary Material) illustrates the risk of bias of nonrandomized studies. The only randomized trial was judged at unclear risk for selection bias; performance bias and detection bias were deemed as an unclear risk;

Table 1: Characteristics of the included studies.

Type of surgery	Study	Number of eyes	Mean age	Follow-up month	Mean number of implants at end of follow-up	Lens status before implant
ERM	Furino et al. [12]	8	74	6, 75	1	8 pseudophakic
	Hattenbach et al. [8]	39	71, 5	4, 5	1, 59	1 phakic, 38 pseudophakic
	Chang et al. [11]	20	63, 9	6	1	20 pseudophakic
	Chatziralli et al. [6]	15	68, 2	12	1, 2	4 phakic, 11 pseudophakic
	Freissinger et al. [9]	46	66, 2	12	1, 67	24 phakic, 22 pseudophakic
RRD	Freissinger et al. [9]	15	60, 5	12	1, 3	3 phakic, 12 pseudophakic
	Chatziralli et al. [11]	14	56, 3	12	1, 4	6 phakic, 8 pseudophakic
	Thanos et al. [10]	17	67	3	1	17 pseudophakic

ERM: epiretinal membrane; RRD: rhegmatogenous retinal detachment.

attrition bias and reporting bias were considered as low risk; and risk of other bias was unclear [6]. Funnel plots inspection and Egger's test showed no evidence of publication bias for the visual outcome (Figure S1 available online in Supplementary Material). Similarly, no evidence of publication bias was found for CMT change in the ERM group (Figure S2 available online in Supplementary Material). Egger's test revealed a risk of publication bias for CMT change in the retinal detachment group.

3.4. Visual Outcome. Data from 5 studies and 3 studies were pooled together for BCVA analysis in the ERM and RRD groups, respectively. The analysis on BCVA change between baseline and last available follow-up after DEX showed a significant visual improvement in the overall population, irrespective of the indication for vitrectomy (MD = −0.28, 95% CI = -0.37, −0.20; $p < 0.001$; Figure 2). However, significant heterogeneity was found ($I^2 = 70.5\%$; $p = 0.01$). A MD of −0.31 (95% CI = −0.40, −0.22) was found in the ERM group and a MD of −0.22 (95% CI = −0.41, −0.03) was found in the RRD group, showing in both cases a significant BCVA improvement following dexamethasone implant (p values <0.001), with no difference between the two groups ($p = 0.41$; Figure 1). However, heterogeneity was significantly high in both groups ($I^2 = 71.9\%$ and $p = 0.03$ for ERM; $I^2 = 62.3\%$ and $p = 0.07$ for RRD).

The analysis on 1-month BCVA change after DEX included one study from the ERM group and 2 studies from the RRD group. This analysis showed a significant visual improvement in the overall population (MD = −0.30, 95% CI = −0.39, −0.21; $p < 0.001$; Figure 3) and in both the ERM and RRD groups (ERM group, MD = −0.31, 95% CI = −0.42, −0.20, $p < 0.001$; RRD group, MD = −0.28, 95% CI = −0.45, −0.10, $p < 0.001$). No significant heterogeneity was found (overall, $I^2 = 0.01\%$, $p = 0.74$; RRD group, $I^2 = 25.9\%$, $p = 0.25$).

The analysis on 6-month BCVA change after DEX included 3 studies from the ERM group and 1 study from the RRD group. This analysis showed a significant visual improvement in the overall population (MD = −0.34, 95% CI = −0.43, −0.24; $p < 0.001$; Figure 3) and in both the ERM and RRD groups (ERM group, MD = -0.35, 95% CI = −0.48, −0.22, $p < 0.001$; RRD group, MD = −0.30, 95% CI = −0.48, −0.12, $p < 0.001$). Overall, no significant heterogeneity was found ($I^2 = 47.5\%$, $p = 0.13$), but this was borderline nonsignificant when considering studies in the ERM group ($I^2 = 67.9\%$, $p = 0.06$).

The analysis on 12-month BCVA change after DEX included a total of 4 studies, two from each group. This analysis showed a significant visual improvement in the overall population (MD = −0.26, 95% CI = −0.39, −0.13; $p < 0.001$; Figure 3) and in the ERM group (MD = −0.29, 95% CI = −0.42, −0.17, $p < 0.001$). BCVA change was nonsignificant in the RRD group (MD = −0.21, 95% CI = −0.52, 0.10, $p = 0.328$). Significant heterogeneity was found overall ($I^2 = 70.5\%$, $p = 0.03$). And in the RRD group ($I^2 = 81.4\%$, $p = 0.02$), there was no significant heterogeneity in the ERM group ($I^2 = 64.4\%$, $p = 0.09$).

No analysis was performed at a 3-month follow-up due to a lack of data.

3.5. Macular Thickness Outcome. Data from 5 studies and 3 studies were pooled together for CMT analysis in the ERM and RRD groups, respectively. The analysis on CMT change between baseline and last available follow-up after DEX showed a significant thickness reduction in the overall population, irrespective of the indication for vitrectomy (MD = −129.75, 95% CI = −157.49, −102.01; $p < 0.001$; Figure 4), with moderate but significant heterogeneity ($I^2 = 44.1\%$; $p = 0.04$). In the ERM group, mean CMT significantly decreased following dexamethasone implant (MD = −133.41, 95% CI = −155.37, −111.45; $p < 0.001$), and no heterogeneity was found across studies ($I^2 = 0\%$; $p = 0.59$). In the RRD group, the change between baseline and postdexamethasone CMT was borderline significant given a wide CI (MD = −128.37, 95% CI = −253.57, −3.18; $p = 0.040$). In this group, significant heterogeneity was shown ($I^2 = 85.6\%$, $p < 0.01$). No difference in CMT improvement was found between the two groups ($p = 0.94$).

The analysis on 1-month CMT change after DEX included 4 studies, two from each group. This analysis showed a significant CMT reduction in the overall population (MD = −174.76, 95% CI = −246.16, −102.76; $p < 0.001$; Figure 5) and in both the ERM and RRD groups (ERM group, MD = −119.20, 95% CI = −153.58, −84.82,

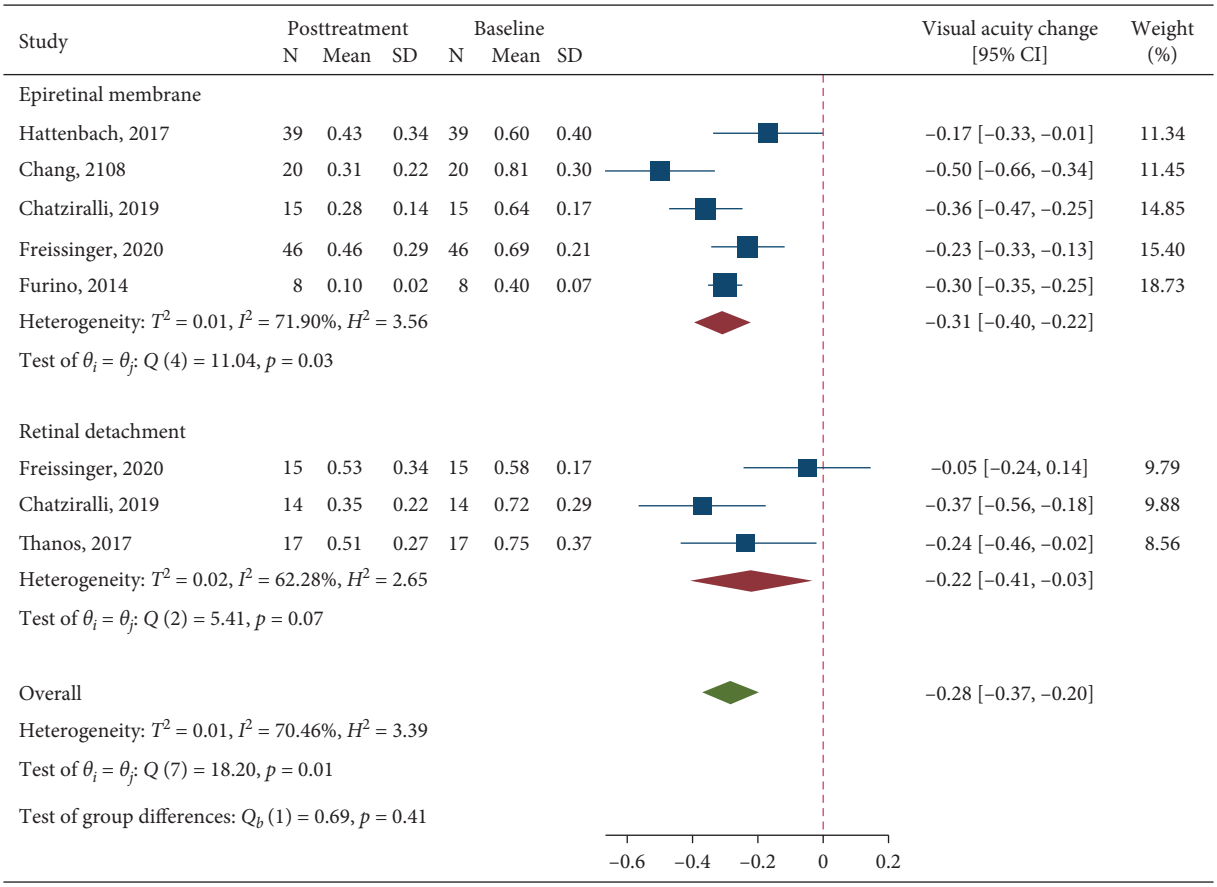


Figure 2: A forest plot showing the mean change in best-corrected visual acuity considering the last available follow-up after treatment with dexamethasone implant.

$p < 0.001$; RRD group, MD = −238.98, 95% CI = −305.74, −172.22, $p < 0.001$). Significant heterogeneity was found when pooling all 4 studies together ($I^2 = 74.6\%$, $p = 0.01$), while this was absent within both the ERM and RRD groups.

The analysis on 6-month CMT change after DEX included 3 studies from the ERM group and 1 study from the RRD group. This analysis showed a significant CMT reduction in the overall population (MD = −118.16, 95% CI = −159.75, −76.57; $p < 0.001$; Figure 5) and in both the ERM and RRD groups (ERM group, MD = −104.75, 95% CI = −138.45, −71.06, $p < 0.001$; RRD group, MD = −195.00, 95% CI = −296.20, −93.80, $p < 0.001$). No significant heterogeneity was found (overall, $I^2 = 51.3\%$, $p = 0.11$; ERM group, $I^2 = 29.1\%$, $p = 0.21$).

The analysis on 12-month CMT change after DEX included a total of 4 studies, two from each group. This analysis showed a significant CMT reduction in the overall population (MD = −156.31, 95% CI = −222.18, −90.45; $p < 0.001$; Figure 5) and in the ERM group (MD = −152.30, 95% CI = −191.15, −113.46, $p < 0.001$). CMT change was nonsignificant in the RRD group (MD = −168.35, 95% CI = −351.84, 15.15, $p = 0.456$). Significant heterogeneity was found overall ($I^2 = 73.2\%$, $p = 0.03$) and in the RRD group ($I^2 = 88.3\%$, $p < 0.01$); there was no significant heterogeneity in the ERM group ($I^2 = 0\%$, $p = 0.50$).

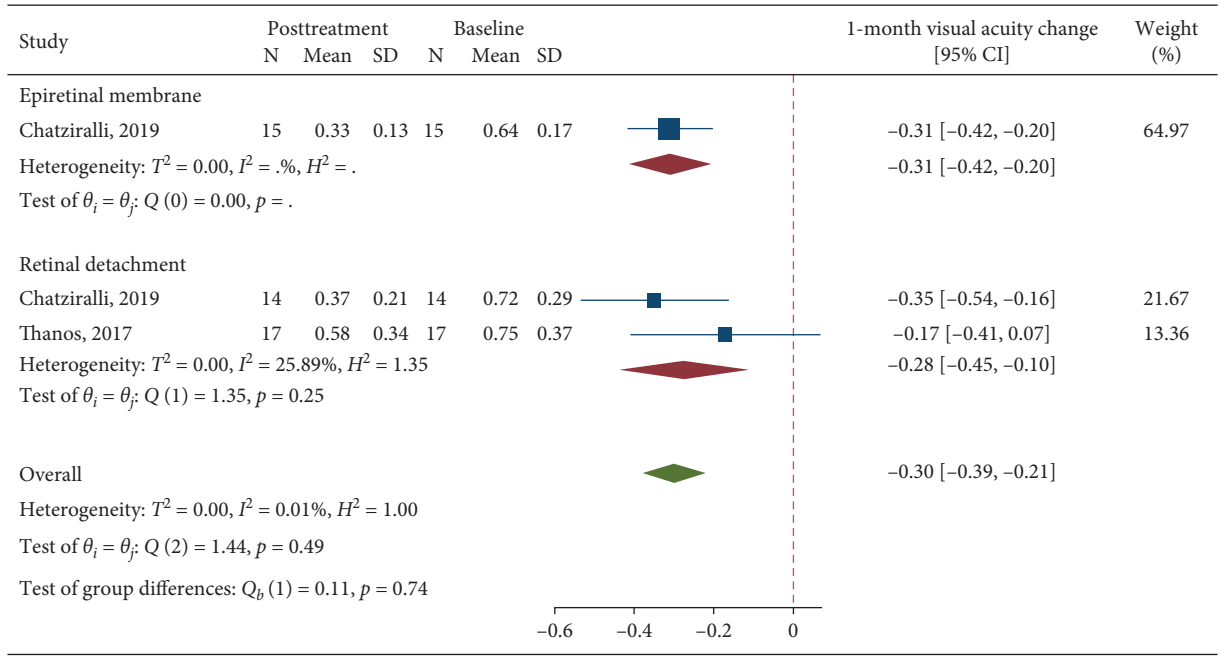
No analysis was performed at a 3-month follow-up due to a lack of data.

4. Discussion

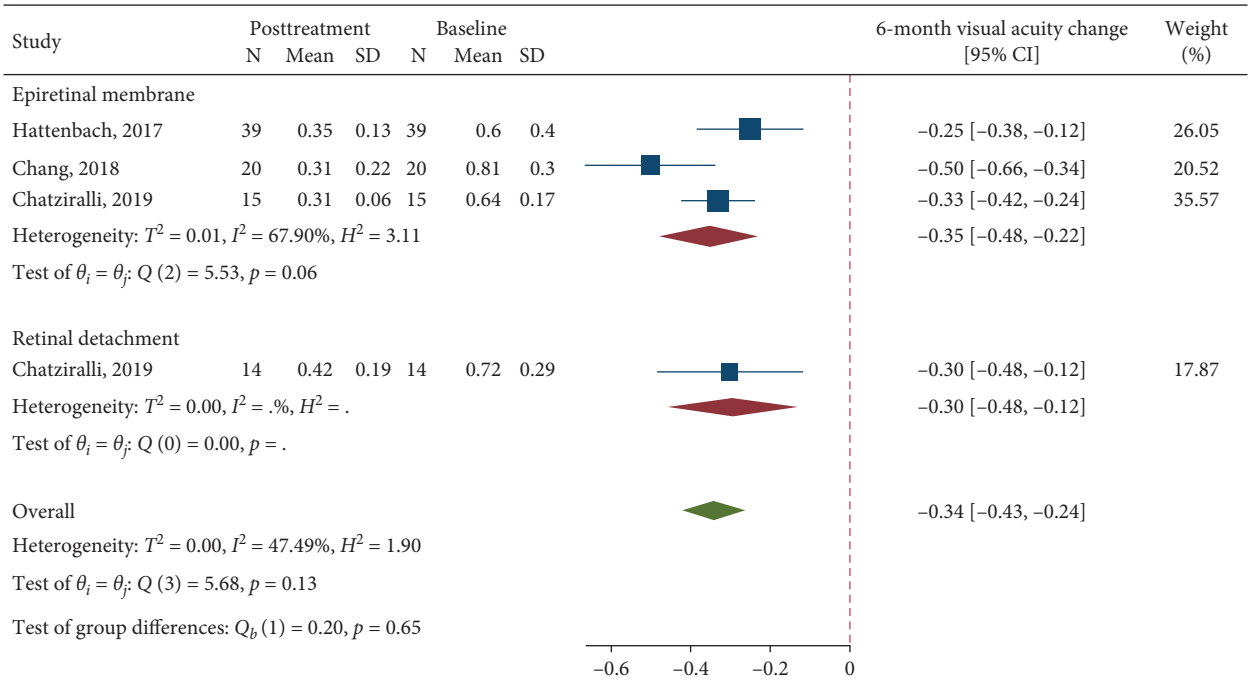
The present meta-analysis showed favorable visual and anatomical outcomes following the use of dexamethasone implant for macular oedema secondary to ERM and RRD vitrectomy.

Postvitrectomy macular oedema is a sight-threatening condition which could affect visual recovery following a successful surgery. This complication has been reported in roughly 15% of cases following RRD vitrectomy [18], while its incidence ranges from 13% to 47% following ERM vitrectomy [2, 19].

The causative mechanisms of postvitrectomy macular oedema have not been completely understood yet. It seems that inflammation plays a key role in this process. Indeed, macular oedema following RRD vitrectomy has been associated with the presence of proliferative vitreoretinopathy (PVR) and with longstanding RRD, which, in both cases, are likely to be linked with an inflammatory status [7]. Furthermore, macula-off RRD has been associated with a higher rate of postvitrectomy macular oedema [7]. It would be interesting to assess whether internal limiting membrane peeling could reduce its onset as this maneuver proved to



(a)



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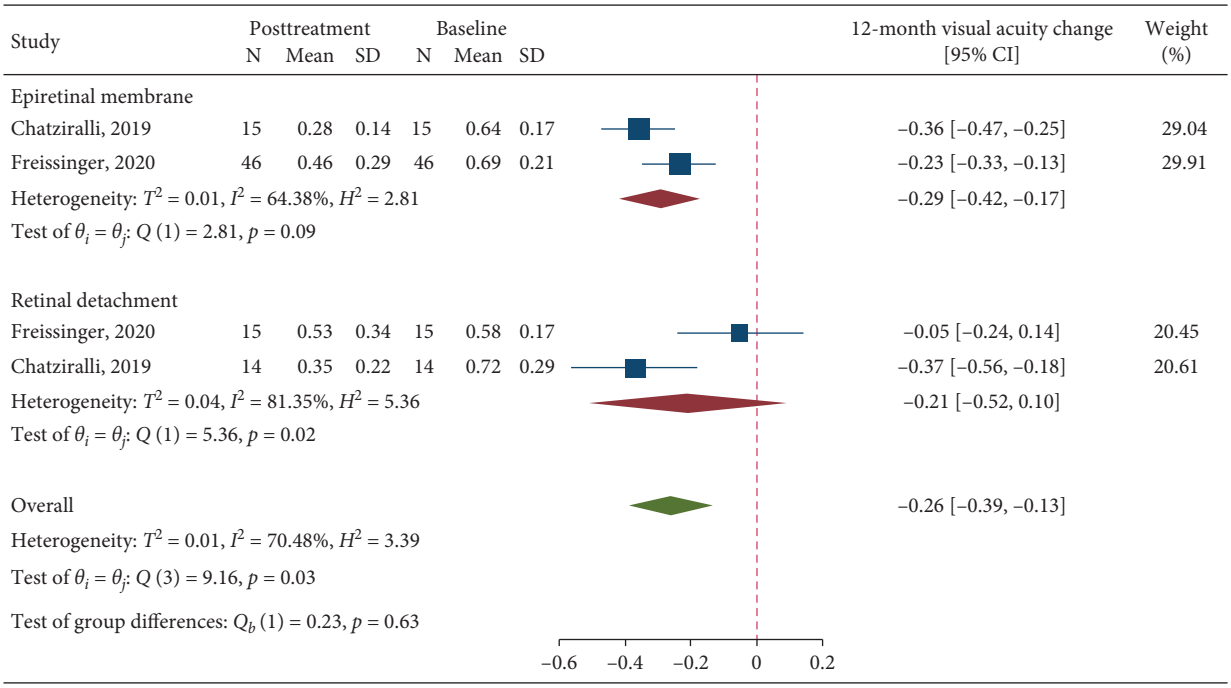


(c)

Figure 3: A forest plot showing mean change in best-corrected visual acuity at 1-month (a), 6-month (b), and 12-month (c) follow-up after treatment with dexamethasone implant.

reduce the risk of both postoperative ERM and RRD recurrence [20]. In case of ERM vitrectomy, macular distortion due to the contractile membrane has been assumed to trigger the inflammatory condition [21].

In this context, the use of the intravitreal 0.7 mg dexamethasone implant has been investigated. DEX is characterized by a potent anti-inflammatory activity and a good safety profile [22]. The implant is licensed in Europe for the treatment of posterior segment inflammation secondary to noninfectious uveitis, macular oedema due to retinal vein occlusion, and diabetic macular oedema (DMO) [23]. Additionally, DEX use has been also reported in other conditions with an inflammatory background, such as pseudophakic cystoid macular oedema [5], inflammation secondary to RRD repair surgery [24], and DMO worsening due to cataract surgery [25].

A remarkable advantage of the slow release implant is its efficacy in vitrectomized eyes, which are less suitable to intravitreal antivascular endothelial growth factor (anti-VEGF) therapy because of a faster washout [26].

Our findings showed both visual and anatomical improvements following DEX treatment for macular oedema secondary to vitrectomy for ERM and RRD.

When considering the last available follow-up, our analyses revealed a significant visual gain following DEX administration in both the ERM and the RRD groups, and in the overall population as well. Similarly, a significant reduction in macular thickness was shown in the overall population. Such an anatomical improvement was evident in the ERM group, while it was borderline significant in the RRD group due to a wide confidence interval.

When considering the different follow-ups, significant visual and anatomical improvements were demonstrated in both groups at 1 and 6 months. At 12 months, significant visual and anatomical improvements were shown in the ERM group, while these were nonsignificant in the RRD group.

While pseudophakic cystoid macular oedema has been widely studied and its spontaneous resolution has been reported up to 90% of cases [27, 28], less evidence is available on the natural history of postvitrectomy macular oedema. Both Chatziralli et al. [6] and Chang et al. [11], the two controlled studies included in this review, showed an unchanged, greater than 400 μm central macular thickness in the untreated control group at the end of a 12- and 6-month follow-up, respectively. Additionally, Chatziralli et al. [6] reported a spontaneous resolution of macular oedema in only 33% of control cases. This might suggest that postvitrectomy macular oedema could be less prone to spontaneous resolution compared with pseudophakic cystoid macular oedema. However, evidence from only two small cohorts of control patients seems too limited to draw any conclusion. Both the two controlled studies included in this review reported on macular oedema secondary to ERM vitrectomy [6, 11], and even less is known on the natural history of macular oedema secondary to RRD vitrectomy. Further studies are warranted to better explore this issue.

Importantly, most of the included studies reported on persistent postvitrectomy macular oedema, which proved unresponsive to topical nonsteroidal anti-inflammatory drugs (NSAIDs) and/or periocular or intravitreal triamcinolone

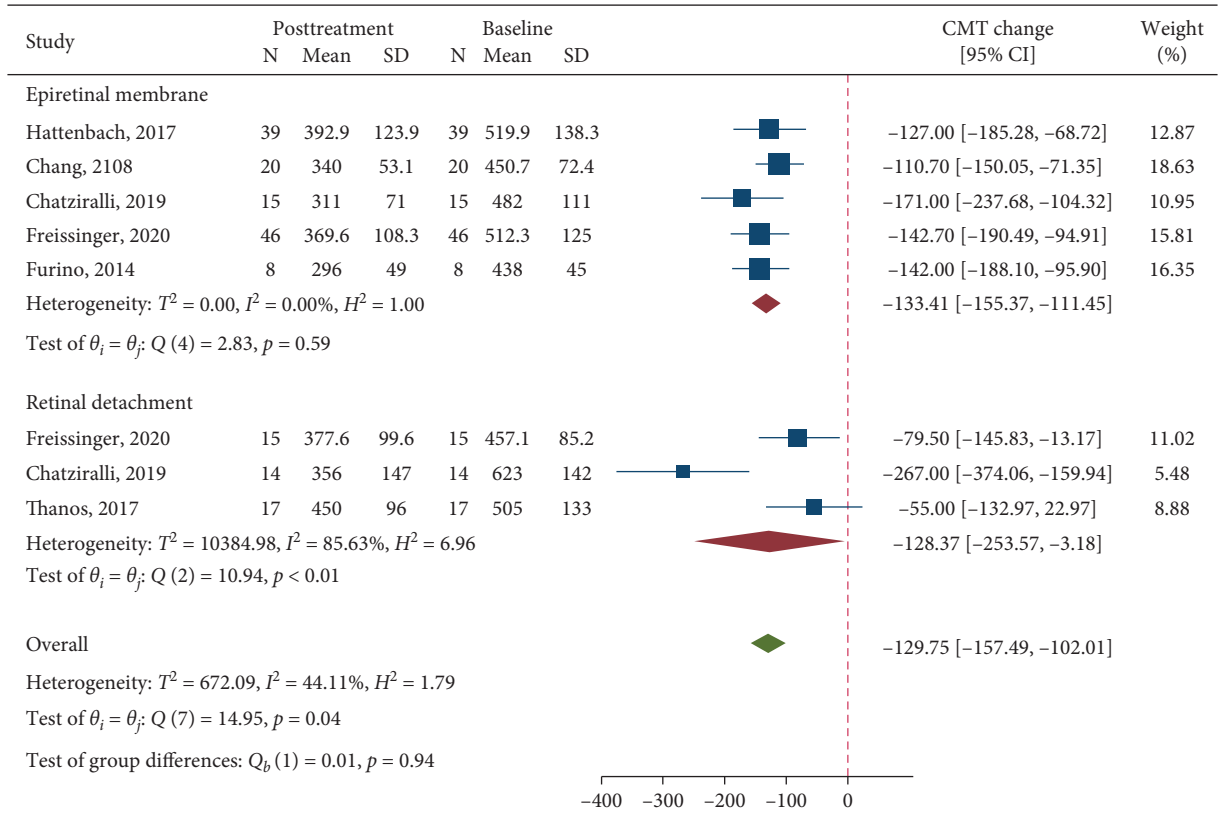
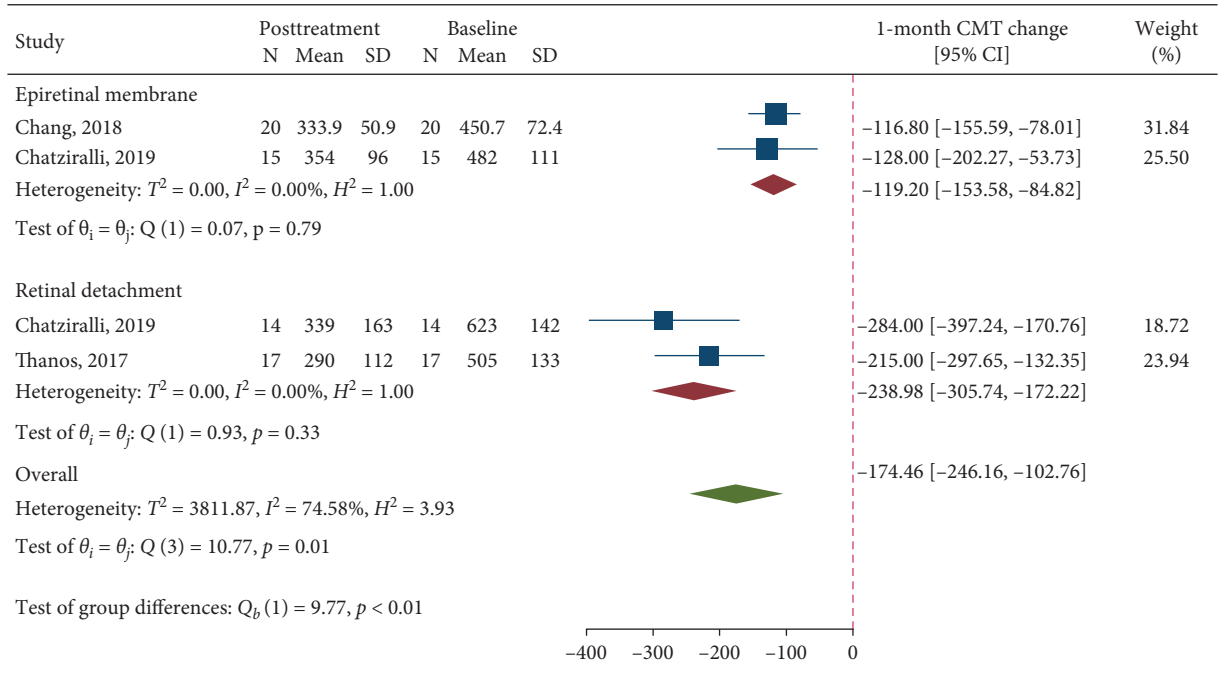


Figure 4: A forest plot showing mean change in central macular thickness considering the last available follow-up after treatment with dexamethasone implant.



(a)

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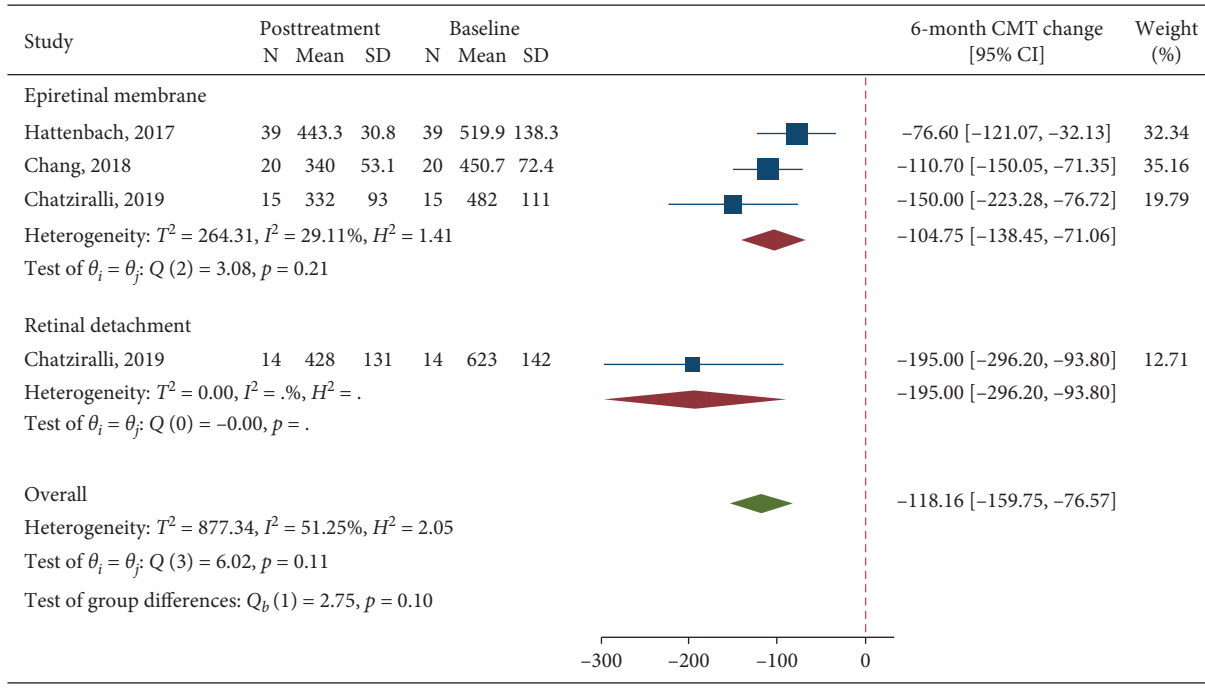

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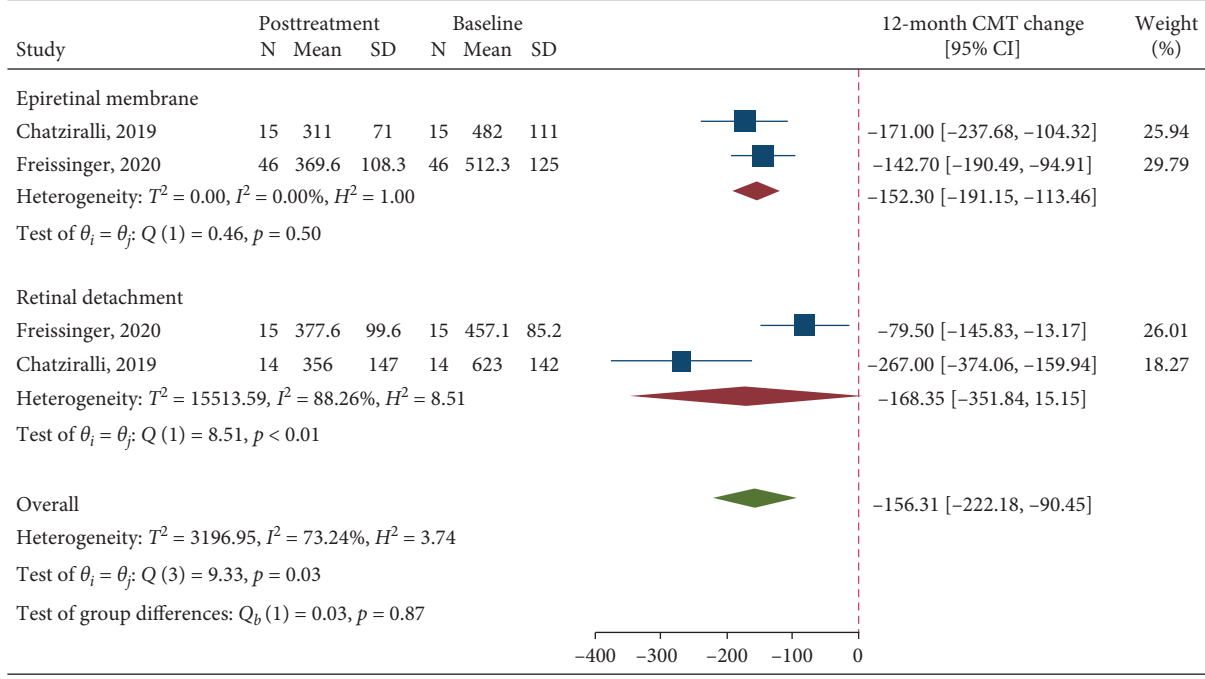

(c)

Figure 5: A forest plot showing mean change in central macular thickness at 1-month (a), 6-month (b), and 12-month (c) follow-up after treatment with dexamethasone implant.

acetonide [8–12]. Only two studies included naïve patients [6, 13]. Chronic postsurgical macular oedema is unlikely to resolve spontaneously and its treatment might prove challenging [5]. The fact that DEX provided both a functional and anatomical improvement in vitrectomized eyes with, in most cases, persistent CMO is worth noting, in particular taking into account that a low number of implants (from 1 to 1.7) was administered over a follow-up ranging from 3 to 12 months.

In this systematic review, we collected DEX-related adverse events, as well. Of note, no case of endophthalmitis was reported by the included studies. In general, the main adverse events related to dexamethasone implant are IOP rise and cataract [23]. Most eyes of the included studies were

pseudophakic at the time of DEX implant. This could be explained by the fact that these eyes had undergone a previous vitrectomy and cataract surgery could have been performed at that time or before.

With regard to IOP rise, the included studies reported this event from 0% to 20% of cases [8, 12]. It is important to point out that a higher rate of ocular hypertension was found in vitrectomized eyes compared to nonvitrectomized ones [29]. Theoretically, the implant could get worse in this condition. However, the included studies showed that all cases were amenable with IOP lowering drops, and in no case, surgery was required.

The following limitations characterized the present study. First, significant heterogeneity was found for BCVA analysis in both groups and for CMT analysis in the RRD group. The presence of high heterogeneity limits the quality of the evidence we provide. The reason for it could be related to the retrospective nature of most of the included studies and to the fact that different eligibility criteria and clinical variables could have been considered by the included studies. Additionally, no analysis was conducted on potential adverse events, such as IOP rise and cataract, due to the limited number of cases reported. Finally, a relatively small number of studies was included. However, a meta-analysis is featured by a greater power and accurate confidence interval compared with an individual study [30, 31].

In conclusion, the use of intravitreal dexamethasone implant for macular oedema following vitrectomy for ERM and RRD allowed improving both visual and anatomical outcomes. The implant represents a valid therapeutic option for this sight-threatening condition.

Data Availability

The data used to support the findings of this study are available in the Supplementary Information file.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Supplementary Materials

Table S1: PRISMA 2009 checklist. Table S2: risk of bias of included studies according to the Methodological Item for Non-Randomized Studies (MINORS). Figure S1: funnel plot for best-corrected visual acuity change. Figure S2: funnel plot for central macular thickness change. (*Supplementary Materials*)

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Research Article

The Role of OCT Angiography in the Assessment of Epiretinal Macular Membrane

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Background. The aim of this observational study is to assess pre- and postoperative retinochoroidal vascular changes in patients undergoing epiretinal macular membrane (ERM) surgery by using optical coherence tomography angiography (OCTA). *Materials and Methods*. 23 eyes affected by ERM and those which underwent phacovitrectomy associated with ERM peeling were enrolled. They were evaluated using structural OCT and OCTA before surgery and at 1, 3, and 6 months postoperatively. *Results*. We found a statistically significant ($p < 0.05$) increase in the superficial capillary plexus vessel density (VD) from baseline to the 6-month follow-up. We observed a large increase in both the perfusion density (PD) and the VD of the deep capillary plexus between baseline and the 6-month follow-up ($p < 0.001$). A significant decrease in the VD and PD of the choriocapillaris (CC) from baseline to the 1st month and a significant increase in CC perfusion density at the 6-month follow-up compared to the preoperative value were revealed. The FAZ area and perimeter after surgery significantly increased during the follow-up ($p < 0.001$) at baseline retinal and choroidal plexi with a lower PD or VD correlated with worse visual acuity ($p < 0.05$ for all plexi). At baseline and at the 1-month follow-up, a significant correlation was found with the FAZ area and the FAZ perimeter: a smaller FAZ area or a smaller FAZ perimeter was correlated to a lower visual acuity. Before surgery, negative correlations ($p < 0.05$) were found between the Govetto ERM stages and perfusion density of the SCP and the DCP and between the Govetto stages and vessel density of the DCP. *Conclusions*. In our study, OCTA detected vascular alterations induced by the presence of the ERM, allowing several correlations with functional data. In these patients, OCTA may be useful to add new potential surgical prognostic factors.

1. Introduction

Epiretinal membrane (ERM) is a pathological condition characterized by the constitution of a fibrocellular layer over the internal limiting membrane (ILM) surface due to fibroblast proliferation after an anomalous posterior vitreous detachment [1]. ERM exerts two forces that stress and distort the retina: centripetal contraction and anteroposterior traction; the contraction of the epiretinal membrane is responsible for an additional thickening,

puckering, folding, or detachment of the retinal layers, alongside with a vascular distortion [2]. Pars plana vitrectomy (PPV) associated with membrane peeling is the standard treatment for this kind of disorder, but postoperative visual prognosis is often unpredictable despite optimal and reproducible anatomical outcomes [3, 4].

Several studies have been conducted to identify markers and signs to predict postoperative visual function [5, 6]; in particular, the introduction of spectral domain optical coherence tomography (SD-OCT) has provided a powerful tool in the diagnosis and comprehension of the natural history and pathophysiology of ERMs, shifting attention from the outer retina to the inner layers [7, 8].

The retinal function also relies on vascularization, but studying ERM can be difficult and complex due to the invasiveness of fluorescein angiography; additionally, the lack of quantitative data and the visualization "en bloc" of the retinal vascular meshwork using fluorescein angiography make it an unsuitable method to evaluate ERM.

Optical coherence tomography angiography (OCTA) is a fast and noninvasive technique which allows the detailed visualization of each retinal plexus without a dye injection.

Thanks to its easy handling and safety, it can also be used to study retinal pathologies without vascular etiologies such as vitreoretinal syndromes. The in-built software permits operators to quantify the vascular alteration which can be correlated to functional parameters, such as visual acuity.

The aim of this observational cross-sectional study is to assess early retinal vascular changes in patients undergoing ERM surgery using OCTA.

2. Materials and Methods

This observational noncomparative cross-sectional study enrolled 21 patients (23 eyes) affected by ERM who underwent phacovitrectomy associated with ERM peeling and internal limiting membrane (ILM) peeling and who were referred to the Eye Clinic (Careggi Hospital, Florence, Italy) from September 2016 to July 2017. They were evaluated using OCT and OCTA before and after surgery.

The inclusion criteria were a diagnosis of ERM detected with B-scan OCT and adequate OCTA image quality to calculate the vessel density and the area of the foveal avascular zone (FAZ) in the superficial and deep vascular plexi (SVP and DVP, respectively) in the choroid and choriocapillaris. Exclusion criteria were opacities that interfered with the acquisition of OCT and concomitant diseases such as diabetic retinopathy, vein or artery occlusion, and glaucoma.

This study adhered to the tenets of the current version of the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000), and written informed consent was obtained from all patients prior to participation in the study. Approval from The Institutional Review Board/Ethics Committee was obtained.

All patients underwent a baseline ophthalmic examination including medical and ocular history, family medical history, measurement of best-corrected visual acuity (BCVA) using the early treatment retinopathy diabetic study (ETRDS) chart, slit-lamp examination of the anterior and posterior segments, measurement of intraocular pressure, dilated fundus examination, and axial length measurement with noncontact partial coherence laser interferometry (IOL Master, version 3.01; Carl Zeiss Meditec, Jena, Germany), B-scan OCT, and OCTA. Patients were evaluated at 1, 3, and 6 months postoperatively. In cases with loss of visual acuity or the development of new symptoms such as scotoma or metamorphopsia, patients were recalled earlier than the standard follow-up date. The RS-3000 Advance 2 spectral domain OCT (NIDEK Co. Ltd., Gamagori, Japan) was used to acquire OCTA and end face images in all eyes. This device uses an 880 nm wavelength with a scanning speed of 53,000 A-scans/sec. A $3\,\text{mm} \times 3\,\text{mm}$ (256×256 scan points) scanning pattern was performed in all eyes. All scans were centered on the fovea based on the live scanning laser ophthalmoscopy (SLO) image. All B-scans were performed 8 times and averaged for a higher sensitivity. A real-time SLO-based active eye tracker was used to compensate for eye movement during image acquisition. In all cases, the SLO image was captured prior to OCTA analysis. Low-quality OCTA images, severe artifacts due to poor fixation, or cases of failed automatic layer segmentation were excluded from analysis. Images were reviewed by two investigators (DB and MD) for segmentation accuracy, as Bontzos et al. found a 14-fold increased risk of motion artifact occurrence in the ERM patients, correlated with the disease severity, mostly in interior plexiform and in the ILM layers [9]. High myopic or hyperopic eyes were excluded to avoid bias in the vascular density measurement.

The default RS-3000 Advance 2 AngioScan software has been used (%) to evaluate the preoperative and postoperative vessel density (defined as the percentage of the total area occupied by vessels) and perfusion density (defined as the total area of perfused vasculature per unit area in a region of measurement).

To combine a vessel density map, images are first binarized in order to separate vessels (white) from what is not vessels (black), and then, all vessels are shrunk to 1-pixel thickness, making these mapped vessels thickness independent; finally, the sum of linear lengths of vessels per mm^2 is then calculated point by point.

To design a perfusion density map, again images are first binarized in order to separate vessels (white) from what is not vessels (black), but vessels are not later shrunk so as to make these mapped vessels thickness dependent; in order to map the vascularization, a percentage is calculated, indicating the vascularized tissue in the 11×11 pixels square centered on the concerned pixel. The spatial division in inner, outer, and whole segments is explained in Figure 1.

In addition, FAZ area, perimeter, and circularity (an index that is equal to 1 when the FAZ shape is a circle) were automatically calculated by the in-built software (Figure 2).

B-scan OCT measurements included central retinal thickness (CRT) and outer nuclear layer (ONL) thickness; a preoperative qualitative analysis was conducted on each structural OCT scan to evaluate the stage of the ERM

according to Govetto OCT classification, the presence of intraretinal cysts pre- and postoperatively, and the restoration of the foveal pit during follow-up examination.

All eyes underwent a standard 25-gauge 3-port pars plana vitrectomy with a wide-angle noncontact viewing system (Resight®; Carl Zeiss Meditec AG, Jena, Germany) using the Constellation Vision System (Alcon Laboratories Inc., Fort Worth, TX, USA). Brilliant Blue G (Brilliant Peel®, Fluoron GmbH, Ulm, Germany) was used to stain and peel the ILM.

A complete vitrectomy was performed, and peripheral retinal photocoagulation was carried out in eyes with retinal tears or holes. Fluid-gas exchange was then performed, followed by tamponade.

A chart review was performed to collect data on visual acuity, VD of the SVP and DVP, CRT, outer nuclear layer thickness, FAZ area perimeter, and circularity preoperatively and at 1, 3, and 6 months postoperatively. Statistical analysis included descriptive statistics of patient demographics and comparative analysis. All statistical analyses were performed using Stata. Descriptive statistics are reported as mean ± standard deviation (SD).

One-way analysis of variance (ANOVA) with repeated measurements was performed to determine the mean changes at each follow-up. The mean of each variable was compared to the baseline data.

The Spearman correlation coefficient was used to evaluate the correlation between the different parameters: a $p > 0.05$ was considered statistically significant.

3. Results

The study sample included 23 eyes of 21 patients (10 (48%) females and 11 (52%) males); 10 (43%) right eyes and 13 (57%) left eyes underwent surgery. The mean age was 74.38 ± 6.33 years. All the data collected are shown in Tables 1–3.

We observed a significant progressive improvement in visual acuity from baseline to the 6-month follow-up.

Concerning the superficial capillary plexus vessel density (SCPVD), we found a statistically significant ($p < 0.05$) increase from baseline to the 6-month follow-up (R: 0.698, $p < 0.05$). We did not observe statistically significant changes in the superficial capillary plexus perfusion density (SCPPD) from baseline to the postoperative follow-up.

By measuring the perfusion density and vessel density of the deep capillary plexus (DCP) before and after surgery, both were observed to have a positive trend. In fact, we observed a large increase in both the PD and the VD of this plexus between baseline and the 3-month follow-up and between baseline and the 6-month follow-up (DCPPD: 3rd month R, 5.322 with $p < 0.001$ and 6th R, 6.009 with $p < 0.001$; DCPVD 3rd month R, 2.105 with $p < 0.001$ and 6th month R, 0.614 with $p < 0.001$).

Regarding the VD and PD of the choriocapillaris plexus (CC), we found a similar positive trend. We observed a decrease in the VD and PD of the CC from baseline to the 1st month (CCPD: 1st month R, −2.173 with $p < 0.05$; CCVD: at the 1st R, −0.884 with $p < 0.05$). We found a significant increase in CC perfusion density at the 6-month follow-up compared to the preoperative value (CCPD: R, 2.478 with $p < 0.05$). Regarding the choroidal plexus, the trend of perfusion density and vessel density was similar to that of the choriocapillaris plexus. In fact, statistically significant data ($p < 0.05$) show a decrease in R compared to baseline (CHPD: R at the 1-month −5.911 with $p < 0.001$ and CHVD: R at the 1-month follow-up was −2.270 $p < 0.001$).

Regarding the FAZ area and perimeter after surgery, we found a gradual enlargement during the follow-ups ($p < 0.05$) but the values at the 6th month remained lower than at baseline (area: R at 6-month follow-up, −0.083 with $p < 0.001$; perimeter: R at 6-month follow-up, −0.417 with $p < 0.001$).

Linear correlations were found between BCVA and OCTA parameters; at baseline retinal and choroidal plexi with a lower perfusion or vessel density of the retinal and choroidal plexi correlated with worse visual acuity (SCPPD R: −0.2783 with $p < 0.05$; DCPPD R: −0.2972 with $p < 0.05$; CHPD R: −0.4217 with $p < 0.05$; DCPVD R: −0.4181 with $p < 0.05$; CHVD R: −0.4700 with $p < 0.05$). Regarding visual acuity, a correlation ($p < 0.05$) was also found with the FAZ area and the FAZ perimeter (FAZ area R: −0.2705; FAZ perimeter R: −0.3492). We observed that a smaller FAZ area or a smaller FAZ perimeter was correlated to a lower visual acuity. At the 1-month follow-up, BCVA remained significantly correlated ($p < 0.05$) to the FAZ area and the FAZ perimeter (R: −0.34 and −0.28, respectively), meaning that a larger FAZ, measured by its area or its perimeter, is associated with better visual acuity.

At the 3-month follow-up, BCVA had significant correlations ($p < 0.05$) with the choroidal plexus perfusion density (R:−0.3962) and the vessel density of the same plexus (R: −0.3095), the same that were present at baseline: a better VA correlated to a higher perfusion in the choroid or greater vessel concentration. The BCVA was also significantly ($p < 0.05$) correlated to the FAZ circularity (R:−0.5342), highlighting that a restoration of the foveal circular shape could positively affect a patient's VA. At 6 months after surgery, the BCVA maintained a significant inverse correlation only with the vessel density of the SCP (R: 0.5103), meaning that, at this time, as the vessel density of the superficial capillary plexus increased, visual acuity decreased. Significant negative correlations ($p < 0.05$) were found between the 3-month follow-up BCVA and the perfusion density of the choroidal plexus and the FAZ circularity both at baseline (CHPD R: −0.2757; FAZ circularity R: −0.3908), suggesting that patients with better visual acuity after 3 months are those who had better conservation of the foveal circularity and better perfusion in the choroidal plexus at baseline.

We classified each ERM using the Govetto [7] OCT classification, and then, we correlated the different ERM stages with the OCT and OCTA parameters. We found some significant correlations both at baseline and at the 3-month follow-up.

At baseline, we found a significant negative correlation ($p < 0.05$) between the Govetto stages and BCVA (R: 0.5342), meaning that as the Govetto stages progress, BCVA

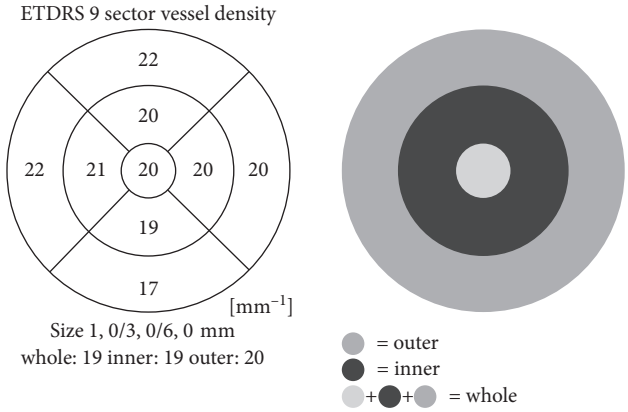


Figure 1: Sector vessel density.

decreases. Before surgery, negative correlations ($p < 0.05$) were found between the Govetto stages and perfusion density of the SCP and the DCP and between the Govetto stages and vessel density of the DCP (SCPPD R:−0.2544; DCPPD R:−0.3788; DCPVD R:−0.4337). Therefore, a higher ranking in this classification is associated with a reduction in perfusion density of the SCP and the DCP and a reduction in vessel density of the DCP. At baseline, there was a significant positive correlation ($p < 0.05$) between the Govetto stages and vessel density of the choriocapillary plexus (CCVD R: 0.2857). Significant negative correlations ($p < 0.05$) were found between the stages and the choroidal perfusion and vessel density, and the perfusion density of the outer retinal choriocapillaris (CHPD R: −0.4809; CHVD R: −0.5030; ORCCPD R:−0.4003). Regarding the FAZ area and the FAZ perimeter, we found significant negative correlations ($p < 0.05$) between these parameters and the Govetto stages (FAZ area R:−0.5741; FAZ perimeter R: −0.4908), meaning that a smaller FAZ area or FAZ perimeter is associated with a higher degree in the ERM classification. Finally, we observed a significant positive correlation ($p < 0.05$) between the Govetto stages and the CRT (crt R: 0,6709), which means that a greater thickness of the central retina corresponds to a higher ranking of Govetto's stages.

Concerning the 3-month follow-up, significant negative correlations ($p < 0.05$) were found between the Govetto stages and perfusion and vessel density of the DCP (DCPPD R: −0.3083; DCPVD R: −0.3579). We also observed significant negative correlations ($p < 0.05$) between the Govetto stages and the perfusion density of the choroidal plexus (CHPD R: −0.2953) and between the Govetto stages and FAZ circularity (FAZ circularity 3 R: −0.3098). At the 3-month follow-up, we also observed positive correlations ($p < 0.05$) between the Govetto stages and choriocapillaris plexus vessel density (CCVD R: 0.3856), the outer retinal choriocapillaris perfusion density (ORCCPD R: 0.3231), and outer retinal choriocapillaris vessel density (ORCCVD R: 0.2855). A compromising ERM at baseline can affect retinal vasculature over time even after its removal.

We made a comparison between the ONL at baseline and the restoration of the foveal pit at the 3-month follow-up. At the 1-month follow-up, the restoration of the foveal pit was observed in 48% of the patients. We found out that the patients with higher preoperative ONL thickness had lower probability of restoration of the foveal pit ($p = 0.0015$).

We compared the patients' ONL at baseline with the patients' data at the 3-month follow-up, and we found various statistically significant correlations ($p < 0.05$). Specifically, ONL at baseline is negatively correlated with CHVD at 3 months (R: −0.3157). ONL at baseline is also positively correlated with the 3-month follow-up FAZ circularity (R: 0.3978) and CRT (R: 0.7475).

In Figure 3, progression graphs are shown.

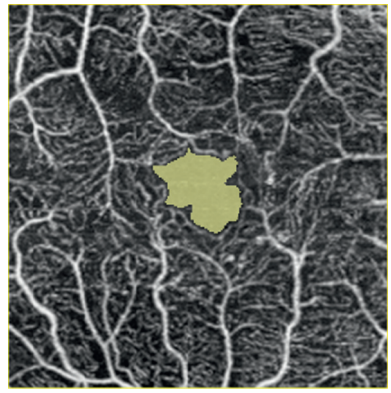
4. Discussion

The presence of an ERM, depending on its thickness and traction force, causes a retinal distortion, in particular in the macular region. By means of fundus oculi examination in patients affected by ERM, an increase in vascular tortuosity and the retinal contraction itself can easily be seen but are difficult to quantify. The use of OCTA has introduced the measurement of different parameters which can be used in this kind of disorder to assess what is distorted and how much the ERM contractions affect the retina.

In this study, a significant increase in retinal and choroidal vessel and perfusion density was found after surgery. Literature highlights that the SCP is greatly affected in ERM-affected eyes [10]. Mastropasqua et al. [11] found that the preoperative perfusion density and vessel density were statistically lower than that in the control group; it can be hypothesized that partial capillary subocclusion occurred related to ERM presence, thus causing flow impairment in the foveal region. However, one of the other possibilities is that actual vessel and perfusion density were not reflected in preoperative OCTA image because the capillaries were folded with ERM, and further studies are needed to confirm those hypotheses.

We found a significant progression and increase in SCP vessel density from baseline to the 6-month follow-up, probably because it is more sensitive to a reopening of little vessels that were suboccluded in the preoperative period.

Regarding the DCP, a significant increase can be seen during the follow-ups both in vessel and in perfusion



FAZ parameter

Area (mm^2)	0.27
Perimeter (mm)	2.68
Circularity	0.47

Figure 2: FAZ parameters.

density, as little capillaries in this plexus can easily be distorted and occluded by ERM tractional forces and its removal causes a gradual reopening and blood flow increase that lasts several months. Lin et al. [12] observed some focal perfusion areas as irregularly shaped patches in DCP, correlated to hypofluorescent areas in fluorescein angiography. As explanation of this phenomenon, they proposed that the tractional stretching forces exerted on the retina empty these capillary patches without affecting the vascular wall; after surgery, a reperfusion with a reappearance of the vascular net can be found (Figure 4).

Rommel et al. proposed that choroidal and choriocapillary networks are affected by ERMs that the impairment in the superficial and the deep retinal plexi may subsequently influence the microvasculature in the choriocapillaris [13].

In our investigation, both these plexi have a peculiar progression: from baseline to the first month, we can see a reduction in vessel and perfusion density and, postoperatively, a significant increase. Li et al. [14] have explained the variations found as retinal blood flow improvement after vitrectomy, followed by retinal arteriolar saturation which increases due to the removal of vitreous body, which could reduce the retinal oxygen consumption and allow oxygen diffusion and transport from the anterior segment. There was no parallel change in venous saturation which suggests that it was possibly caused by better oxygen use during tissue repairment during this period.

Regarding the FAZ area, its behavior is peculiar: a significant reduction was found after peeling at the 1-month follow-up, but later, a gradual enlargement was observed. Some papers [15, 16] suggest that a reduced FAZ area increase after surgery can be caused by a collateral effect of the ILM peeling. One explanation is that the ILM may have some intrinsic forces stretching the retina centrifugally, and its peeling may remove such forces leading to a centripetal movement. The second hypothesis is that the structural changes in the Muller cells, caused by damage during ILM removal, may influence the inner retinal movement. These cells also act as a scaffold that stretches the macula outwards, the removal of their footplates which are anchored to the ILM stop this action, and the macula may move inwards. Those hypotheses have, although, to be confirmed by further studies with a larger number of participants.

At baseline, we found that retinal and choroidal plexi with lower perfusion or vessel density are correlated to worse visual acuity, highlighting that ERM causes a full thickness retinal and choroidal impairment. Gradually, these correlations disappear and only the SCP vessel density remains significantly related to visual acuity after 6 months. Probably, as the innermost retinal layers are the most affected [7] and ERM surgery can also damage this region [17], the SCP vascular network could be an indirect sign of any injury received. Also, the FAZ area and the FAZ perimeter are correlated to BCVA at baseline. Some authors [18, 19] suggest that a vessel crowding in the FAZ area impairs visual acuity because of light interference in a clear optical zone when perifoveal vessels are pulled inward and prevent light reaching photoreceptors, dispersing light before it reaches outer retinal layers. Interestingly, BCVA at the 3-month follow-up and the FAZ circularity calculated at baseline are correlated, suggesting that patients with better visual acuity after 3 months are those who had better conservation of foveal circularity; the FAZ circularity may quantify the disruption of the terminal capillary ring at the fovea, and it may be a better measurement to assess the degree of microvascular damage at the FAZ, which is more related to vision [20].

The 3-month BCVA had direct correlation to preoperative choroidal perfusion density; tractional forces can also affect the choroidal layers [13], especially the subfoveal choroidal thickness (SFCT) and the perfusion of Haller's layer (HLP) decreasing from morning to afternoon, before slightly increasing again in the evening. These variations differ from healthy control patients where the thinning is during the daytime and the thickening during the night, and the explanation proposed is that flow alteration in the superficial and deep capillary plexi may subsequently influence microvasculature in the choriocapillaris.

Other studies have proposed a choroidal involvement in ERM natural history and the correlation of this vascular network with visual acuity [21]: the foveal region obtains most of its oxygen from the choroid; in this macular stress condition, we can hypothesize that higher values of perfusion can provide better retinal oxygenation and subsequently consent a better functional outcome during follow-up.

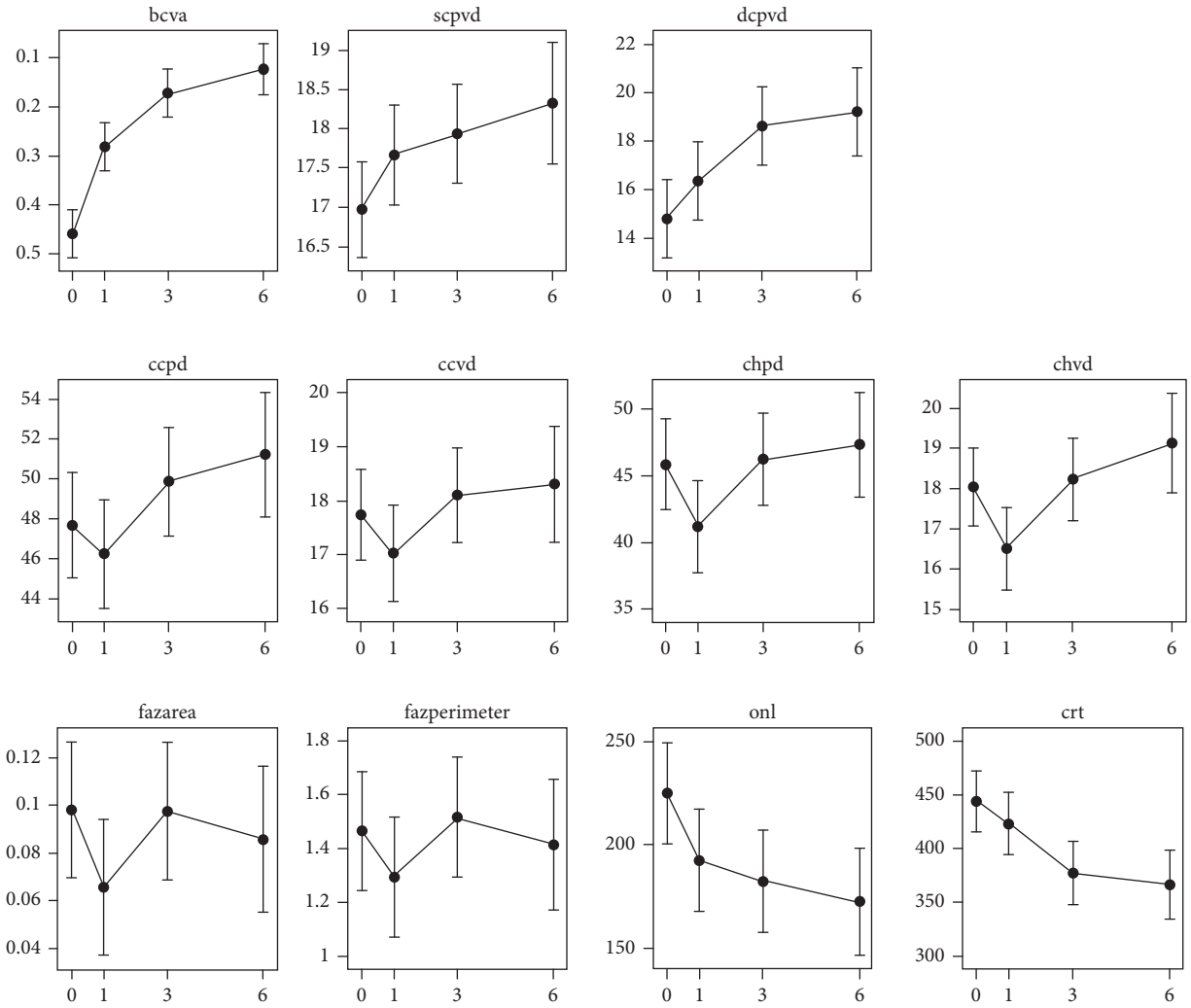


Figure 3: Progression graphs. On the abscissa, the time expressed in months is presented.

In our study, we have analyzed the possible correlations that the new ERM, OCT-based, Govetto classification could have with the various parameters studied using OCTA both before and after surgery.

Before surgery, the Govetto stages had negative correlations with the perfusion density and the vessel density of the DCP and with the perfusion density of the SCP. Consequently, we may hypothesize that, in the preoperative period, a higher ranking in the Govetto classification is associated not only with lower visual acuity but also with a significant alteration in retinal microcirculation. These correlations between the Govetto stages and the vessel density and perfusion density of the DCP have also been found at the 3-month follow-up, meaning that a preoperative Govetto stage 3 or 4 epiretinal macular membrane is associated in the postoperative period with a worse restoration of retinal circulation (Figure 5).

In our study, we also observed significant negative correlations at baseline between the Govetto stages and the FAZ area and FAZ perimeter, meaning that a smaller FAZ area or FAZ perimeter are associated with a higher rank in the ERM Govetto classification.

We found significant correlations between preoperative ONL thickness and the restoration of the foveal pit after 3 months. The ONL has recently been seen as one of the most distorted retinal layers in the natural history of ERMs [7]. We found that a thicker ONL is associated with a more infrequent restoration of the foveal pit. A hypothesis that we can put forward is that an abnormal elongation of this layer could be an indirect sign of a loss of flexibility of the full thickness retina; further studies are needed to assess whether there is a thickness measurement over which it is hard to achieve a restoration of the normal anatomical retinal shape after surgery.

Our study has several limits: the sample size is relatively small, and a larger number of patients should be evaluated to confirm our results. The follow-up period was relatively

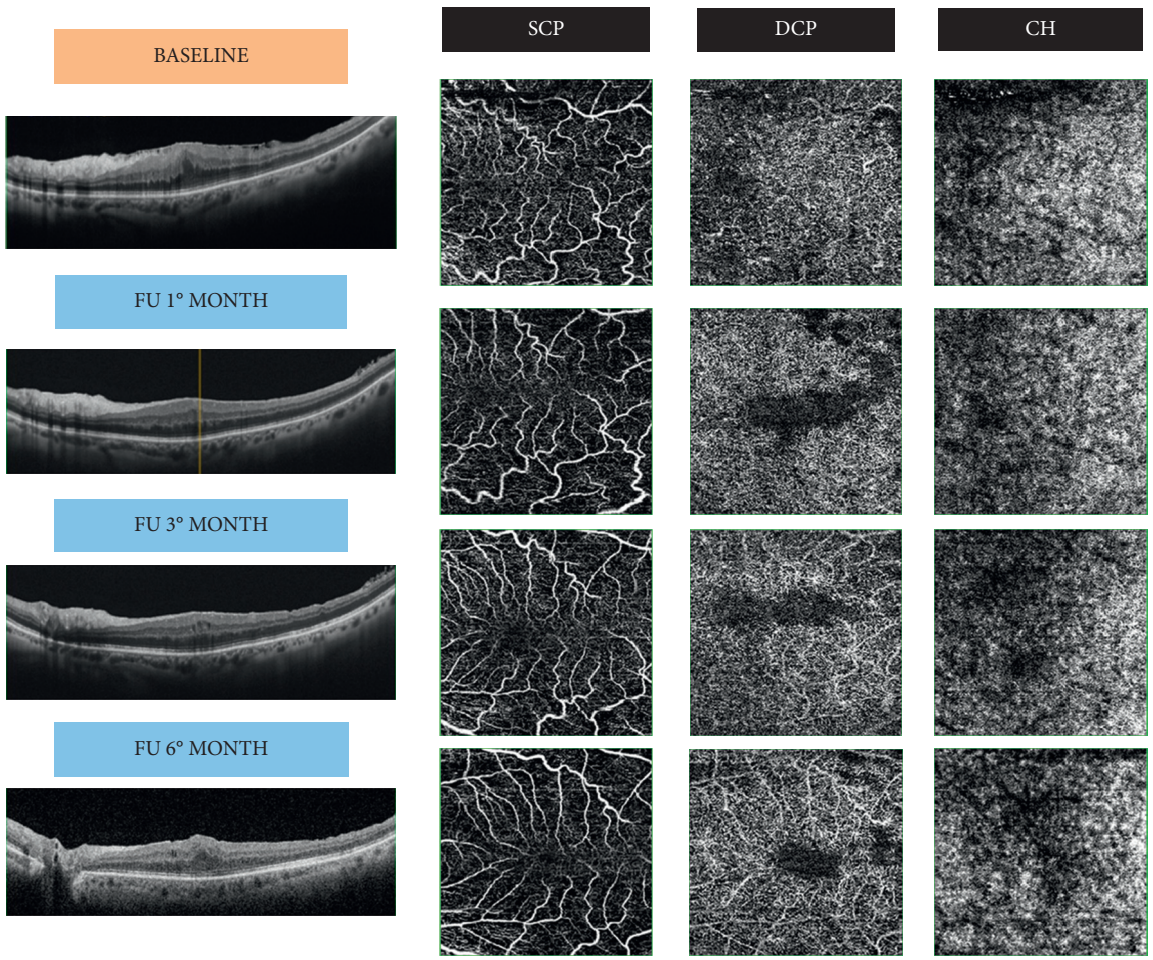


Figure 4: Vascular changes after ERM removal in VD. FU: follow-up; SCP: superficial capillary plexus; DCP: deep capillary plexus; CH: choroid.

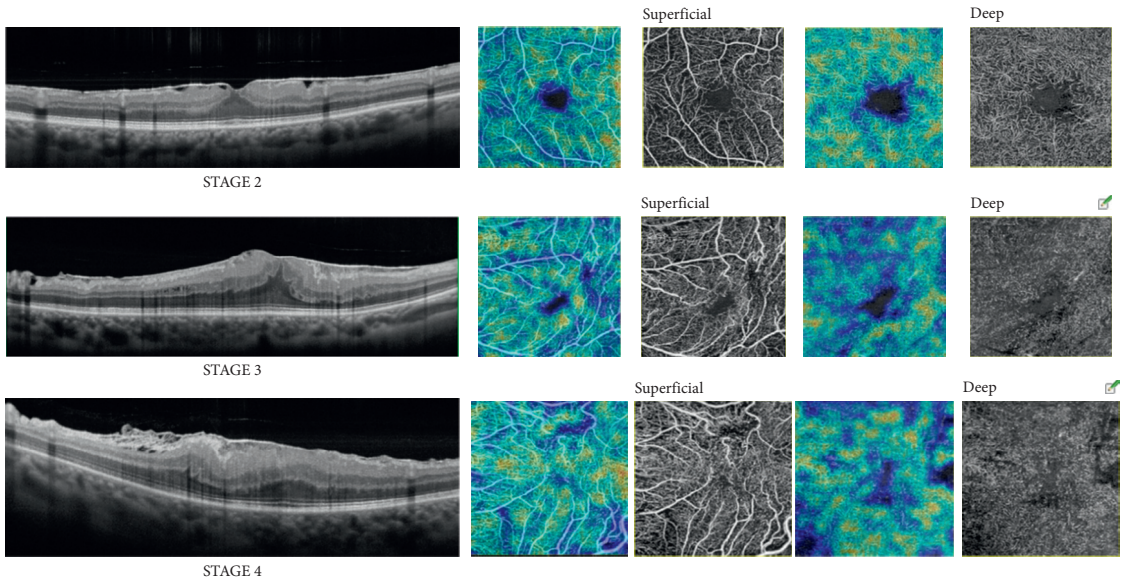


Figure 5: Vessel density and perfusion density correlated to ERM status.

Table 1: Patients' demografical and anatomical data.

Follow-up	Age (year)	Axial length (mm)	Best corrected visual acuity (logMAR)	Govetto classification (eyes)	Central retinal thickness (μm)	Outer nuclear layer thickness (μm)
Baseline	75,27 ± 6,33	23.61 ± 0.78	0,47 ± 0,19	1:4 2:9 3:7 4:3	445,91 ± 78,86	230 ± 65,26
1st month			0,28 ± 0,15**		432,67 ± 90,56 *	201,45 ± 59,05
3rd month			0,16 ± 0,12**		384,35 ± 59,23	192,37 ± 58,04
6th month			0,11 ± 0,12**		375,18 ± 62,03	179,45 ± 53,25 *

* $p < 0.05$; ** $p < 0.01$

short, and further prospective randomized studies with longer observation periods are necessary to confirm these results.

We have revealed the presence of intraretinal microcysts in the extrafoveal region in 2 patients both at the 1st month of follow-up and at the 3rd although they have not interfered with proper layer segmentation and the FAZ calculation and measurement. For this reason, we do not believe that the data obtained could be related to the presence of a pseudophakic edema. Our hypotheses have the necessity to be confirmed by further and larger studies.

5. Conclusions

The purpose of our study was to understand how preoperative alterations can affect the postoperative visual results. The most significant quantitative alterations of retinal vascularity involve the FAZ and the retinal and choroidal plexi and are correlated to ERM severity, measured using the Govetto classification.

To date, the exact timing of ERM surgery is not strictly defined. Generally, a worsening of a patient's symptoms, such as an increase in metamorphopsia or a decrease in visual acuity, leads to surgery. These factors, however, are not standard and quantifiable and sometimes occur late in the disease, so the choice of surgical timing is still very arbitrary.

OCTA could be useful to evaluate retinal circulation in a rapid and noninvasive way and can be performed at the same time as the structural OCT necessary for the diagnosis and classification of ERM. Since vitreoretinal surgery is elective, further studies are necessary to define the role and clinical usefulness of OCTA in the routine assessment of patients affected by ERM and to help establish the correct surgical timing (Table 1)

Data Availability

The data used to support the findings of this study are available from the corresponding author on reasonable request.

Disclosure

The research did not receive any specific funding.

Conflicts of Interest

The authors declare that there are no conflicts of interest in any materials discussed in this article.

Supplementary Materials

Table 1: vessel density parameters. Table 2: perfusion density parameters. Table 3: FAZ parameters. (*Supplementary Materials*)

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Research Article

Autologous Lens Capsule Flap Transplantation for Persistent Macular Holes

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Purpose. To analyze the anatomical and functional outcomes after autologous lens capsule transplantation in patients with persistent macular hole. *Methods*. This is a retrospective observational study of five eyes of five patients treated with vitrectomy and autologous lens capsular flap transplantation. Complete ophthalmic examination was performed preoperatively and seven days and 1, 3, 6, 12, and 18 months after surgery. *Results*. Successful macular hole closure was achieved in all patients. The mean minimum macular hole diameter before the surgery was 666.8 μm, and the mean basal diameter was 1086.4 μm. The mean visual acuity before lens capsular flap transplantation was 20/200, while after surgery, it was 20/125. *Conclusions*. Autologous lens capsular flap transplantation is a potential alternative treatment for patients with large persistent macular holes after other operative techniques have failed.

1. Introduction

Pars plana vitrectomy with internal limiting membrane (ILM) peeling has been a standard procedure in macular hole (MH) treatment for over a decade [1]. On average, hole closure is achieved in 88–100% of the cases [2, 3].

Operative failures might occur with large, persistent holes, exceeding 400 μm in diameter. Such failures have encouraged surgeons to search for modifications to the conventional technique, often using autologous tissue as a scaffolding for cell migration from the surrounding retina, including inverted ILM flap, autologous ILM graft from the surrounding retina, autologous retina, autologous blood application, and lens capsule [4–10].

One modified technique involves transplanting material from the anterior or posterior lens capsule onto the MH [5, 7, 8] (Figures 1 and 2). This technique proved effective in persistent holes after extensive ILM peeling and is the main topic of this article.

2. Materials and Methods

This report concerns five eyes with persistent full-thickness MH in five female patients (average age 60.6 years; range 43–73 years). All patients were treated unsuccessfully by 20-gauge vitrectomy with ILM peeling and were scheduled for modified lens capsular flap transplantation. Written consent for the surgical procedure was obtained from all patients.

A silicone oil tamponade with its subsequent removal was used in four patients, whereas the remaining patient received an air tamponade.

All patients underwent a full preoperative ophthalmic examination. The slit-lamp biomicroscopy was performed after dilating the pupils with 1% tropicamide solution.

SD-OCT examinations were performed using the SPECTRALIS HRA + OCT system (Heidelberg Engineering, Germany). The analysis included B-scans, performed 12 mm from the center at the fovea level. Preoperatively, the minimum hole diameter and the base diameter at the retinal pigment epithelium level were measured.

Transplantation of a flap harvested from the posterior lens capsule was performed in four pseudophakic patients, and phacovitrectomy was done in one patient, using material from the anterior lens capsule of the same eye to close the hole.

All patients underwent surgery by the same surgeon (S. C.). Postoperative examinations took place one day and 1, 3, 6, 12, and 18 months after the surgery. The patients

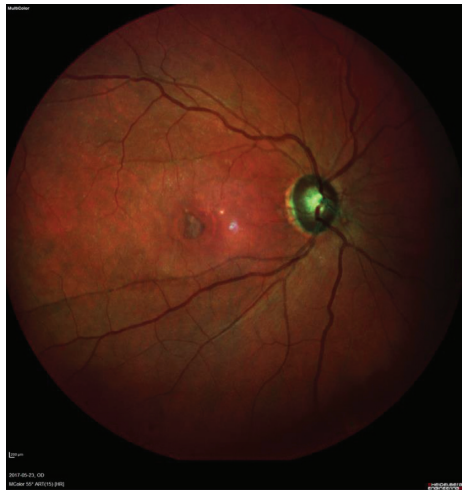


Figure 1: A macular hole closed surgically with a lens capsular flap.

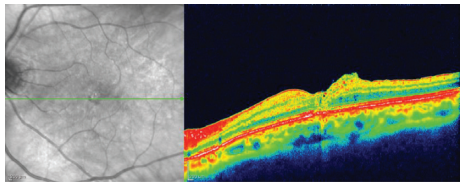


Figure 2: Spectral-domain optical coherence tomography (SD-OCT) image of a macular hole closed surgically with a lens capsule.

underwent a full ophthalmic examination during the follow-up visits that included SD-OCT, similar to the preoperative schedule.

2.1. Surgical Technique

2.1.1. Step 1. All surgeries were performed following peri-ocular anesthesia and with a 20-gauge system.

In an eye with an immature cataract, surgery began with its removal and the implantation of an artificial lens in the posterior capsule. The anterior capsule was stained with trypan blue for better visualization, followed by capsulo-rhexis with a cystotome needle.

In the four pseudophakic patients, the surgery began with posterior lens capsule staining by direct injection of trypan blue, followed by posterior rhexis with an ILM forceps.

During the operation, Membrane Blue Dual® (Dorc, Rotterdam, the Netherlands) was used to stain the remaining ILM around the MH to exclude the possibility of performing an autologous free ILM flap. The dye was rinsed out after 1 min.

The size of the capsular flap harvested in each case was larger than the diameter of the MH.

2.1.2. Step 2. After harvesting the lens capsular flap, it was placed gently with the outer surface over the MH. The eye was filled completely with perfluorocarbon liquid (PFCL) to decrease the risk of the displacement by residual fluids.

2.1.3. Step 3. In four cases, a direct exchange of PFCL with 1000 Cs silicone oil was performed to ensure that the unattached posterior capsular flap was not lost. In the one case where an anterior capsular flap was employed, PFCL/air exchange was performed and the patient was informed about the necessity of maintaining a face-down position for three days after the surgery.

3. Results

3.1. Overall Results. Successful MH closure was achieved in all patients. The silicone oil endotamponade was removed after one week. The mean minimum MH diameter before surgery was 666.8 μm, and the mean basal diameter was 1086.4 μm. The mean best-corrected visual acuity improved significantly (Figure 3).

Before the lens capsular flap transplantation, the mean preoperative visual acuity was 20/250, while it was 20/125 after surgery. Detailed data are presented in Table 1.

3.2. Case Examples. The postoperative scans showed closure of the hole with gradual restoration of the retinal layers. Figures 4(a)–4(d) and Figures 5(a)–5(d) show cases of anterior and posterior lens capsular flap transplantation, respectively.

4. Discussion

Considering the variety of operative techniques available for MH treatment, it is possible to reduce the number of persistent holes. In the traditional, conventional, operative technique of vitrectomy with ILM peeling, the gas promotes for cell migration, allowing the closure of the hole and separation of the pigment epithelium from the liquid. In the inverted ILM flap technique or when transplanting ILM from the margin of the retina, it is for the ILM flap to bridge the hole, while the air serves as an additional stabilizer [8, 10].

Vogt et al. found positive immunoreactivity of macroglia and microglia cells in the transplanted posterior lens capsule (PLC) [11]. Michalewska et al. suggested that if a segment of the peeled-off ILM is left attached, it might provoke gliosis inside the retina and ILM surface. Comparable immunostaining of the PLC material and ILM may suggest that the MH closure mechanism in the inverted ILM flap technique and PLC transplantation is similar [11].

Chen and Yang hypothesized that the lens capsule, like the basement membrane, facilitates bridging the retinal tissue above the hole (like an ILM flap) [5]. The lens capsule has a pliable consistency. Moreover, it has a higher density than the ILM, making it easier to settle on the retinal surface and be directed to the designated place [5]. The use of lens capsular flap transplantation requires some technical aspects to be discussed. First, the graft size should be more than 1 mm larger than the MH diameter, even in cases of large hole. A very important tip is to close the infusion line to decrease fluid turbulence and to avoid transplant displacement.

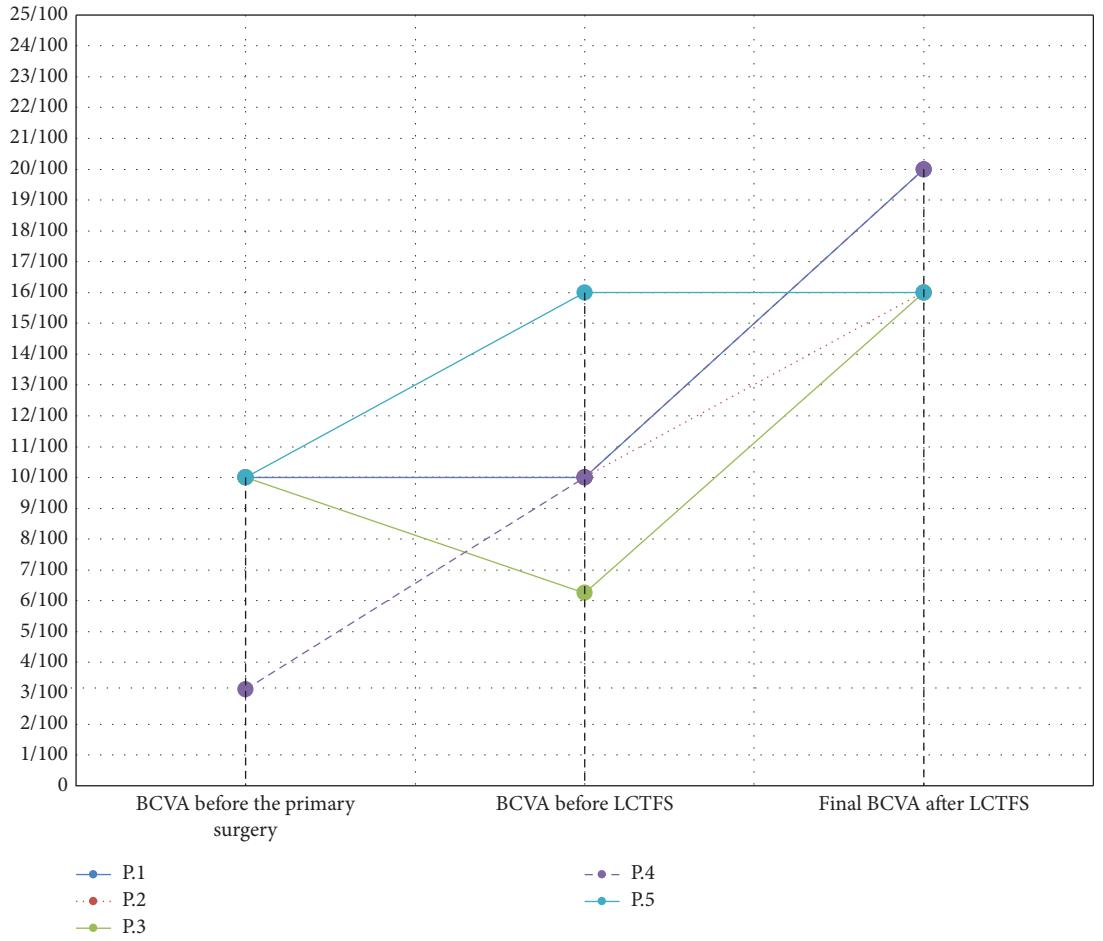
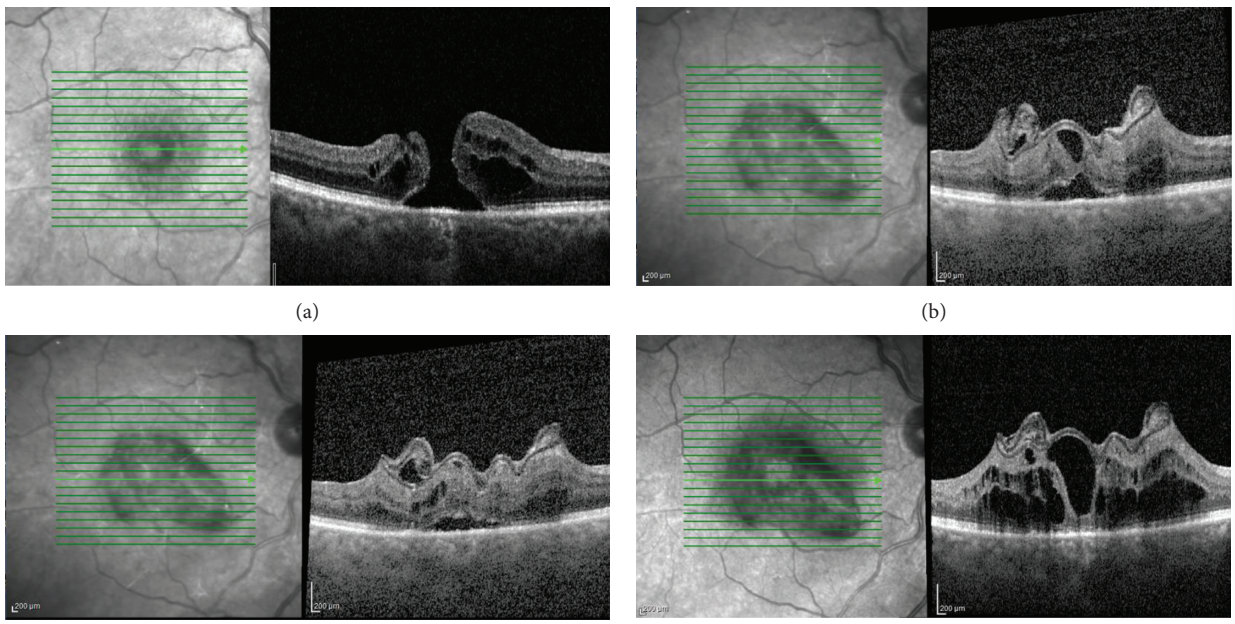


Figure 3: Changes in the BCVA from baseline to 18 months after the surgery.

Table 1: Patients' data.

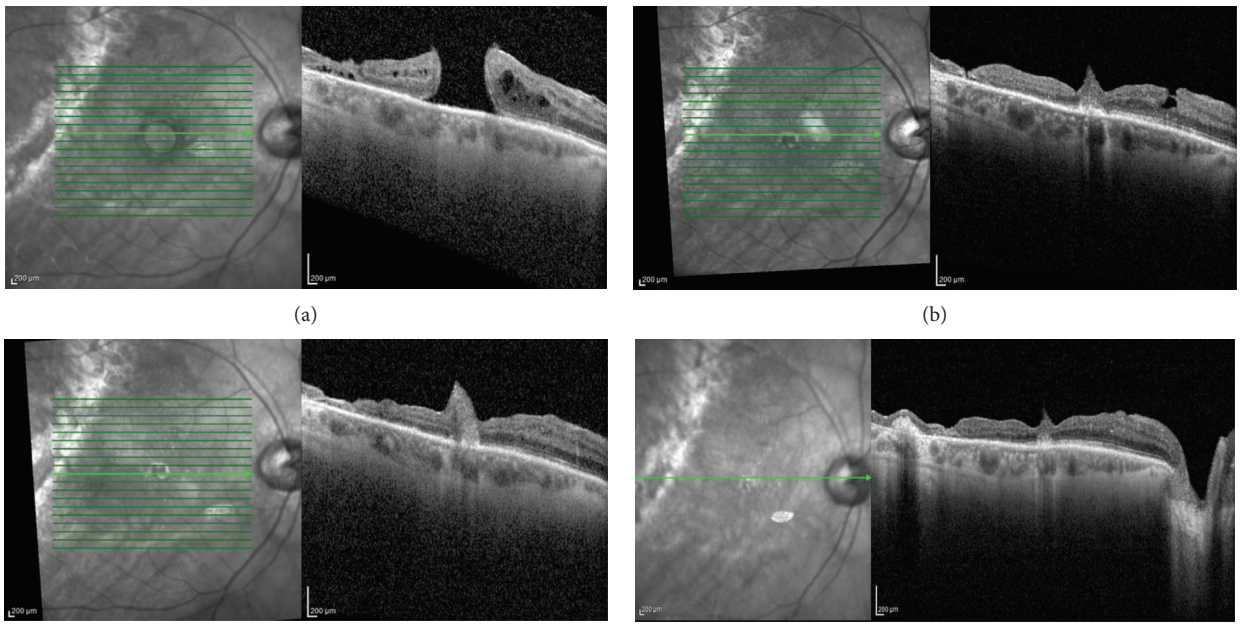
Patient no.	Sex/age	MH etiology	BCVA before the primary surgery (Snellen)	BCVA before lens capsule transplant surgery (Snellen)	Final BCVA post-op. (Snellen)	MH (min/basal) before the primary surgery (Snellen)	MH (min/basal) before LCTFS (μm)	Transplant	Previous surgical procedures/primary pathology
1	F/43	Primary	0, 1 20/200	0, 1 20/200	0, 2 20/100	936/1705	951/1396	Posterior capsule	(1) Phacovitrectomy + sil.oil/MH
2	F/68	Primary	0, 1 20/200	0, 1 20/200	0, 16 20/125	605/1020	603/1017	Posterior capsule	(1) Vitrectomy + 100%air/MH
3	F/60	Primary	0, 1 20/200	0, 06 20/320	0, 16 20/125	905/1508	1065/1611	Posterior capsule	(1) Vitrectomy + ILM peeling + sil. oil/MH with retinal detachment (2) Sil. oil removal/persistent MH
4	F/59	Secondary (after blunt trauma)	0, 03 20/640	0, 1 20/200	0, 2 20/100	582/647	445/600	Posterior capsule	(1) Phacovitrectomy + 100% air/MH
5	F/73	Primary	0, 1 20/200	0, 16 20/125	0, 16 20/125	389/1150	270/808	Anterior capsule	(1) Vitrectomy + 100% air/MH

F: female; BCVA: best-corrected visual acuity; MH: macular hole; LCTFS: lens capsular flap transplantation surgery; No.: number; sil. ol: silicone oil.



(a) (b) (c) (d)

Figure 4: Macular hole closure over time after anterior lens capsular flap transplantation. Vertical SD-OCT scans: (a) baseline, (b) one month after surgery, (c) six months postoperatively, and (d) 12 months postoperatively. Scale bar = 200 μm.



(a) (b) (c) (d)

Figure 5: Macular hole closure over time after posterior lens capsular flap transplantation. Vertical SD-OCT scans: (a) baseline, (b) one month after surgery, (c) six months postoperatively, and (d) 12 months postoperatively. Scale bar = 200 μm.

Another interesting issue worth clarifying is the graft orientation. We tried to place lens capsular transplants with the outer surface onto the hole, as it is smoother than the inner one and contains no cells. However, it might be difficult to differentiate between the sides after the manipulations under the PFCL.

There are certain differences between using the anterior and posterior capsules during surgery. The anterior capsule is thicker and when used in conjunction with PFCL adheres firmly to the retinal surface. With the anterior capsule implantation in mind, it was decided to use an air endotamponade in this patient (no. 5 in Table 1). In this case, we observed intraretinal edema with almost complete external limiting membrane restoration, ellipsoid zone, and clearly seen retinal pigment epithelium. First, the anterior capsule was not very smooth, and it contained cells that promoted

cell migration; second, we may have unintentionally placed the transplant in an upside-down orientation during manipulations under the PFCL.

In the four eyes in which a posterior capsular autograft was performed, silicone oil was used for endotamponade to prevent dislocation of the flap. The silicone oil was removed after one week. We observed flap incorporation into the retinal tissue during follow-up SD-OCT scans of two patients (Figure 2; patient nos. 1 and 2). The foveal contour was defined as a U-shape closure with small irregularity. We observed a type of plug in the other two patients (Figures 4(b)–4(d); patient nos. 3 and 4) which probably confirmed that the flap, like the basement membrane, could bridge the hole and represent a membranous noncellular tissue. We know that this might influence BCVA but the exact impact is unknown [12].

The final visual acuity improved over the preoperative state, but it remained relatively poor. It should be mentioned that, unlike our patients, the holes would remain open after performing a classical vitrectomy with ILM peeling [10].

5. Conclusions

Lens capsular flap transplantation gives hope to patients with large MH, in whom other operative techniques have failed. Therefore, it seems reasonable to retain the posterior capsule during combined surgeries in case it will be needed for other indications.

Our work was based on a small case series. Even though positive postoperative results were achieved, it is necessary to repeat the study with a larger cohort.

Data Availability

The patient data used to support the findings of this study are included within the article.

Additional Points

Partial results from this study (12-month follow-up) were presented at the MaculArt 2019 Meeting, June 2019, and EVRS 2019, May 2019.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Multimodal Imaging of Lamellar Macular Holes

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Evolution of imaging techniques has renewed interest in the diagnosis of lamellar macular hole (LMH) and greatly implemented the possibilities of gaining more detailed insights into its pathogenesis. Among noninvasive techniques, optical coherence tomography (OCT) is considered the primary examination modality to study LMHs, given its ability to image foveal structure and its widespread availability. OCT also allows to resolve the epiretinal materials associated with LMH, i.e., tractional epiretinal membranes (ERMs) and epiretinal proliferation (EP). En face OCT reconstructions are useful to confirm the foveal abnormalities shown by the eyes with LMH, whereas OCT angiography may reveal alterations of the size and shape of the foveal avascular zone and alterations of the density of the superficial and deep vascular plexuses. On slit-lamp biomicroscopy or fundus camera examination, LMH appears as a round or oval, reddish lesion at the center of the macula, slightly darker than the surrounding retina. The associated tractional ERM, causing wrinkling and glistening of the retinal surface, is usually readily appreciable, whereas EP is hardly apparent on biomicroscopy or fundus photography since the retina surface appears smooth. When imaged with blue fundus autofluorescence (B-FAF) imaging, LMHs are characterized by an increased autofluorescent signal, the intensity of which does not correlate with the thickness of the residual outer retinal tissue. Green reflectance and blue reflectance (BR) images clearly show the increased reflection and wrinkling of the retinal surface caused by tractional ERM associated with LMH. BR and multicolor imaging enable the visualization of EP associated with LMH in the form of a sharply demarcated dark area and in the form of a yellowish area surrounding the hole, respectively. Scarce data regarding invasive imaging techniques, such as fluorescein angiography, for the study of LMH are available in the literature. The aim of this review is to evaluate the contribution that each imaging modality can provide to study the morphologic characteristics of LMH.

1. Background

The term lamellar macular hole (LMH) was introduced in 1975 by Gass [1], who identified, by slit-lamp biomicroscopy, an oval reddish macular lesion resulting from cystoid macular edema, secondary to the rupture of the roof of a foveal cyst. In the following years, the term LMH has been used to refer to foveal alterations with certain characteristic on biomicroscopic examination, independent of the pathogenesis (idiopathic or secondary to other pathologies).

Evolution of imaging techniques and especially the advent of widespread use of optical coherence tomography (OCT) has renewed interest in the diagnosis of LMH and greatly implemented the possibilities of gaining more detailed insights into its pathogenesis.

Preliminary studies based on time-domain OCT suggested that LMH could be the consequence of an aborted process of full-thickness macular hole formation, leading to avulsion of part of the inner fovea because of vitreofoveal traction [2, 3]. Other studies proposed that anteroposterior

and tangential forces exerting centripetal or centrifugal traction on the fovea might be involved in the pathogenesis of LMH [4, 5]. However, more recent spectral-domain OCT studies challenged these assumptions suggesting that true LMH might be the result of remodelling of the foveal tissue occurring in absence of overt epiretinal tractional forces [6–10]. True LMHs are often associated with a tissue of intermediate reflectivity, usually thicker than standard, tractional epiretinal membranes (ERMs), observed on the retinal surface. This tissue, originally described by Witkin et al. [4] as "thickened ERM," subsequently renamed "lamellar hole-associated epiretinal proliferation" [8] is nowadays referred to as epiretinal proliferation (EP) [10] since it is not exclusive to LMH but can be found also in a wide spectrum of retinal diseases, including full-thickness macular holes, posterior uveitis, macular pucker, age-related macular degeneration, diabetic retinopathy, refractory macular edema, vein occlusion, and high myopia [11].

Histopathologic studies have evidenced significant differences in the composition of tractional ERM versus EP. [6, 12, 13]. Specifically, myofibroblasts dominate in highly reflective membranes, whereas membranes of medium reflectivity consist primarily of fibroblasts and hyalocytes.

In order to propose a clear definition of LMH based on new retinal imaging and to differentiate LMH from other similar but distinguishable entities like schisis of the fovea associated with ERM and pseudohole, an international panel of vitreoretinal experts has recently proposed new OCT-based criteria for the diagnosis of these three entities. According to the panel, the features characterizing LMH are the presence of irregular foveal contour, foveal cavity with undermined edges, and presence of pseudooperculum and/or thinning of the fovea. Associated pathological changes can include EP, foveal bump, and ellipsoid line disruption. Such a definition is similar to what was previously considered as a 'true' or degenerative LMH [14, 15].

Conversely, schisis of the fovea associated with ERM has been named ERM foveoschisis and features the presence of contractile ERM, foveoschisis at the level of Henle fiber layer (HFL) and optionally microcystoid spaces in the inner nuclear layer (INL), and retinal thickening and wrinkling. In the literature, this entity has been previously referred to as "tractional" LMH and/or pseudohole with lamellar cleavage of its edges [14, 15].

Finally, macular pseudohole (PSH) features a foveal center sparing ERM, retinal thickening with verticalised or steepened foveal profile, and optionally presence of microcystoid spaces in the INL and near-normal central foveal thickness. Such a definition is similar to that previously proposed by the International Vitreomacular Traction Study Group [16].

One main aspect differentiating LMH from ERM foveoschisis and PSH resides in the assumption that only LMH is associated with loss of tissue. As specified earlier, presumed signs of retinal cell loss on OCT in presence of LMH are the undermined edges, foveal thinning, and a posterior vitreous detachment associated with pseudooperculum. However, OCT imaging may not be fully reliable in distinguishing loss of tissue.

It was proposed that blue fundus autofluorescence (B-FAF), another imaging modality, could overcome some limits of OCT and discriminate loss of tissue by showing an increased autofluorescent signal at the fovea [17]. Nevertheless, ERM foveoschisis, LMH, and PSH all feature an increased autofluorescent signal at the fovea. Furthermore, there is uncertainty if the increased autofluorescence associated with LMH and PSH represents an actual loss of foveal tissue or a centrifugal displacement of neurosensory tissue containing macular pigment or a combination of both [17–19].

More recently, the potentialities of multicolor imaging (MCI) in studying LMH and in particular the EP associated with LMH have been investigated. Nevertheless, like B-FAF, MCI does not provide clues regarding the loss of tissue.

Thus, despite advancements in imaging technology, at present only histological studies appear able to definitely confirm the presence of retinal tissue loss associated with LMH.

The aim of the present paper is to give an overview about the imaging modalities used to study LMH and the contribution that each of them can give in better understanding the pathogenesis of this fascinating vitreomacular disease.

2. Methods

To identify and select the relevant articles regarding retinal imaging features in eyes with LMH, a research was performed on PubMed (https://www. ncbi. nlm. nih. gov/pubmed/) using the following terms (or combination of terms): "lamellar macular hole" or "LMH" or "epiretinal membrane" or "ERM" or "lamellar hole-associated epiretinal proliferation" or "LHEP" or "epiretinal proliferation" or "EP" or "foveoschisis", last accessed 17 August 2020.

During the period under review, patients with a LMH and an ERM foveoschisis were classified as "degenerative LMH," or "tractional LMH" or "lamellar hole".

All references of the included articles were also screened to guarantee no omission of literature. For study selection, the inclusion criteria were (1) accurate description of LMH features using imaging techniques and (2) articles written in English. The selection was then reviewed by the authors and a final list of 42 papers agreed (Figure 1) to be used as the basis for the review. Of these, 34 directly regarded LMH, whereas the remaining 8 were considered for the differential diagnosis of LMH with similar conditions or for the description of multimodal imaging techniques.

3. Results

3.1. Slit-Lamp Biomicroscopy and Fundus Camera Photography. On slit-lamp biomicroscopy or fundus camera (FC) examination (Figure 2), LMH appears as a round or oval, reddish lesion at the center of the macula, slightly darker than the surrounding retina [1]. The associated EP, if present, is hardly apparent on biomicroscopy or fundus photography since the retina surface appears smooth [8]. A central reddish lesion is also visible in ERM foveoschisis. The

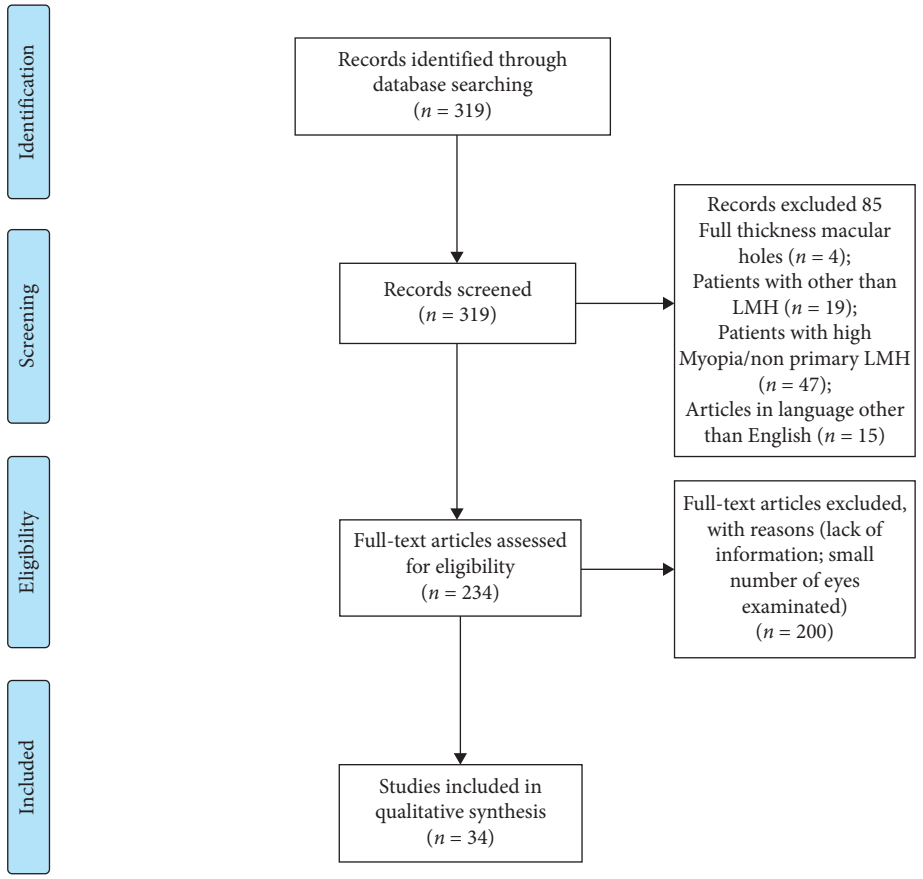
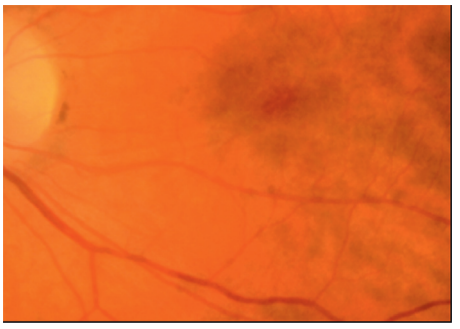


Figure 1: Flow diagram showing the methodology followed to review the literature and select the papers of interest.



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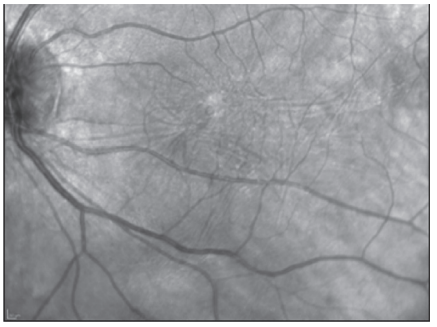
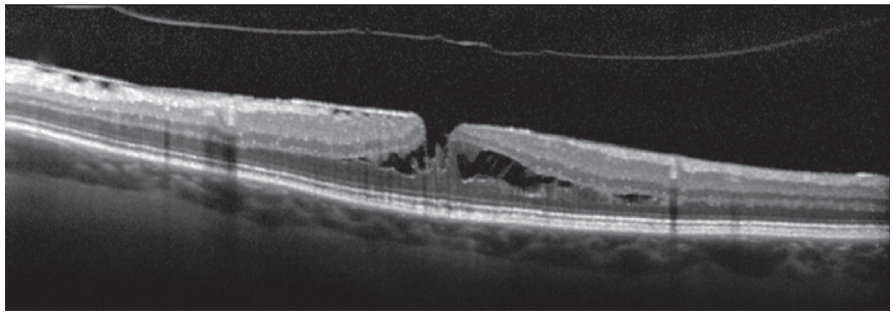


(b)

Figure 2: Continued.



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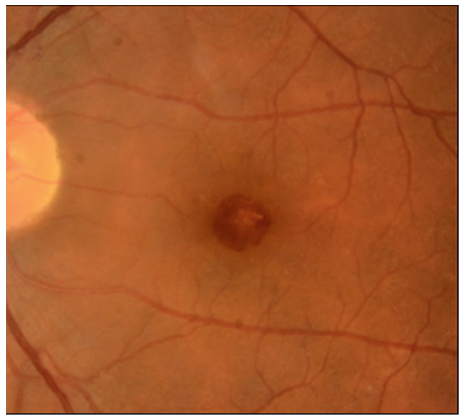

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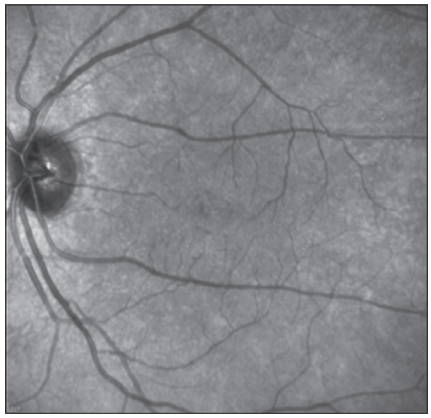

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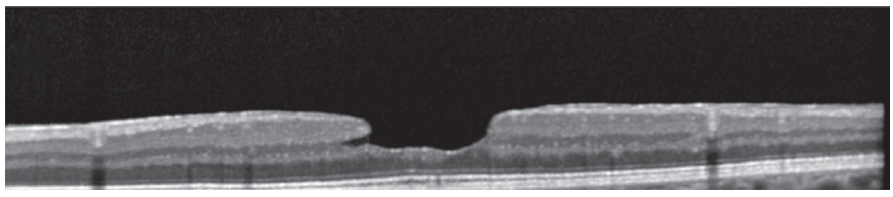


(f)

Figure 2: (a–c) Fundus camera (FC) color photograph, infrared (IR) image, and optical coherence tomography (OCT) of epiretinal membrane (ERM) foveoschisis. (a) On FC there is an oval reddish lesion at the fovea, (b) whereas on IR image, wrinkling of the retinal surface is appreciated; (c) on OCT there is an ERM over the inner limiting membrane (ILM) with the presence of hyporeflective spaces between the ERM and the ILM and a foveoschisis at the level of Henle fiber layer. (d–f) FC color photograph, IR image, and OCT of lamellar macular hole (LMH). (d) On FC a round reddish lesion at the fovea is noted; (e) on IR image the retinal surface appears smooth; (f) on OCT irregular foveal contour, foveal cavity with undermined edges, thinning of the fovea, foveal bump, and ellipsoid line disruption are present.

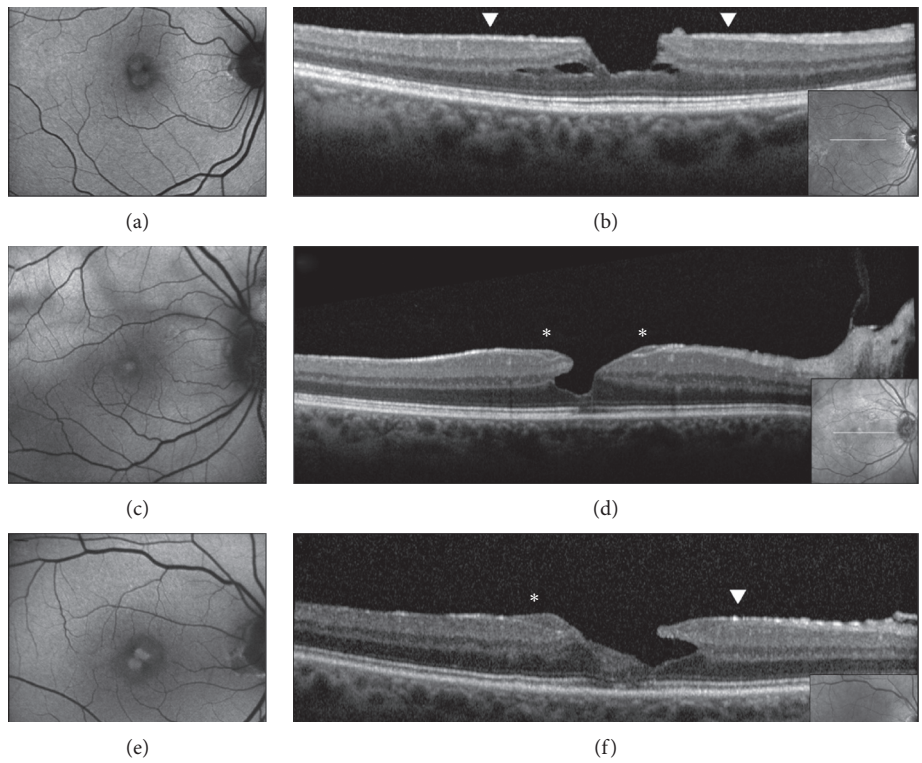


Figure 3: Blue fundus autofluorescence (B-FAF) (a, c, e) and optical coherence tomography images (OCT) (b, d, f) in eyes with epiretinal membrane (ERM) foveoschisis and lamellar macular hole (LMH). On B-FAF images, areas of increased autofluorescence at the center of the fovea can be present in both conditions. On OCT images, ERM foveoschisis is, by definition, associated with a tractional epiretinal membrane (arrowheads, b), whereas LMH may be associated with epiretinal proliferation (EP, d, asterisks) or with concomitant ERM and EP (f, arrowhead and asterisk, respectively). Intraretinal schisis and usually intact external limiting membrane (ELM) and ellipsoid zone (EZ) are noted in presence of ERM foveoschisis (b) whereas undermined edges and disrupted ELM and EZ are noted in presence of LMH. The horizontal white arrows on the infrared image (small squares within the B-FAF images) indicate the location of the corresponding OCT scans.

associated tractional ERM, causing wrinkling and glistening of the retinal surface, is usually readily appreciable on fundus examination.

In the time-domain OCT era, Haouchine et al. [3] showed that only 28% of LMH cases diagnosed with OCT were recognized as LMH on fundus examination. Likewise, Witkin et al. [4] reported that only 37% of LMHs diagnosed using an ultrahigh resolution OCT were detected clinically on fundus examination. It must be noted that, in these series, true LMH and ERM foveoschisis were both grouped under the unique definition of LMH.

However, these data show the limits of slit-lamp biomicroscopy and fundus photography for the correct diagnosis of LMH and for the differential diagnosis with similar-looking macular pathologies.

3.2. Optical Coherence Tomography. Using time-domain OCT, Haouchine et al. [3] first defined the criteria for the OCT-based diagnosis of LMH. Later, Witkin et al. [4] refined the classification using ultrahigh-resolution OCT. They proposed 4 basic criteria: (1) an irregular foveal contour; (2) a break in the inner fovea; (3) a dehiscence of the inner foveal retina from the outer retina occurring either between outer plexiform layer (OPL) and outer nuclear layer or only within the ONL; and (4) an absence of a full-thickness foveal defect with intact foveal photoreceptors. Of note, Witkin and associates reported two distinct appearances of epiretinal material associated with LMH: one was constituted by a thin highly reflective line immediately anterior to and separate from the retinal nerve fiber layer (RNFL); the other was a moderately reflective material filling the space between the outer border of the ERM and RNFL and it was named "unusual thick membrane" (Figures 2 and 3). A few years later, Parolini et al. [6] renamed these "thick membranes" as "dense membranes" and showed irregularities and disruption of the outer retinal bands (ORB) at the fovea (i.e., external limiting membrane and ellipsoid and interdigitation zone) in association with them, thus challenging the validity of criterion 4 (intact photoreceptors) of the classification proposed by Witkin and associates. On the basis of OCT and histopathologic analysis, Parolini et al. [6] proposed to make a distinction between tractional membranes (thin and hyperreflective on OCT and with predominance of α-smooth muscle actin [SMA]-positive cells on histology analysis) and dense membranes (thick on OCT and with predominance of collagen fibrils on histology analysis) associated with LMH. For these reasons and based on different outcomes after surgery, Gaudric et al. [14] subsequently proposed that LMH with tractional membranes should be regarded as a

subcategory of PSH in which a lamellar dissection caused by the separation of the inner and outer retinal layers had occurred. Gaudric et al. suggested that the name "macular pseudoholes with lamellar cleavage of their edges" (instead of LMH) would be more appropriate to define these foveal lesions. In 2014, Pang et al. [8] renamed the formerly described "thick" or "dense" epiretinal material as "lamellar hole-associated epiretinal proliferation" (LHEP). They found LHEP, a material of intermediate reflectivity and of variable thickness in 30.5% of the eyes with LMH of their retrospective series. Reportedly, 97% of these eyes with LHEP had disruption of the ellipsoid zone and 88% had visible connecting tissue from the base of the LMH to LHEP, this feature suggesting that LHEP may originate from within the inner retinal defect. Of interest, despite they noticed that LHEP did not induce tractional effects such as distortion or edema of the underlying normal retinal tissue, splitting of the retina in the region of Henle fiber layer (HFL) was reported in 98% of eyes with LHEP. On the basis of these imaging observations, Pang et al. reiterated the hypothesis originally proposed by Parolini and Bottoni et al. [6, 7] that the two types of LMH associated with different types of epiretinal membranes may have different pathogenetic origin. In 2016, taking into consideration the characteristics of the epiretinal material associated with LMH and other specific features on OCT imaging, Govetto et al. [15] proposed to classify LMH in 2 types: degenerative and tractional LMH. The degenerative type was characterized by the presence of EP, ratio between inner and outer diameter of the hole of more than 1 : 2, presence of a foveal bump, a round-edged intraretinal cavitation, and, in the large majority of the cases, a disrupted ellipsoid zone. The tractional type was characterized by the presence of a tractional membrane, a ratio between inner and outer diameter of the hole generally less than 1 : 2, intact ellipsoid layer, and a sharp-edged schisis-like appearance between outer plexiform and outer nuclear layers. In the series by Govetto et al., 10.78% of the eyes examined shared common features of both degenerative and tractional LMH. Other series confirmed the occurrence of these "mixed-cases" and reported the concomitant presence of EP and tractional ERM in a substantial higher number of cases [17–19]. Further studies reported that the presence of EP resulted frequently associated with peculiar morphologic and functional features of LMH. For instance, a worse BCVA, a thinner CFT, a cavitated appearance of the retina, and the disruption of the outer retinal bands were typically associated with EP [6–9, 14, 17, 18–20]. On the other hand, other OCT features were similar in lamellar macular defects associated or not with EP. For example, measurements of the horizontal and vertical diameters of the holes at the level of the OPL and their stability over time appeared rather similar in cases with and without EP [19].

In 2020, Hubschman [10] and a panel of vitreoretinal experts proposed a new OCT-based definition of LMH based on three mandatory and three optional criteria. Among the mandatory criteria (irregular foveal contour, foveal cavity with undermined edges, and other signs evoking a loss of foveal tissue), the concept of a foveal cavity with undermined edges is considered as a key feature of LMH because it is regarded as highly suggestive of retinal cell loss. A cavity with undermined edges is characterized by an angle between the surface of the retina and the edge of the hole lower than 90°; such morphology must be present in at least two B-scans separated 242 μm apart to make the diagnosis valid. In this classification, the occurrence of EP, ellipsoid zone disruption, and foveal bump is considered optional for the diagnosis because it is not always present in association with LMH. The lesions showing the above reported mandatory signs may be referred to as "primary" and "nonprimary" LMH, depending on the aetiology, respectively, idiopathic or secondary to known pathologies. Such a definition is similar to what was previously considered as a "true" or degenerative LMH [14, 15].

Conversely, the cases previously referred to in the literature as "tractional" LMH and "macular pseudohole with stretched edges" have been renamed by the panel as "ERM foveoschisis" (Figure 4). The two mandatory criteria for the diagnosis of ERM foveoschisis are the presence of a contractile ERM and foveoschisis at the level of HFL; optional criteria are the presence of microcystoid spaces in the INL, retinal thickening, and retinal wrinkling.

In contradistinction to ERM foveoschisis characterized by the presence of contractile ERM by definition and foveoschisis at the level of HFL, mechanical tangential traction does not seem to be relevant in LMH (Figures 2, 3, 5, and 6).

3.3. En Face OCT. En face OCT images are coronal-view images generated after computerized flattening along a specific retinal layer boundary that allow layer-by-layer analysis of the retinal tissue and may overcome some limitations of OCT cross-sectional images that may not provide detailed evaluation of traction, including traction strength and direction [21].

Gaudric et al. [14] noted that, in eyes with tractional ERM causing splitting of the retinal tissue, en face OCT images focused on the ERM showed several eccentric epicenters of contraction while images focused on the inner retina showed intraretinal folds induced by the ERM contraction. A rather similar aspect was observed in eyes with PSH in which en face OCT image focused on the surface of the internal limiting membrane (ILM slab) showed the radial folds of the ERM and of the inner limiting membrane converging toward the fovea, i.e., the epicenter of the membrane contraction in PSH. As specified above, on the basis of cross-sectional and en face OCT images, the authors proposed that macular pseudoholes with lamellar cleavage of their edge must be considered pseudoholes (Figure 4). In fact, en face OCT focused on the retinal surface and on the inner retina in case of true LMH shows a smooth retinal surface without any retinal folds [14] (Figures 5 and 6).

Using en face OCT, Clamp et al. [21] measured the area of intraretinal splitting in 42 eyes with lamellar macular defects. All the 42 eyes included in the study exhibited an area of intraretinal schisis according to the definition proposed by Witkin et al. [4] and only 7 did not present with an ERM. Thus, it is likely that the majority of "LMHs" described in this

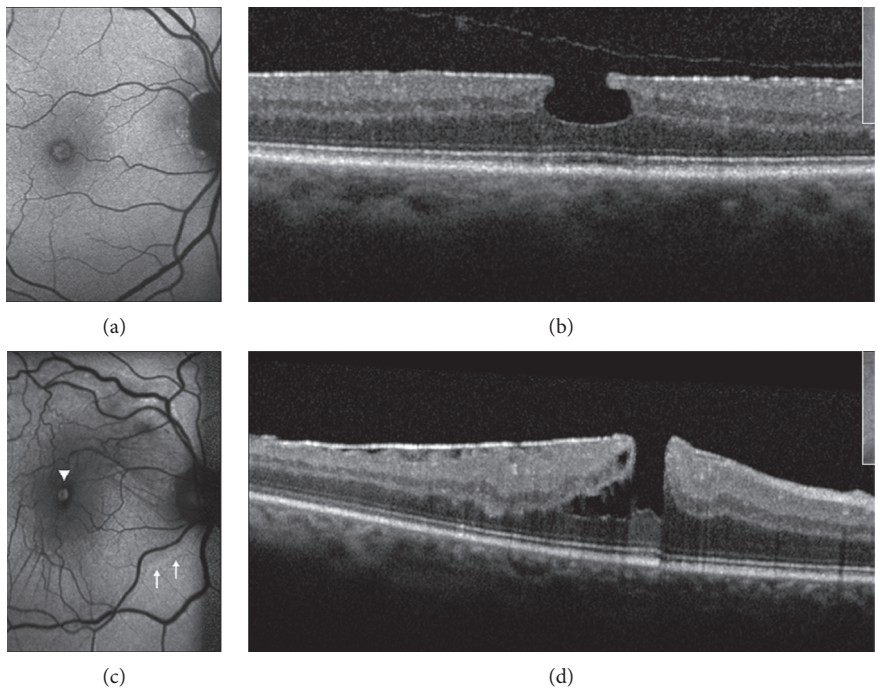


Figure 4: Blue fundus autofluorescence (B-FAF) and optical coherence tomography images (OCT) in an eye with standard macular pseudohole (PSH) and in an eye with PSH with lamellar cleavage of its edges according to Gaudric et al. [14]. B-FAF (a, c): an increased autofluorescent signal is present at the fovea in both cases. On OCT (b), standard PSH is characterized by foveal centre sparing epiretinal membrane, retinal thickening, verticalised/steepened foveal profile, and near normal central foveal thickness. PSH with lamellar cleavage of its edges (d) shows in addition an intraretinal schisis. and has been reclassified as epiretinal membrane foveoschisis by Hubschman and coworkers [10].

series were ERM foveoschisis rather than true LMH according to the most recent classification by Hubschman and associates. Clamp et al. [21] found that the eyes with ellipsoid zone disruption had significantly greater mean intraretinal schisis area and worse mean visual acuity than eyes without ellipsoid disruption. They also found a strong relationship between horizontal linear schisis diameter and the area of intraretinal schisis but the relationship was not linear, as would be expected if all of the foveal lesions were circular. Instead, some LMHs demonstrated stellate, ovoid, or semicircular pattern with the greatest linear diameter along the vertical or oblique axis. The strands of retinal tissue within the intraretinal split observed on en face images were interpreted as Müller cell and photoreceptor cell processes as originally proposed by Witkin et al. [4]. However, this pattern is not pathognomonic for LMH because it is seen in other vitreoretinal interface disorders including vitreomacular traction syndrome, full-thickness macular hole (FTMH), and myopic schisis. In 98% of the cases, the intraretinal splitting occurred within the border between HFL and the synaptic component of the outer plexiform layer.

Using en face OCT, Hirano et al. [22] identified 3 groups of LMHs, all characterized by the presence of an ERM: the first group lacked retinal folds and parafoveal epicenter of constriction (PEC) in the ERM (PEC-ERM) sign of a localized strong contraction in the parafovea; ellipsoid zone disruption and LHEP were seen in 69% and 81% of this group, respectively. The other two groups presented retinal folds associated with retinal cleavage and retinal folds associated with retinal cleavage and PEC-ERM, respectively. As reported by the authors, 81% of the eyes in the first group could be classified as "degenerative LMH" according to Govetto et al. [15], whereas the eyes in the second and third group were classifiable as tractional LMH in 95% and 100% of the cases, respectively. By contrast, PSH showed retinal folds but lacked PEC-ERM and retinal cleavage. Based on these results, the authors reiterated Gaudric's hypothesis that MPHs with stretched edges are part of the spectrum of MPH and are induced by ERM contraction. Nevertheless, on the basis of the current imaging technology, they acknowledged the difficulty of supporting the assumption of Takahashi [2] and Pang [13] who suggested that the loss of inner foveal tissue is a key characteristic of true LMH.

In a recent multimodal imaging analysis, Govetto et al. [23] showed that ERM foveoschisis presents with a characteristic radial "spoke-wheel" appearance on en face OCT imaging (segmented at the level of the outer nuclear layer-HFL complex) and this appearance would be consistent with the disposition of parafoveal Müller cells (Figure 7). Comparing en face OCT and fluorescein angiography findings, the authors speculated that the intraretinal splitting characteristic of ERM foveoschisis may be considered a subtype of macular edema in which intraretinal spaces are created by mechanical displacement of cells rather than disruption of the inner and/or outer retinal barriers. This

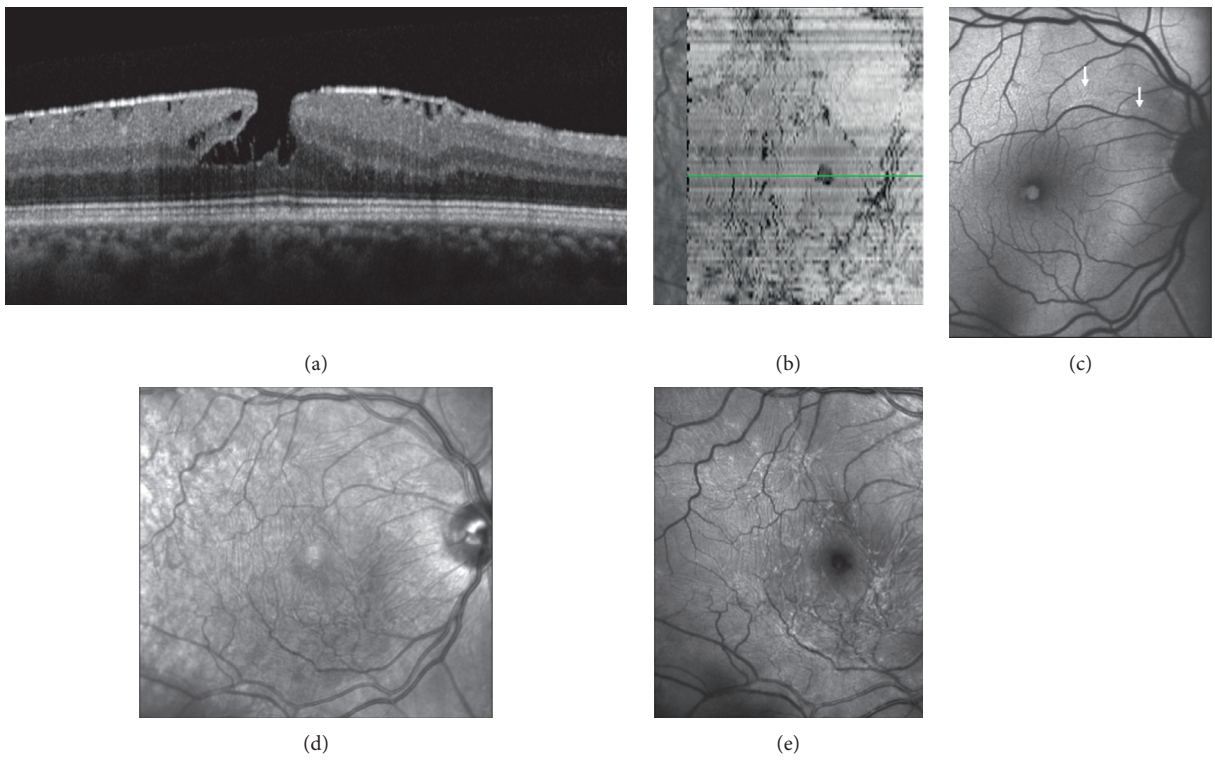


Figure 5: Multimodal imaging of epiretinal membrane (ERM) foveoschisis. (a) Structural optical coherence tomography (OCT) shows the hyperreflective line corresponding to the ERM on the retinal surface and the intraretinal schisis at the level of the Henle fiber layer. (b) On en face OCT (segmentation at the level of the vitreoretinal interface) signs of traction like folds and retinal wrinkling are visible in the macular area. The horizontal green line indicates the location of the corresponding structural OCT scan. (c) Blue fundus autofluorescence shows an area of increased signal at the fovea and retinal vessel printings at the superonasal aspect of the macula (arrows). Superficial wrinkling of the inner retina is notable on the infrared image (d) but is better visualized on the green reflectance image (e) where several foci of traction are also evident.

assumption fits well with previously published studies on the biomechanics of the parafoveal Müller cells [24].

3.4. Blue Fundus Autofluorescence. Blue fundus autofluorescence (B-FAF) imaging is a modality that relies on the fluorescence generated by the bisretinoids of lipofuscin in retinal pigment epithelial (RPE) cells and is influenced by absorbent or autofluorescent materials anterior to the RPE monolayer [25, 26]. The autofluorescent signal may be recorded by a confocal scanning laser ophthalmoscope (cSLO) or by a fundus camera. Confocal scanning laser ophthalmoscopes have a confocal capability by which only conjugate points on the fundus are imaged whereas points not lying on the conjugate planes are rejected. Commercially available cSLO use an excitation wavelength of 488 nm generated by an argon or solid-state laser and a wide band-pass barrier filter with a short wavelength cutoff inserted in front of the detector set at around 500 nm. By contrast, fundus camera system uses an excitation filter from 535 to 580 nm and a barrier filter from 615 to 715 nm. In eyes without disease-related abnormalities, B-FAF imaging of the macula shows reduced signal at the fovea (because of absorption of the blue light by the macular pigment) and a distinct increase at about the foveal margin, followed by a further gradual increment toward the outer macula.

When imaged with B-FAF imaging, LMHs and ERM foveoschisis are characterized by an increased autofluorescent signal, the intensity of which does not correlate with the thickness of the residual outer retinal tissue [17]. Interestingly, lesions classified as PSH on the basis of OCT may have an appearance similar to LMH and ERM foveoschisis on B-FAF imaging [17].

The significance of this area of increased B-FAF signal is not clear. This feature might represent an actual loss of foveal tissue or a mere centrifugal displacement of neurosensory tissue containing macular pigment or both [17, 19]. At present, B-FAF cannot answer this question.

In a study by dell'Omo et al., the increased autofluorescent signal at the fovea appeared to be similar in size in the presence of lamellar holes associated with tractional ERM or EP [19]. In fact, diameters of the holes measured on B-FAF images did not differ between eyes with and without EP at baseline and did not change significantly during the follow-up period [19].

Thus, LMHs, foveoschisis ERM, and PSH, although with different features based on OCT, may appear to be indistinguishable based on FAF imaging (Figures 3 and 4). Interestingly, the size of the area of increased autofluorescence may decrease after surgery both in eyes with ERM foveoschisis and in eyes with true LMH associated with EP. This seems to suggest that, at least in part, the increased

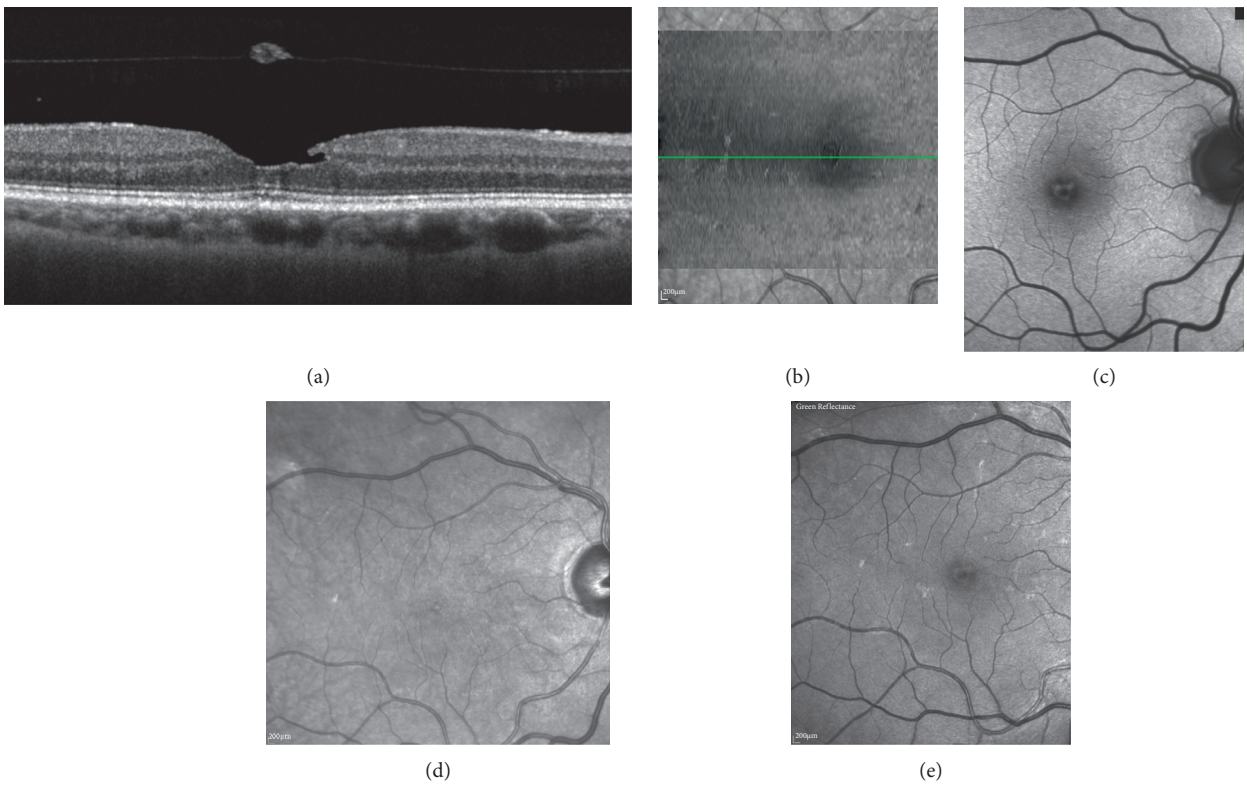


Figure 6: Multimodal imaging of lamellar macular hole. (a) Structural optical coherence tomography (OCT) shows irregular foveal contour, foveal cavity with undermined edges, posterior vitreous detachment with pseudooperculum, and thinning of the fovea at its center. (b) On en face OCT (segmentation at the level of the vitreoretinal interface), no signs of traction like folds and retinal wrinkling are visible in the macular area. Blue-fundus autofluorescence (c) shows an area of increased signal at the fovea partially masked by the pseudo-operculum. On infrared (d) and on green-reflectance (e) images, the retinal surface appears smooth.

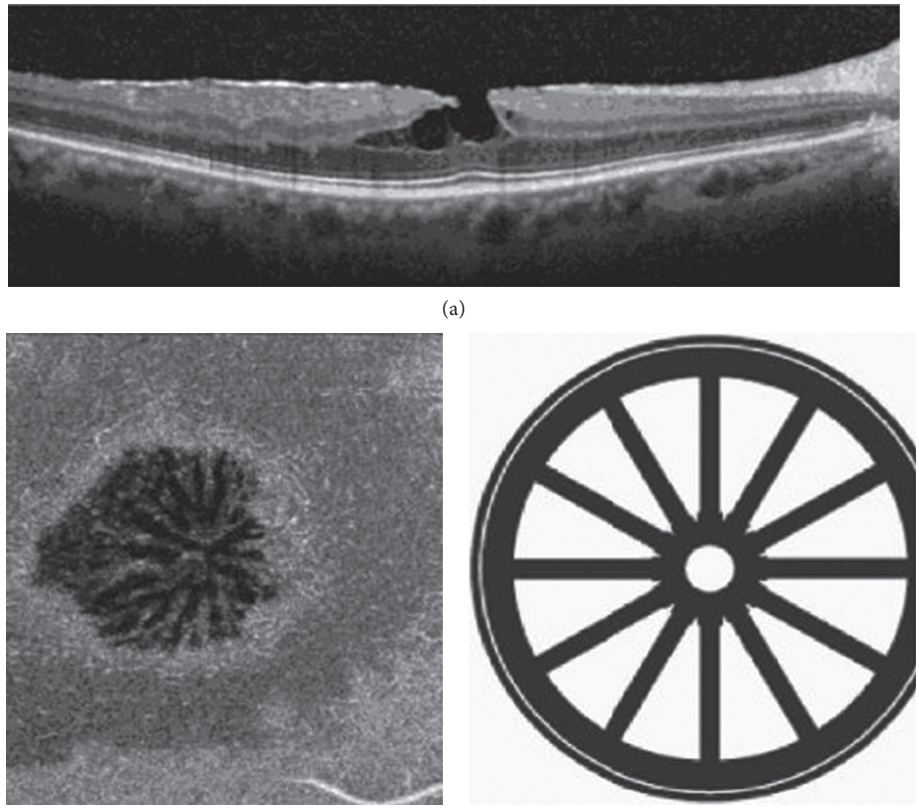
autofluorescent signal observed preoperatively in eyes with LMH and ERM foveoschisis originates from displaced rather than lacking retinal tissue. Another application of B-FAF in eyes with ERM foveoschisis is its capacity of showing the presence of retinal vessel printings (RVPs), which are a useful sign for indirectly evaluating the tangential traction related to ERM [27, 28] (Figures 4 and 5).

In a retrospective series [19] of 84 eyes with lamellar defect at the fovea, RVPs were detected in none of the 11 eyes with associated EP, in 16.3% of the eyes with tractional ERM, and in 7.3% of eyes with the coexistence of EP and ERM. These results appear to confirm the scarce contractile characteristics of EP.

In an observational three-center study in which patients with lamellar defect were examined with B-FAF and SD-OCT according to prespecified imaging protocols, dell'Omo et al. [29] found that, independently from the associated epiretinal material (tractional ERM or EP), a strong correlation exists between the diameters of the holes measured from B-FAF images and those measured at the OPL level from OCT images (Figures 8 and 9). Conversely, no correlation was found between the length of disrupted EZ and B-FAF diameter. This is important because areas with disrupted EZ on OCT images (indirectly suggesting loss or rarefaction of photoreceptors) may potentially show increased B-FAF levels relative to surrounding areas with healthy photoreceptors. In fact, unbleached photoreceptor pigment has a similar, although lesser, effect on the appearance of B-FAF as macular pigment, as it absorbs and therefore attenuates the excitation light available to elicit autofluorescence at the level of the RPE [30].

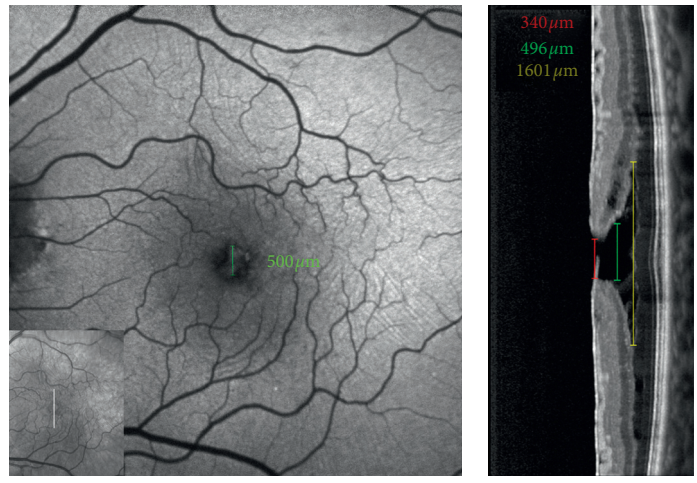
These findings suggest that the loss or displacement of retinal tissue within the OPL layer might be the main culprit of the increased B-FAF signal observed in eyes affected by macular lamellar defects associated with either tractional ERM or EP.

Recently, dell'Omo et al. [31] described a distinct vitreomacular interface disorder termed foveal abnormality associated with epiretinal tissue of medium reflectivity and increased blue light fundus autofluorescence signal (FATIAS) (Figure 10). Distinguishing features of FATIAS are an abnormal foveal contour either in the form of a step or in the form of a shallow foveal pit and reduced foveal thickness on SD-OCT imaging; the presence of a tissue of medium reflectivity on the innermost portion of the foveal pit; the absence of overt ERM or EP; the absence of intraretinal cysts or splitting/cavitation between the inner and outer retinal layers; the integrity of the outer retinal bands; an increased B-FAF signal at the fovea; good BCVA. It is possible that some cases of FATIAS may represent LMH in an early stage, although the retrospective analysis by



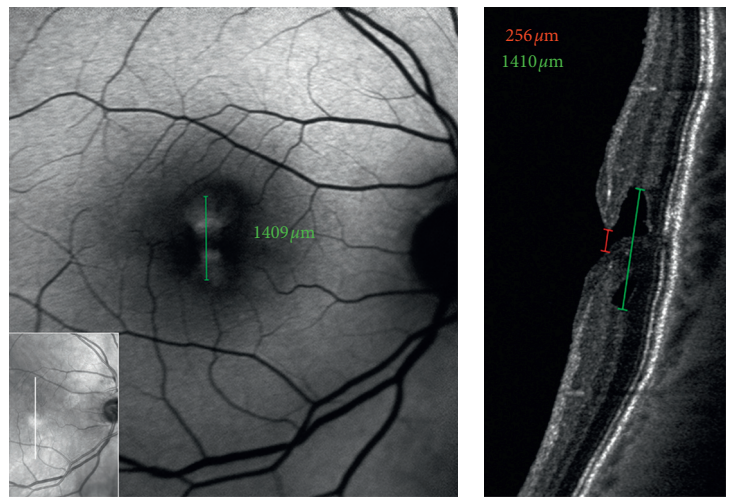
(a) (b) (c)

Figure 7: Structural and en face optical coherence tomography (OCT) of epiretinal membrane (ERM) foveoschisis. A structural OCT illustrates an ERM foveoschisis, with a sharp split at the level of the outer nuclear-Henle fiber layers complex. (a) Tractional ERM is visible. (b) The en face OCT segmented at the level of the outer nuclear-Henle fiber layers complex illustrates hyporeflective intraretinal cystoid spaces disposed in a radial pattern centered into the fovea. Such disposition may recall a "spoke-wheel" shape as shown in the drawing (c).



(a) (b)

Figure 8: Blue fundus autofluorescence (a) and optical coherence tomography (OCT, b)-based measurements in an eye with epiretinal membrane foveoschisis. The horizontal white arrow on the infrared image (small square within the B-FAF image) indicates the location of the corresponding OCT scans; the green caliper on the B-FAF image indicates where the diameter of the increased area of autofluorescence was measured. The measurements on OCT image are taken at the level of the inner limiting membrane (red line), Henle fiber layer (green line), and schisis (yellow line) level. Note the similarity between the diameter of the area of increased autofluorescence measured from B-FAF image and the diameter measured at the level of the Henle fiber layer from OCT image.



(a) (b)

Figure 9: Blue fundus autofluorescence (a) and optical coherence tomography (OCT, b)-based measurements in an eye with lamellar macular hole. The horizontal white arrow on the infrared image (small square within the B-FAF image) indicates the location of the corresponding OCT scans; the green caliper on the B-FAF image indicates where the diameter of the increased area of autofluorescence was measured. The measurements on OCT image are taken at the level of the inner limiting membrane (red line) and Henle fiber layer (green line). Note the similarity between the diameter of the area of increased autofluorescence measured from B-FAF image and the diameter measured at the level of the Henle fiber layer from OCT image.

dell'Omo et al. showed that none of the cases worsened morphologically or functionally over years-long follow-up.

3.5. Blue Reflectance, Green Reflectance, Infrared, and Multicolor Imaging. The characteristics of the epiretinal materials associated with LMH and ERM foveoschisis are of great relevance since a tractional ERM or EP can be found in more than 80% of the eyes with LMH and, a tractional ERM is found, by definition, in 100% of the eyes with ERM foveoschisis [10].

Traditional color fundus photography taken with FC uses a flash of white light to illuminate the retina and image quality may suffer because of light scattering, a broad depth of focus, poor pupil dilation, or media opacities. Alternatively, cSLO uses scanning laser to produce en face grayscale images that may hold several advantages over FC including higher spatial resolution, narrow depth of focus, and better penetration through a small pupil or media opacities [32].

The Spectralis (Heidelberg Engineering, Heidelberg, Germany) uses a cSLO to capture three simultaneous reflectance images in three different laser wavelengths: (1) blue reflectance (BR; 488 nm), (2) green reflectance (GR; 515 nm), and (3) infrared reflectance (IR; 820 nm). Multicolor imaging compiles these three reflectance patterns into a single en face image, providing a pseudocolor representation of the fundus that simultaneously details retinal findings at varying depths. This allows a higher contrast compared with standard FC due to suppression of scatter light.

The three monochromatic images allow visualization of distinct information from specific layers of the retina and choroid. Blue laser is absorbed by macular pigment and can capture details of superficial retinal structures, whereas green laser is absorbed by hemoglobin and provides vascular details of the retina in addition to giving a good reflectance image of surface retinal disease. Because of the longer wavelength, near-infrared laser penetrates deeper into the retina, allowing better imaging of the retinal pigment epithelium and the choroid [32–34].

In presence of transparent media, green reflectance and blue reflectance images clearly show the increased reflection and wrinkling of the retinal surface associated with tractional ERM (Figure 5). Conversely, infrared reflectance reveals less detectability of epiretinal membranes. However, especially in elderly people, green-blue wavelengths may be blocked by lens opacities or the high reflectance from the surface of the retina may not allow an adequate visualization, thus resulting in images of poor quality. In these cases, infrared reflectance, with its deeper penetration, may be used. Using infrared imaging, Acquistapace et al. [35] identified three different categories of tangential traction associated with tractional epiretinal membranes in eyes with lamellar macular defects, categorizable as ERM foveoschisis according to the recent classification of Hubschman et al. [10]: (1) unidirectional, i.e., folds directing to a center of traction not in the fovea; (2) pluridirectional, i.e., more centers of traction with different directions of folds; and (3) concentric, i.e., all folds directing to the center of the fovea.

Differently from conventional ERMs, EPs are typically not visible or detectable by ophthalmoscopy or color fundus photography [8, 9]. dell'Omo et al. have recently shown that BR and multicolor imaging enables the en face visualization of EP associated with LMH in the form of a sharply demarcated dark area and in the form of a yellowish area surrounding the hole, respectively [36] (Figure 11).

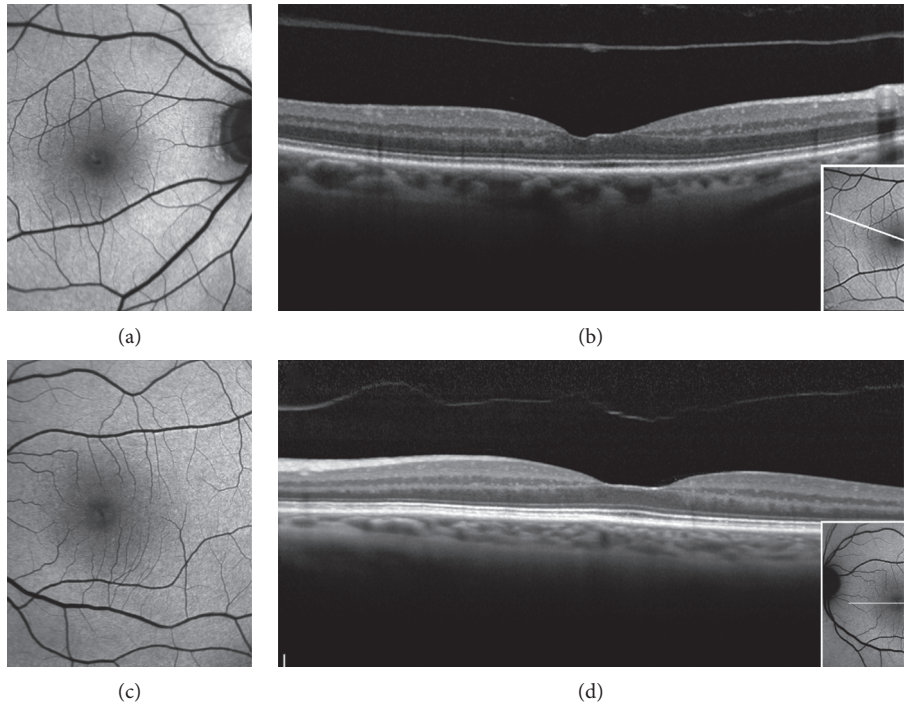


Figure 10: B-FAF and OCT imaging of Foveal Abnormality associated with epiretinal Tissue of medium reflectivity and Increased blue-light fundus Autofluorescence Signal (FATIAS). In the step type, the B-FAF image shows an area of increased autofluorescent signal (a), and, in the OCT image, there is an asymmetric contour of the foveal pit with one side more elevated than the other (b). The white lines on the B-FAF images in the small squares indicate the OCT scan level. In the rail type, the B-FAF image shows an increased autofluorescent signal at the fovea (c), and the OCT profile is characterized by a shallow foveal pit and a rail of tissue of medium reflectivity that is thicker in the central part and thinner at the edges of the foveal pit and that is similar to epiretinal proliferation (d).

This has been related to the block of the blue light transmission caused by the yellow pigment contained within the EP tissue [37].

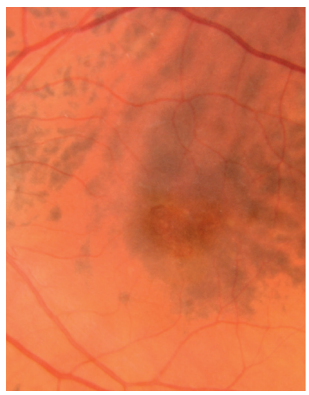
3.6. OCT Angiography. OCT angiography (OCTA) is a recently developed technique that provides depth resolved images of blood flow in the retina and choroid without injection of dye. With its capability of imaging the intermediate and deep retinal capillary plexuses, the OCTA opens a wealth of possibilities for disease description and quantification, including research into pathogenesis of disease.

In a retrospective study, Pierro et al. [38] analyzed 10 eyes with lamellar defects associated with tractional ERM but not with EP (thus comparable to ERM foveoschisis) and compared them with healthy controls. They found that the foveal avascular zone (FAZ) area in the superficial capillary plexus (SCP) was similar in the two groups whereas the FAZ area in the deep capillary plexus (DCP) was recognizable only in 30% of the cases with LMH. The eyes where the FAZ was not recognizable at the deep capillary plexus (DCP) presented a nonspecific, irregular cystic pattern. The vessel density at the superficial capillary plexus (SCP), DCP, and choriocapillaris did not differ between eyes with LMH and controls.

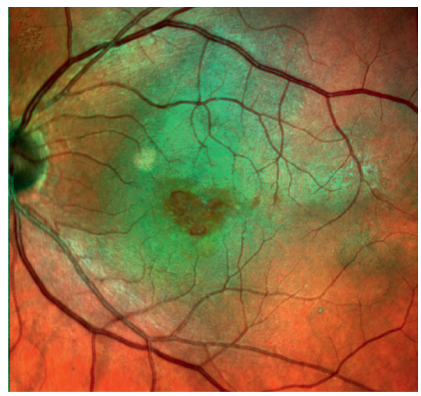
In a study by Ahn et al. [39], 19 eyes with LMH were studied with OCTA and compared with 19 age- and gender-matched normal controls. Axial length, subfoveal choroidal thickness, and vessel density (VD, i.e., the percentage of the area occupied by vessels in a selected region) of the choriocapillaris in the LMH group did not vary from normal controls. Since no specific details are provided in the paper, it is not possible to evaluate how many of the lesions considered by the authors could be classifiable as true LMH or ERM foveoschisis.

Yeo et al. [40] investigated the microvascular changes in 63 eyes with LMH (42 tractional and 21 degenerative according to the definition of Govetto et al. [15]) comparing the FAZ area and foveal and parafoveal VD with those obtained in a control group. Compared with control eyes, those with tractional LMH had smaller FAZ area, higher foveal VD, and lower parafoveal VD whereas eyes with degenerative LMH had lower parafoveal VD in both plexuses. In addition, foveal VDs in both plexuses and parafoveal VD in SCP were significantly correlated with BCVA in eyes with degenerative LMH (Figure 12).

3.7. Fluorescein Angiography. Ophthalmic fluorescein angiography is an important clinical procedure used to investigate and document the status of the retinal and choroidal vascular systems. To date, there are few data in the literature on the use of fluorescein angiography in LMH. Gass originally described and increased fluorescent signal due to a window defect corresponding to the lamellar hole



(a)



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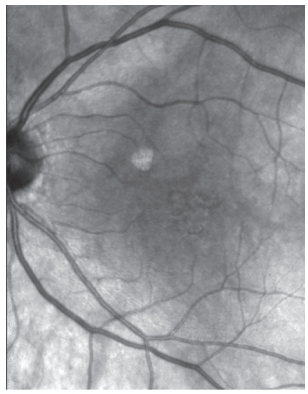

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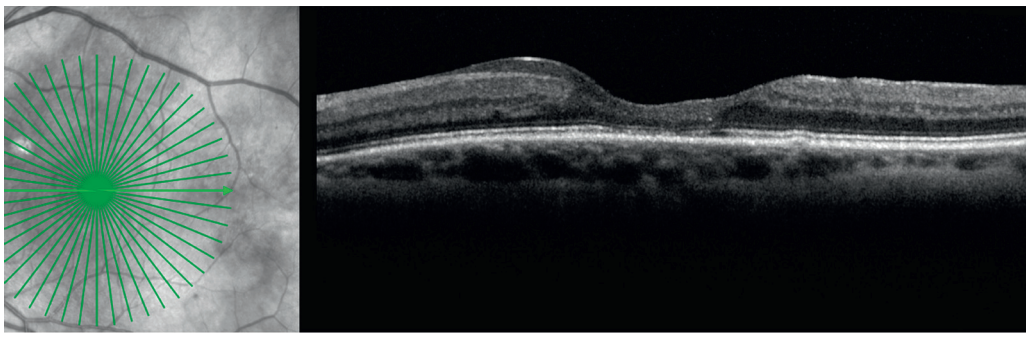
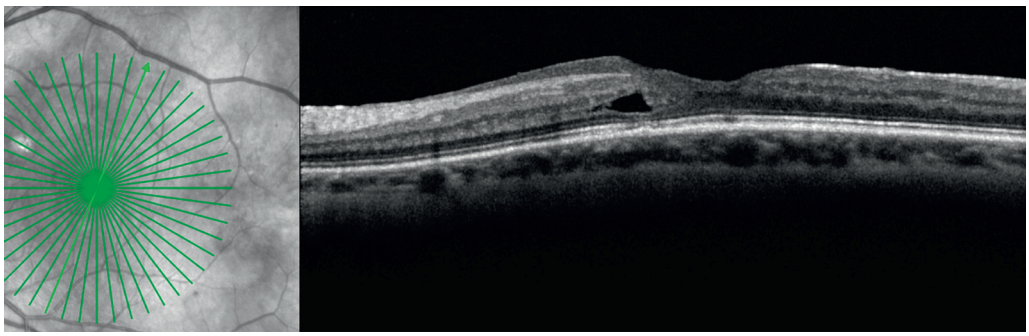
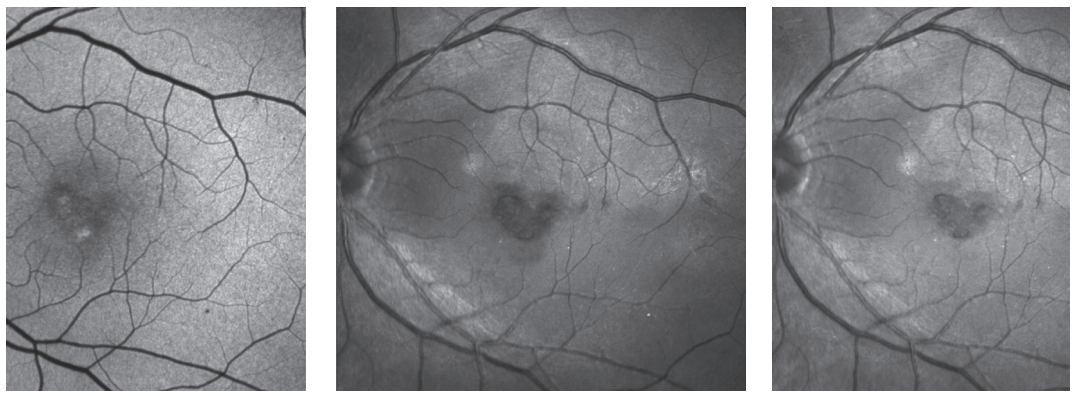


(d)



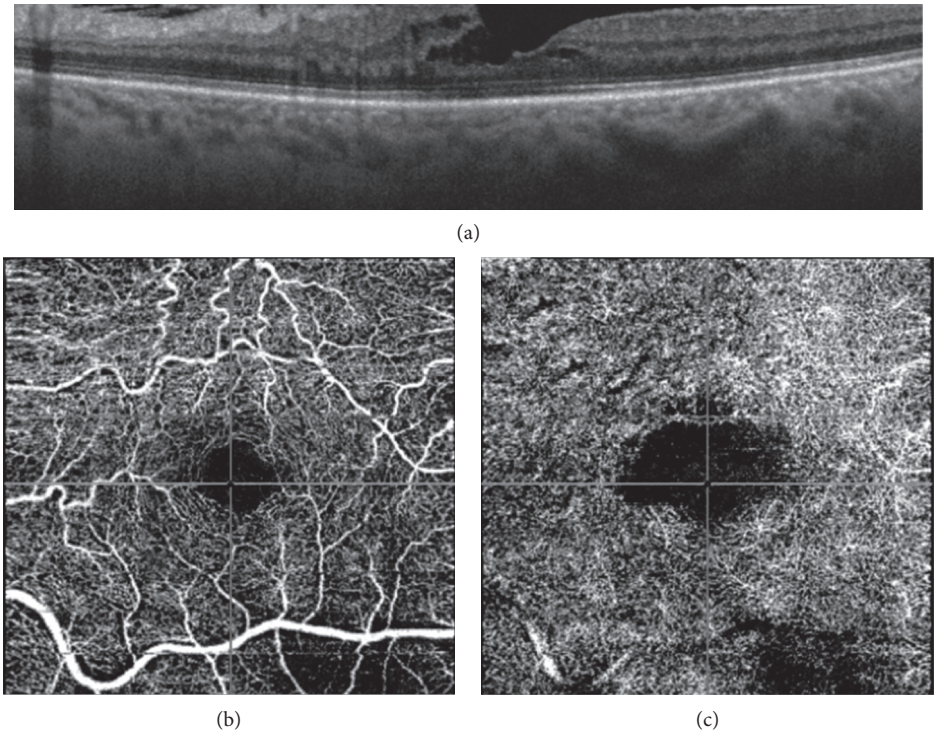
(e)

Figure 11: Continued.



(f) (g) (h)

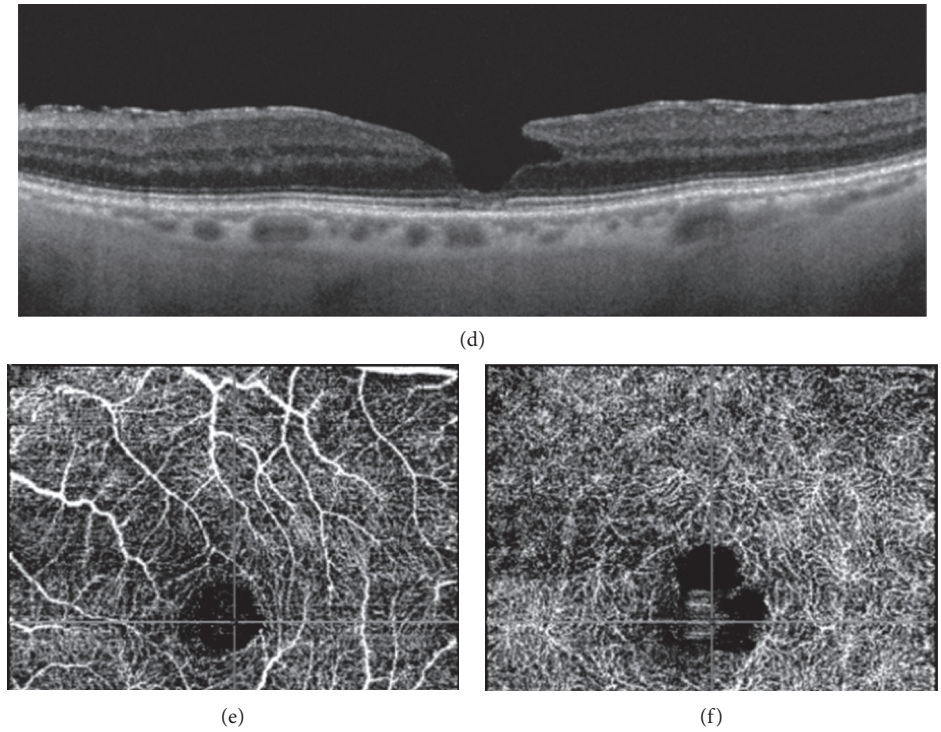
Figure 11: Multimodal imaging of a lamellar macular hole (LMH) with associated epiretinal proliferation (EP). On color fundus photograph (a), an oval reddish foveal lesion with no distortion or wrinkling of the surrounding retinal tissue is visible. On multicolor image (b), a yellowish area around the hole is visible, but its boundaries are not clearly delineated. On infrared reflectance image (c), no remarkable features are noted. On horizontal and oblique optical coherence tomography sections (d and e), EP in the form of material with medium reflectivity is observed on the retinal surface around the hole. On blue-fundus autofluorescence imaging (f), discrete areas of increased autofluorescent signal are visible. On blue-reflectance image (g), a sharply demarcated dark area, surrounding the hole, is evident. This area corresponds precisely to the surface covered by the EP on OCT scans. On green reflectance image (h), there are no peculiar findings corresponding to the area with EP.



(a)

(b) (c)

Figure 12: Continued.



(d)

(e) (f)

Figure 12: Optical coherence tomography (OCT) and OCT angiography of the eyes with epiretinal membrane (ERM) foveoschisis and lamellar macular hole (LMH). The tractional ERM associated with the foveoschisis (a) causes distortion and tortuosity of the superficial vessels (b). The foveal avascular zone (FAZ) of the deep capillary plexus appears enlarged (c). In the eye with LMH (d), the superficial vessels are not distorted (e). The FAZ of the deep capillary plexus appears enlarged with an irregular contour (f).

[1]. In the paper by von Rükmann et al., 46 eyes FTMH and 5 eyes with pseudoholes were analyzed [41]. According to these authors, autofluorescence imaging with the cLSO makes the assessment of macular holes possible with accuracy comparable with that of fluorescein angiography [41].

In a recent report, Govetto et al. [23] performed macular narrow-angle (30 degrees) fluorescein angiography in a small series of 12 eyes diagnosed with ERM foveoschisis and found no apparent dye leakage in any of the included patients**.** Conversely, dell'Omo et al. found that eyes with LMH and eyes with ERM foveoschisis may show abnormal leakage at the posterior pole and in the periphery, focal vasculitis, and hyperfluorescence of the disc when studied with fluorescein angiography. These angiographic features may suggest the role of blood-retinal barrier breakdown and perhaps of inflammation in the pathogenesis of LMH [42].

4. Conclusions

Lamellar macular hole is a partial-thickness foveal defect, with variable morphologic features difficult to identify using biomicroscopy alone. Advancements in imaging and availability on the market of new equipment and processing techniques have deepened our knowledge about the morphologic characteristics, natural history, and long-term prognosis of this disease.

In the recent years, particular interest has been focused on the type of epiretinal membranes that can be associated with LMH, their relationship with histopathology studies, and their relevance from a pathogenetic point of view. The role of several imaging modalities has been explored for the detailed study of these membranes and other morphologic characteristics and new classification systems have been proposed. However, it is unknown at present which are the factors that may lead to a different pathway of evolution in the development of true LMH and ERM foveoschisis. Similarly, it is still not clear which imaging modality may best evidence the alleged loss of tissue that, according to most recent definitions, should be associated with true LMH.

Refinement in imaging techniques will hopefully provide in the near future further insights into this challenging vitreoretinal disease.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

No conflicts of interest exist for any of the authors.

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Research Article

Pars Plana Vitrectomy versus Intravitreal Injection of Ranibizumab in the Treatment of Diabetic Macular Edema Associated with Vitreomacular Interface Abnormalities

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Purpose. To compare the efficacy of pars plana vitrectomy (PPV) versus intravitreal injection (IVI) of ranibizumab (RBZ) in the treatment of diabetic macular edema (DME) associated with vitreomacular interface abnormalities (VMIA). *Methods*. The records of patients presenting with DME and VMIA throughout 2016 to 2018 were retrospectively analyzed. The patients were divided into 2 groups: group I received IVIs of RBZ and group II underwent PPV with internal limiting membrane peeling. The main outcome measures were the change in the LogMAR corrected distance visual acuity (CDVA) and central subfield thickness (CSFT) on optical coherence tomography over 6 months. *Results*. At 6 months, mean CDVA improved by 0.22 ± 0.21 in group I patients ($p < 0.001$), while in group II, it improved only by 0.09 ± 0.22 ($p < 0.115$). Fifty-five percent of group I and 60% of group II patients had stable CDVA (within 2 lines from baseline) at 6 months. Significant improvement in vision (gain of 2 or more lines) was seen in 45% and 30%, respectively. Worsening of vision (loss of 2 or more lines) was seen only in 2 patients in group II, but none in group I. The mean CSFT improved significantly in both groups (by 162 μ and 216 μ, respectively; $p < 0.001$). The mean CSFT at 6 months was similar in both groups (354 μ and 311 μ, respectively; $p = 0.172$). *Conclusions*. Both treatments resulted in anatomical improvement of DME with concurrent VMIA. Visual improvement was more pronounced in the IVI group, although this may have been affected by other confounding factors.

1. Introduction

Diabetic macular edema (DME) is the most common cause of moderate visual loss in diabetic patients [1, 2]. The posterior hyaloid (PH) and vitreomacular interface abnormalities (VMIA) play a role in the pathogenesis of DME. It has been demonstrated that there is a high prevalence of an attached or partially attached PH in cases of DME and that the spontaneous release of the PH is associated with resolution of DME [3–5]. VMIA tend to occur in about 6–22% of eyes with DME [6–8]. VMIA include epiretinal membrane (ERM) and vitreomacular traction (VMT) [9, 10]. Vitreomacular adhesion is considered a normal finding in the natural course of posterior vitreous detachment (PVD) and is not graded as part of VMIA [9].

Intravitreal injection (IVI) of anti-vascular endothelial growth factor (anti-VEGF) agents has become the mainstay of treatment for nontractional DME [11]. VMIA have been shown in some studies to be predictive of a reduced therapeutic effect to anti-VEGF injections [12, 13], while other studies found no association [14].

The treatment of primarily tractional DME is essentially surgical. Pars plana vitrectomy (PPV) with removal of all tractional elements including the PH with or without internal limiting membrane (ILM) peeling is the procedure employed, resulting in both anatomical and visual improvement in many cases [15, 16]. The role of PPV in nontractional refractory DME is controversial, with only some studies showing visual and anatomical improvement [17–19].

The aim of this work was to compare the efficacy of PPV versus IVIs of ranibizumab (RBZ) (Lucentis, Novartis) in the treatment of patients with DME associated with VMIA by determining the change in corrected distance visual acuity (CDVA) and central subfield thickness (CSFT) on optical coherence tomography (OCT) over a period of 6 months.

2. Subjects and Methods

The study was designed to be a retrospective comparative trial. The records of patients presenting with DME associated with VMIA to the Ophthalmology Department of Alexandria University between January 2016 and December 2018 were reviewed. The study was approved by the Ethics Committee of Alexandria University and adhered to the Tenets of the Declaration of Helsinki.

2.1. Inclusion Criteria

(1) A confirmed diagnosis of diabetes mellitus.

(2) Age ≥ 18 years.

(3) CDVA between and including 6/9 and 6/120 (measured by a Snellen chart).

(4) A diagnosis of DME associated with VMIA:

  (a) DME with CSFT > 305 μm in females or CSFT > 320 μm in males as measured by the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany)

  (b) VMIA (VMT, ERM, or both) detected by the Spectralis OCT and defined below.

(5) Patients receiving treatment in the form of IVIs of RBZ (group I) or PPV (group II). The choice of treatment methods was determined by the treating clinician.

(6) Follow-up data available for 6 months during which the patient did not receive other alternative treatments for DME. The use of a postoperative course of steroid eye drops and nonsteroidal anti-inflammatory drops was allowed.

2.2. Exclusion Criteria

(1) Ocular diseases other than diabetic retinopathy including significant cataract, glaucoma, or uveitis.

(2) Active proliferative diabetic retinopathy (PDR) requiring prompt panretinal photocoagulation (PRP) (patients with PRP performed >3 months could still be included).

(3) Vitreous hemorrhage.

(4) Severe central ischemic maculopathy defined as the foveal avascular zone (FAZ) >1000 μm in diameter and a completely destroyed FAZ capillary outline [20].

(5) Advanced diabetic eye disease with tractional retinal elevation involving the macula (including tractional retinal detachment or tractional retinoschisis).

(6) Recent previous treatment for DME (including IVIs of anti-VEGF or grid laser in the last 3 months, or IVIs of steroids in the last 6 months).

(7) Previous PPV.

(8) Previous cataract surgery within the last 3 months.

2.3. OCT Imaging. Two independent reviewers graded the OCT images to confirm the presence and subtype of VMIA. Only patients in which both reviewers agreed to the presence of DME with concurrent VMIA were included in the study.

2.4. OCT Patterns

(1) Vitreomacular traction (VMT): The international vitreomacular interface study (IVTS) group defined VMT by the following criteria being present on at least 1 B-scan on OCT:

  (a) Perifoveal PVD.

  (b) Persistent vitreous attachment in a 6 mm-diameter circle centered around the fovea.

  (c) Association of the attached vitreous with retinal anatomic changes at the site of vitreous attachment (distortion of foveal surface, intraretinal cysts, elevation of the foveal floor, or a combination of them).

  VMT can be focal (≤1500 μm) or broad (>1500 μm) [9].

(2) Epiretinal membrane (ERM): ERM is seen as a hyper-reflective band along the inner retinal surface. It can be partially adherent or globally adherent to the retinal surface [10].

(3) Both VMT and ERM.

2.5. Group I. Patients received IVIs of 0.5 mg/0.05 mL RBZ. The injection protocol was determined by the treating clinician.

2.6. Group II. Patients underwent standard 23-gauge PPV with induction of PVD and complete removal of the vitreous gel. This was followed by ERM and ILM peeling assisted with the use of brilliant blue G 0.025%.

2.7. Outcome Measures. Primary outcome measures were the mean change in CDVA and CSFT at 6 months, and the secondary outcomes were postoperative complications (such as significant cataract, high IOP >30 mmHg not controlled by eye drops, vitreous hemorrhage, retinal detachment, and endophthalmitis).

2.8. Statistical Analysis of the Data. CDVA was converted to LogMAR units for statistical purposes. Statistical analysis was performed using IBM SPSS software package, version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The

Kolmogorov–Smirnov test was used to verify the normality of distribution. Quantitative data were described using mean ± standard deviation. Significance of the obtained results was judged at the 5% level.

3. Results

A total of 40 patients were included from the records, 20 of which received IVIs of RBZ (group I) and 20 underwent PPV (group II). Table 1 shows the baseline characteristics of the patients in both groups. Most characteristics were well balanced between the two groups, but some differences were noted:

(1) More patients in group II had more advanced stages of diabetic retinopathy as compared with group I ($p = 0.047$, chi-squared test). Quiescent PDR was present in only 20% of patients in group I compared with 60% in group II.
(2) Group I had 13 treatment naïve patients as compared with only 5 in group II ($p = 0.024$). On the other hand, there were 7 patients in group II who had previous macular laser treatment as compared with a single patient in group I ($p = 0.024$).
(3) There was a larger proportion of phakic patients in group I (60%) as compared with 25% in group II ($p = 0.025$).

At baseline, there was no significant difference between the 2 groups in the mean LogMAR CDVA. From months 1 to 5, the CDVA became significantly better in group I compared with group II ($p < 0.05$, Student's t-test) (Table 2, Figure 1). At 6 months, mean CDVA in group I was 0.56 ± 0.29 compared with 0.74 ± 0.29 in group II. Although the difference in the mean CDVA between the 2 groups was 0.18 LogMAR at 6 months, it did not reach statistical significance ($p = 0.061$).

Also, when assessing the change in vision as a categorical value, the differences between both groups were not statistically significant ($p = 0.351$, chi-squared test) (Table 3). More than half of the patients in each group had stable CDVA (within 2 lines from baseline) at the end of the study. Significant improvement in vision (2 or more lines) was seen in 45% of patients in group I and 30% of those in group II. Worsening of vision (loss of 2 or more lines) was seen only in 2 patients in group II but none in group I.

A difference between the groups was observed when assessing the change in the mean CDVA within each group. CDVA significantly improved during the 6 months of the study by 0.22 ± 0.21 in group I patients ($p < 0.001$, ANOVA test). In group II, on the other hand, mean CDVA did not improve significantly with the mean CDVA improving by 0.09 ± 0.22 ($p = 0.115$).

Baseline mean CSFT was similar in both groups ($516\,\mu m \pm 93$ in group I versus $527\,\mu m \pm 116$ in group II, $p = 0.759$), and both groups showed a significant reduction of CSFT during the study period (Table 2, Figure 2). In group I, mean CSFT decreased to $354\,\mu m \pm 105$ at 6 months ($p < 0.001$). In group II, mean CSFT decreased to $311\,\mu m \pm 94$ at 6 months ($p < 0.001$). When comparing the 2 groups, the final CSFT was not statistically significant ($p = 0.172$). A significantly lower CSFT in group II as compared with group I was only present in months 1 and 5 of the study ($p = 0.036$ and 0.038, respectively).

Seven out of 20 patients achieved a dry macula at the end of the study in group I as compared with 11/20 in group II. Improvement in macular thickness (reduction of CSFT ≥10% of baseline) was noted in 11/20 patients in group I and in 8/20 in group II. Two patients in group I had persistent DME (CSFT change <10% of baseline) (Figure 3), while 1 patient in group II had worsening of DME (increase in CSFT

Table 1: Baseline characteristics of the patients in the two groups.

	Group I ($n = 20$)		Group II ($n = 20$)		p value
Gender					
Male	8	(40%)	6	(30%)	$p = 0.507$
Female	12	(60%)	14	(70%)	
Age (years)	67 ± 8		63 ± 11		$p = 0.233$
Diabetes					
Type 1	0	(0%)	1	(5%)	$p = 1.000$
Type 2	20	(100%)	19	(95%)	
Diabetic retinopathy					
Moderate NPDR	10	(50%)	5	(25%)	
Severe NPDR	6	(30%)	3	(15%)	$p = 0.047^*$
Quiescent PDR	4	(20%)	12	(60%)	
HbA1c (%)	8.1 ± 0.4		8.2 ± 0.3		$p = 0.169$
Previous treatment					
None	13	(65%)	5	(25%)	
IVIs of anti-VEGF/ steroids	6	(30%)	8	(40%)	$p = 0.024^*$
Macular laser	0	(0%)	4	(20%)	
Both	1	(5%)	3	(15%)	
VMIA					
ERM	14	(70%)	11	(55%)	
VMT	4	(20%)	6	(30%)	$p = 0.645$
ERM and VMT	2	(10%)	3	(15%)	
Subtype of VMIA					
ERM					
Partially adherent	8/16	(50%)	9/14	(64%)	
Globally adherent	8/16	(50%)	5/14	(36%)	$p = 0.680$
VMT					
Broad	1/6	(17%)	3/9	(33%)	
Focal	5/6	(83%)	6/9	(67%)	
Lens					
Phakic	12	(60%)	5	(25%)	$p = 0.025^*$
Pseudophakic	8	(40%)	15	(75%)	
CDVA (LogMAR)	0.78 ± 0.29		0.83 ± 0.28		$p = 0.618$
CSFT (μm)	516 ± 93		527 ± 116		$p = 0.759$

*Statistically significant at $p \leq 0.05$. Group I: ranibizumab; Group II: pars plana vitrectomy; NPDR: nonproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; HbA1c: hemoglobin A1c; IVIs: intravitreal injections; anti-VEGF: anti-vascular endothelial growth factor; VMIA: vitreomacular interface abnormalities; ERM: epiretinal membrane; VMT: vitreomacular traction; CDVA: corrected distance visual acuity; CSFT: central subfield thickness.

Table 2: Changes in visual acuity and OCT measurements during the study period.

Months	CDVA (LogMAR)		^{t}p value	CSFT(μm)		^{t}p value
	Group I ($n = 20$)	Group II ($n = 20$)		Group I ($n = 20$)	Group II ($n = 20$)	
Baseline	0.78 ± 0.29	0.83 ± 0.28	0.618	516 ± 93	527 ± 116	0.759
1st	0.63 ± 0.27	0.83 ± 0.27	0.027*	446 ± 107	382 ± 77	0.036*
2nd	0.59 ± 0.26	0.79 ± 0.24	0.017*	404 ± 106	348 ± 83	0.068
3rd	0.60 ± 0.27	0.79 ± 0.26	0.032*	381 ± 112	325 ± 88	0.090
4th	0.58 ± 0.28	0.78 ± 0.25	0.024*	370 ± 105	321 ± 90	0.129
5th	0.57 ± 0.30	0.78 ± 0.27	0.030*	384 ± 106	317 ± 93	0.038*
6th	0.56 ± 0.29	0.74 ± 0.29	0.061	355 ± 105	311 ± 94	0.172
^{F}p value	<0.001*	0.115		<0.001*	<0.001*	

Group I: ranibizumab; Group II: pars plana vitrectomy; t: Student's t-test; F: F test (ANOVA); CDVA: corrected distance visual acuity; CSFT: central subfield thickness. *Statistically significant at $p \leq 0.05$.

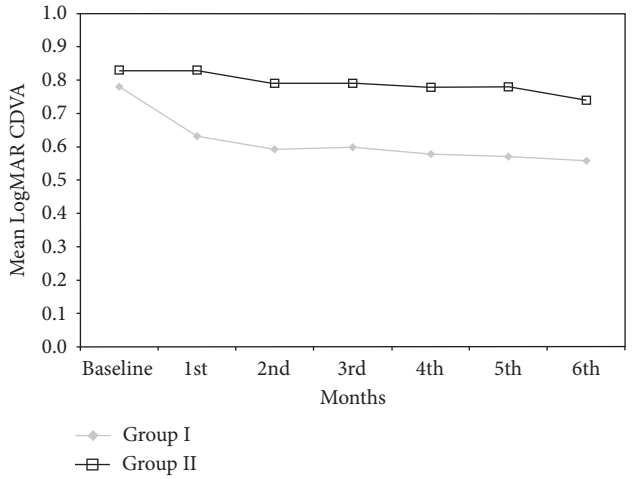


Figure 1: Change in the mean corrected distance visual acuity in the two groups.

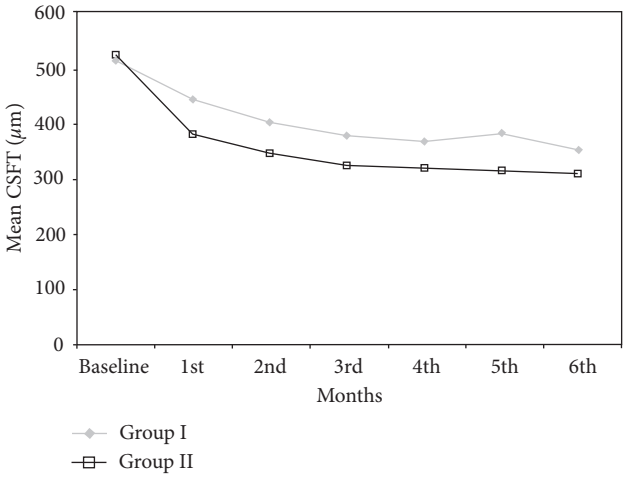


Figure 2: Change in the mean central subfield thickness in the two groups.

Table 3: Categories of CDVA change.

CDVA	Group I ($n = 20$)		Group II ($n = 20$)		^{MC}p
	No.	%	No.	%	
Improved ≥2 lines	9	(45)	6	(30)	
Stable within 2 lines	11	(55)	12	(60)	0.351
Lost ≥2 lines	0	(0)	2	(10)	

CDVA: corrected distance visual acuity; Group I: ranibizumab; Group II: pars plana vitrectomy; MC: Monte-Carlo correction of the chi-square test; p: p value for comparing between the two studied groups.

≥10% of baseline) (Figure 4). Overall, the differences between both groups was not statistically significant ($p = 0.208$).

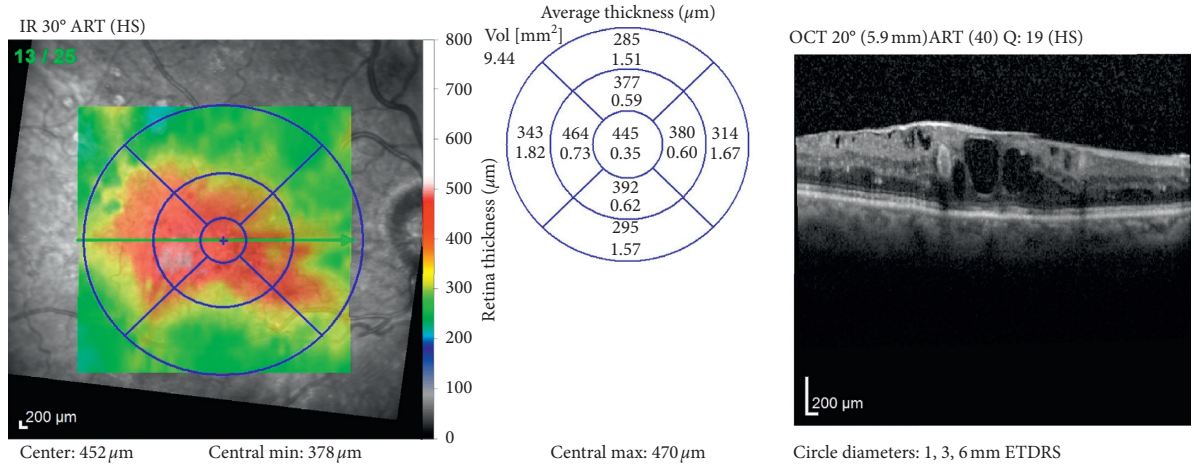
Eighty five percent of the patients receiving RBZ (17/20 patients) had no change to their VMIA status. One patient with VMT showed progression and worsening of traction with persistent DME and stable VA. Another patient with VMT showed complete PVD with resolution of traction and complete resolution of DME and was one of two patients requiring only 3 IVIs during the 6 months of the study. A third patient with a combined ERM and VMT showed partial release of VMT after receiving injections.

The mean number of IVIs for group I patients was 5.1 ± 1.1. The minimum number of IVIs was 3 ($n = 2$), and the maximum was 6 ($n = 11$). There were no major complications observed in either group. Only 1 phakic patient out of 5 in group II had progression to a moderately dense nuclear cataract at the 6-month endpoint of the study.

4. Discussion

The cause of macular edema in a diabetic patient with concurrent VMIA can be multifactorial. It is likely a mixture of mechanical traction and capillary hyperpermeability secondary to the microvascular alterations associated with the metabolic abnormalities of diabetes. It is sometimes difficult to determine which factor predominates, and there is no consensus on the best treatment approach in these cases. The current study attempted to compare both treatment options, namely IVI of anti-VEGF and PPV.

In both groups, ERM was the most common form of VMIA (62.5% of the whole cohort), while the least common form was having both an ERM and VMT (12.5% of the whole cohort). This pattern is similar to what was reported in other studies [14, 21].



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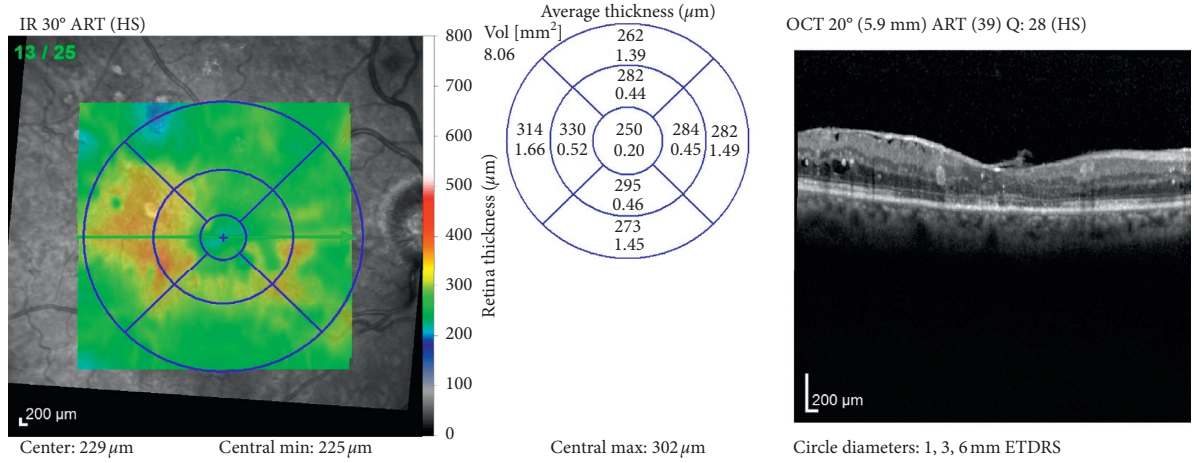

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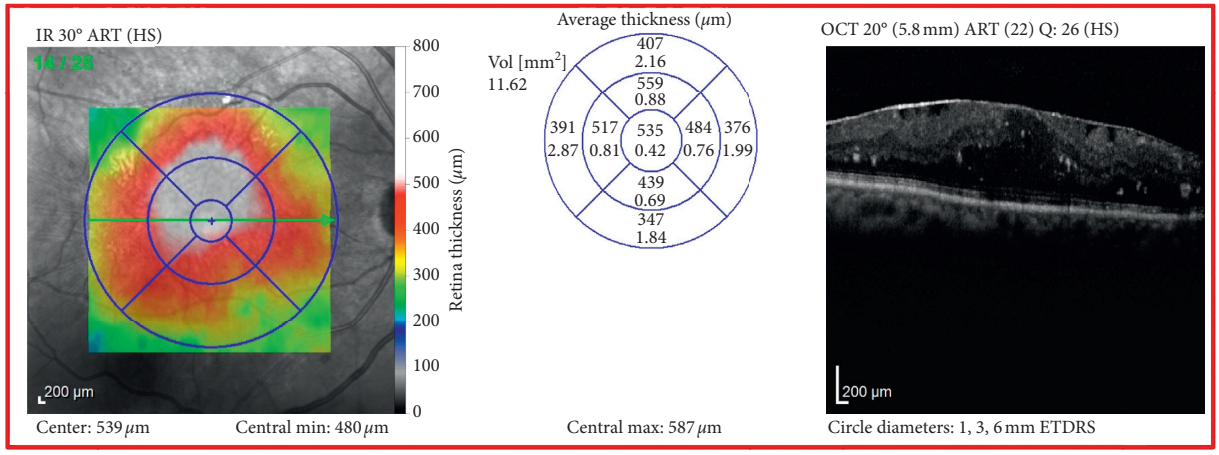

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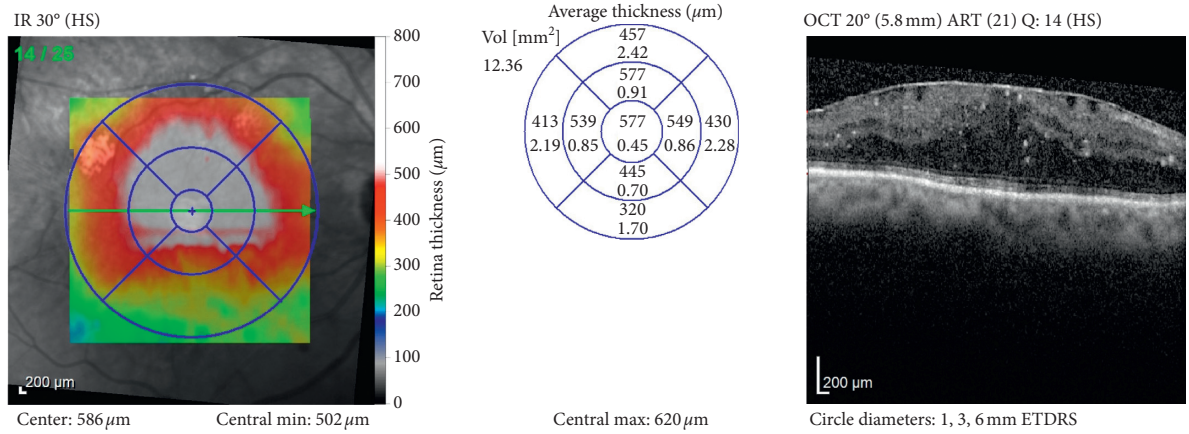

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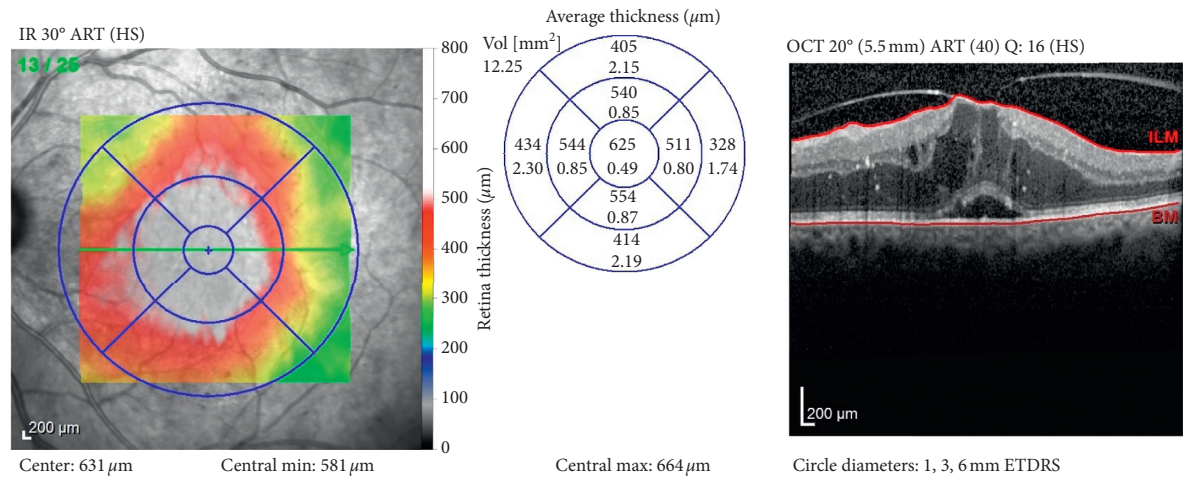

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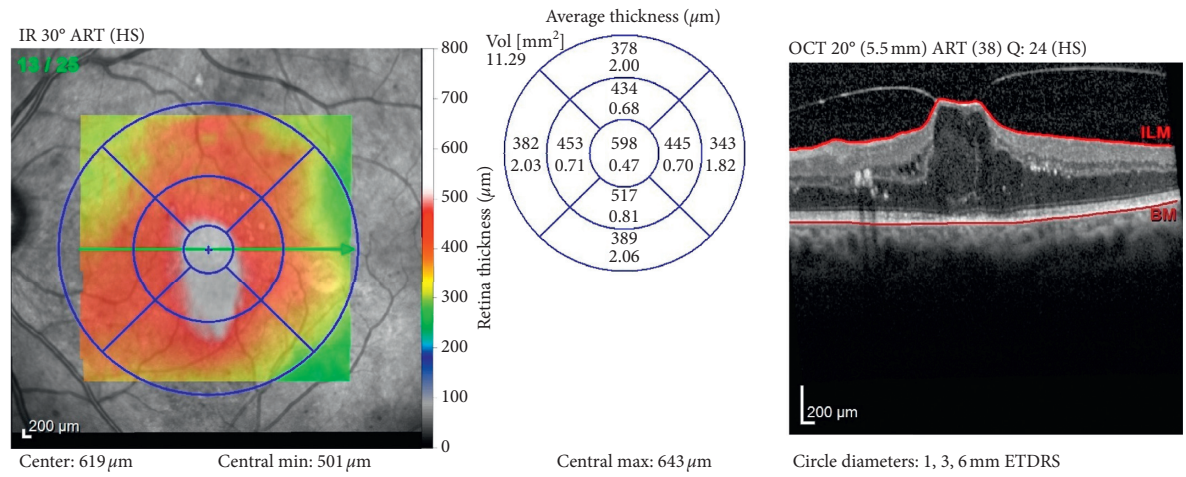
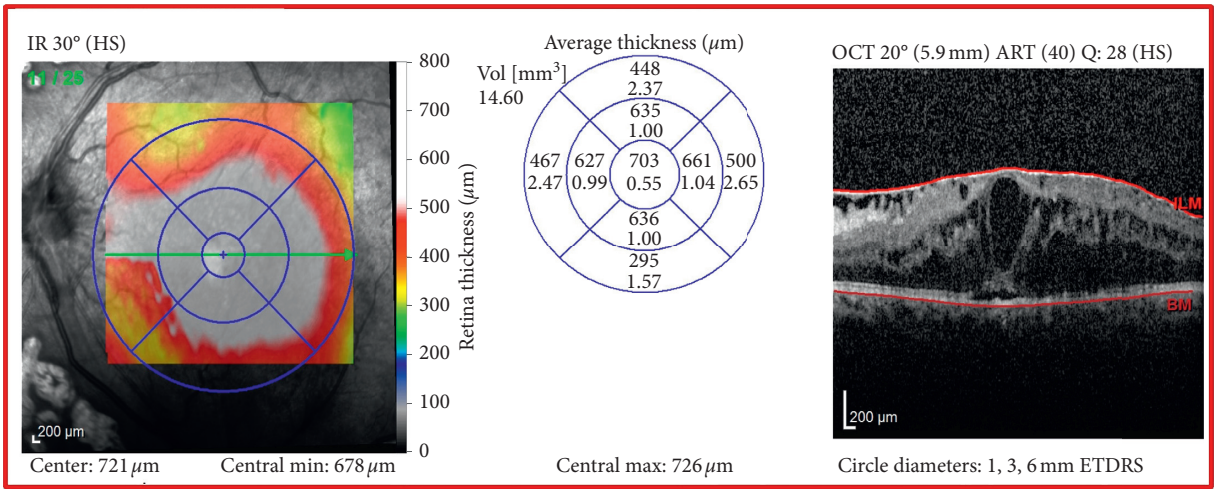


(f)

Figure 3: Sample cases from group I. Case 1: (a) baseline OCT scan of DME with concurrent ERM, CDVA 0.3; and (b) OCT scan at the end of the study after 4 IVIs of RBZ with resolution of the central DME, CDVA improved to 0.18. Case 2: (c) baseline OCT scan of DME with concurrent ERM, CDVA 0.6; and (d) OCT scan after 6 IVIs of RBZ with persistent nonresponding DME, CDVA 0.7. Case 3: (e) baseline OCT scan of DME with concurrent focal VMT, CDVA 0.6; and (f) OCT scan after 6 IVIs of RBZ partial improvement in parafoveal edema, progression of VMT, and persistent central DME, CDVA 0.6.



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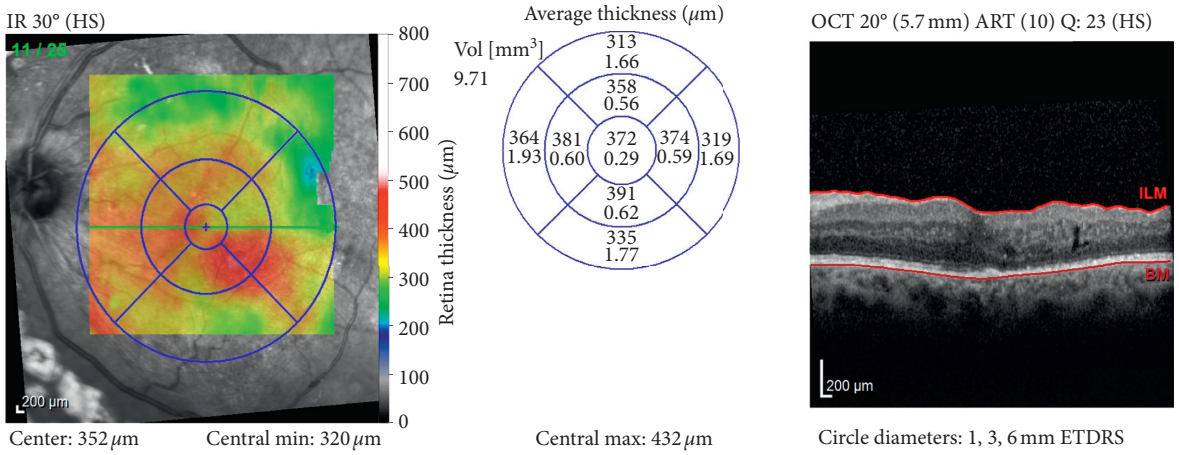

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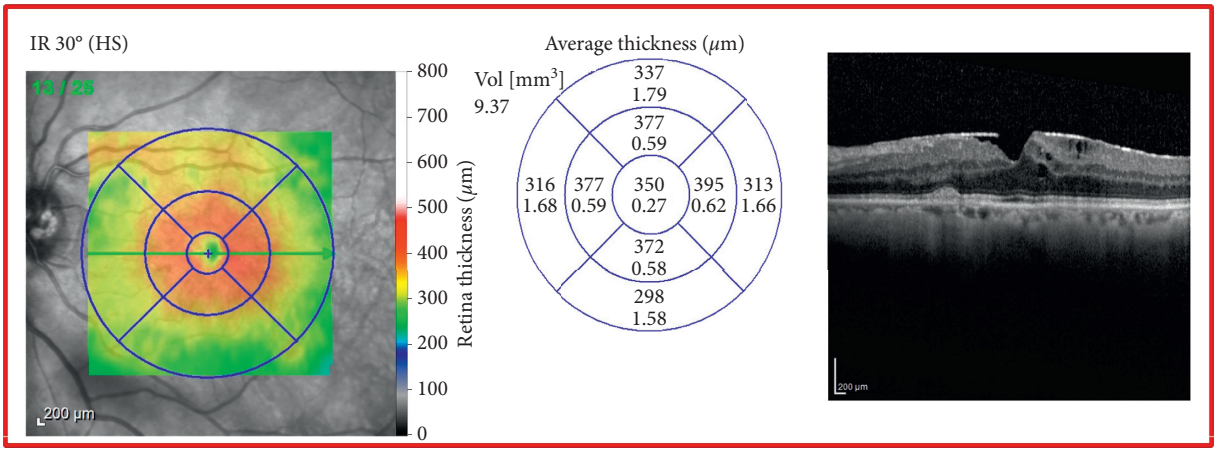

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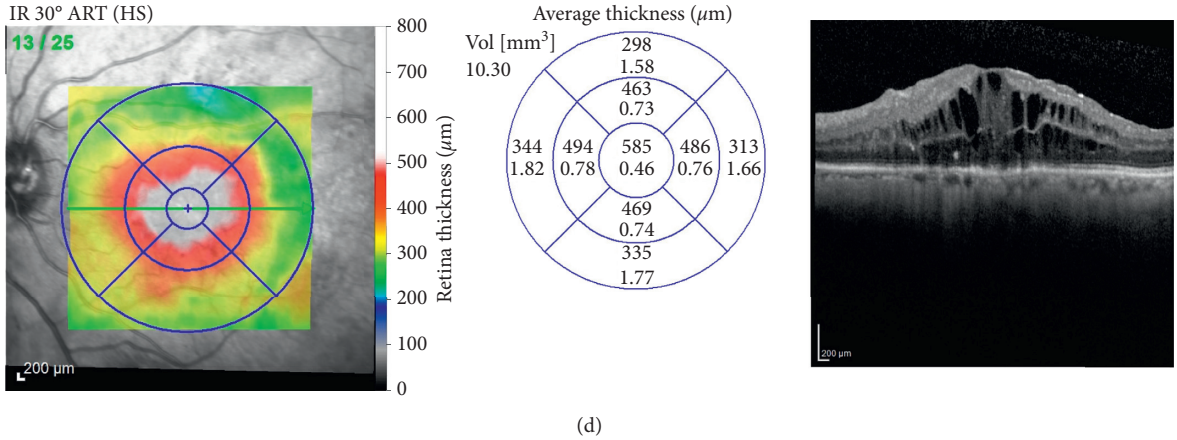
Figure 4: Continued.



(d)

Figure 4: Sample cases from group II. Case 1: (a) baseline OCT scan of DME with concurrent ERM, CDVA 1.0; and (b) OCT scan 6 months after PPV showing marked improvement in central macular thickness, CDVA improved to 0.77. Case 2: (c) baseline OCT scan of DME with concurrent ERM, CDVA 0.82; and (d) OCT scan 6 months after PPV showing worsening of cystoid macular edema, CDVA dropped to 0.92.

4.1. Outcomes of IVIs of Anti-VEGF in DME with Concurrent VMIA. In the current study, group I patients treated with RBZ had a significant improvement in CDVA (a mean improvement of 0.22 LogMAR) and 45% had 2 or more lines of improvement in vision. They also had a significant reduction in CSFT on OCT (a mean reduction of 162 μm) with 35% achieving a dry macula at 6 months.

Previous studies of anti-VEGF in DME with concurrent VMIA had variable results.

A post hoc analysis of the DRCR.net Protocol I results concluded that DME patients with surface wrinkling on fundus photos had less improvement in vision and less reduction of CSFT on OCT [22]. Similarly, a small study by Wu et al. concluded that DME patients with VMIA had a less favourable response, visually and anatomically, 1 month after a single IVI of BVZ [12, 23].

A larger prospective study by Wong et al. included 104 eyes with DME treated by IVIs of RBZ over a year. A clinically significant ERM at baseline was predictive of worse final visual and anatomic outcomes [13]. On the other hand, Mikhail et al. did not find an association between VMIA and visual or anatomic outcomes after injections. They retrospectively reviewed the records of 146 eyes with DME who were treated with IVIs of RBZ and followed for a mean of 9 months. Patients with VMIA at baseline (according to the IVTS criteria) presented with lower visual acuity; nevertheless, the presence of VMIA did not reduce the response to treatment with RBZ [14].

4.2. Outcomes of PPV in DME with Concurrent VMIA. In the current study, group II patients undergoing PPV were not observed to have a significant improvement in VA. The mean CDVA improved only by 0.09 LogMAR. Improvement in VA by ≥2 lines was observed in 30% of patients, 10% lost ≥2 lines of VA, and 60% maintained stable vision within 2 lines of baseline vision. On the other hand, a significant reduction in CSFT on OCT was observed in the PPV group with a mean reduction of 216 μm and 55% of patients achieving a dry macula at the end of the study.

The DRCR.net evaluated the outcomes of PPV in 87 eyes having DME with VMT. The presence of VMT was determined by the clinical assessment of the investigator rather than by OCT criteria. ILM peeling was done in 54% of the cases. At 6 months, median VA did not improve significantly (+3 letters compared with baseline). Improvement in VA ≥10 letters was seen in 38%, while 22% had worsening of VA by ≥10 letters and 40% remained stable within 10 letters. There was a significant reduction in CSFT on OCT by 160 μm at 6 months. Around 43% of patients had a CSFT ≤250 μm at 6 months [16].

Another cohort of 20 patients with tractional DME was followed up by Bonnin et al. for a mean of 5.3 years after undergoing PPV with ILM peeling. Patients showed a significant improvement in VA (mean improvement of 0.3 LogMAR) and OCT thickness (mean reduction of 243 μm in CSFT). Improvement in VA by ≥2 lines was seen in 25% of patients, 12.5% lost ≥2 lines of VA, and 62.5% maintained stable VA within 2 lines of baseline VA [17].

A retrospective study by Pessoa et al. reviewed 46 eyes with tractional DME who underwent PPV with ILM peeling. Patients were determined to have VMIA according to the OCT classification of the IVTS. At 12 months, there was a significant improvement in the median VA by 23 letters and a significant reduction of CSFT by 215 μm on OCT. The VA was observed to continue to improve gradually along the 12 months of the study, while the reduction in CSFT occurred mainly in the first 3 months but was minimal thereafter. An improvement in VA by ≥10 letters was achieved in 60% of cases. Worsening by ≥10 letters was seen in 13% of cases, and 27% had stable VA at 12 months [21].

In summary, all studies showed a definite anatomical improvement although this did not always correlate with vision improvement.

4.3. Comparison of Outcomes between Anti-VEGF and PPV. The mean CDVA was not different between both groups at baseline. There was an earlier and more prominent improvement in mean CDVA in the IVI group, although at the end of the study the 0.18 LogMAR difference did not reach statistical significance. One explanation is that the PPV group had 2 patients with more than 2 lines loss of VA at 6 months as opposed to none in the IVI group. This may have affected the mean CDVA outcome of the whole PPV group. The cause of visual loss in one of those 2 patients was migrating hard exudates that coalesced into a plaque and was eventually encroaching upon the fovea. The other patient had thinning of the macula on OCT. These atrophic changes in the macula sometimes called the "floor effect" have been previously reported. The proposed theory for that relies on the fact that the ILM is much more adherent to the retina and foot plates of Müller cells in diabetic retinopathy. The peeling of this adherent ILM may induce injury to the Müller cells, resulting in their collapse and subsequently retinal thinning [24].

Also, it might be argued that vision improvement in the PPV group may have been limited by post-PPV cataract progression. The effect of that was probably minimal as only 5 out of 20 patients in group II were phakic at baseline and only 1 of those had progression to a moderately dense nuclear cataract at the end of the study. The presence of a larger proportion of patients with more advanced stages of DR and with a history of previous macular laser treatment in the PPV group at baseline may have limited their potential for visual improvement.

Both groups showed similar reduction in CSFT and had similar rates of patients achieving dry macula or demonstrating improvement in DME. In the IVI group, no patients had worsening of DME, but 2 patients had persistent nonresponsive DME. In the other group, there was one patient with worsening of cystoid macular edema after PPV. Overall, the pattern of improvement of CSFT was that of an earlier reduction in thickness in the PPV group as compared with a more gradual reduction in the IVI group.

The study had some limitations, mainly those inherent to its retrospective design. This includes selection bias and the imbalance in some baseline characteristics between the groups. A prospective randomized controlled trial with a large sample size would allow randomization of any confounding factors and would provide sufficient power to study the treatment response in the different subtypes of VMIA (ERM and VMT) separately. Long-term follow-up data would help determine the longevity of the treatment benefits and the recurrence rate of DME with different types of treatment.

5. Conclusions

In conclusion, both treatment options resulted in anatomical improvement of DME. Visual improvement was more pronounced in the IVI group, although this may have been affected by other confounding factors. Both mechanical and biochemical factors contribute to retinal thickening in cases of DME with VMIA. An optimal treatment option is yet to be determined. It might be that no single treatment is best and that a combination between both IVIs and PPV may offer a better option in a certain subgroup of patients with DME and concurrent VMIA as it can address multiple factors in the underlying disease processes.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Additional Points

Intravitreal ranibizumab and pars plana vitrectomy are suitable treatment options for diabetic macular edema with concurrent vitreomacular interface abnormalities. Both provide similar anatomical results, while intravitreal injections seem to offer better visual outcomes on the short term.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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Research Article

Revision Surgery for Idiopathic Macular Hole after Failed Primary Vitrectomy

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Purpose. To investigate the anatomical and functional outcomes of revision surgery after failed primary surgery for idiopathic macular hole (MH). *Methods*. All consecutive patients with MH were identified from a cohort of patients operated between 2014 and 2018 at the CHU de Québec-Université Laval (Québec). The clinical and anatomical features of patients with unclosed MH after primary surgery were retrospectively collected. Our primary outcome was MH nonclosure rate after revision surgery. Our secondary outcomes were best-corrected visual acuity (BCVA) with ETDRS scale and MH size of eyes with revision surgery preoperatively and at 3 and 12 months after revision surgery. *Results*. In our cohort of 1085 eyes, 926 eyes met inclusion criteria and were analyzed in the study. We identified 22 eyes with failed primary surgery (2.4%), of which 20 underwent revision surgery. We had no bilateral MH in these 22 eyes. The nonclosure rate of MH after revision surgery was 15%. The mean final BCVA for closed MH after revision surgery was 55 ± 19 letters. Compared to the initial presentation, the mean change in visual acuity (VA) for closed MH was +4 ± 31 letters and +16 ± 17 letters at 3 and 12 months after the revision surgery, respectively. At initial presentation, patients with failed primary surgery had a baseline MH size of 665 ± 226 μm. The mean MH size after failed primary surgery was 607 ± 162 μm and 546 ± 156 μm for the three unclosed MHs one month after revision surgery. *Conclusion*. The success rate of revision surgery in eyes with unclosed MH is 85%. After successful revision surgery, eyes demonstrated an improvement in VA and closure of the MH.

1. Introduction

A full-thickness macular hole (MH) is a defect of all the neurosensory retinal layers involving the fovea, resulting in a marked reduction in visual acuity (VA) and metamorphopsia. Most MHs are idiopathic in etiology although MH may also be secondary to other causes such as trauma, high myopia, age-related macular degeneration (AMD), retinal detachment, and type 2 macular telangiectasia [1]. Idiopathic full-thickness MHs result from changes at the vitreomacular interface. The mechanism is not yet fully understood, but perifoveal vitreous traction related to the process of posterior vitreous detachment (PVD) has been proposed as the primary mechanism [2]. The mainstay of MH treatment is a pars plana vitrectomy with endotamponade using SF_6, C_3F_8, air, or silicone oil [1]. The reported rate of successful surgical closure of idiopathic MH varies between 78% and 96% [3]. Management options after a failed primary vitrectomy for idiopathic MH include observation, tamponade exchange, and revision vitrectomy with different approaches to the internal limiting membrane (ILM). Other surgical techniques that have been employed for challenging cases include retinal autografts, amniotic membrane grafts, and induced retinal detachment at the macula. However, limited data exist on the best approach for unclosed idiopathic MH as well as their outcomes following

reoperation. A large variation in surgical techniques and small study sizes may contribute to the difficulty of evaluating optimal management of MH refractory to primary vitrectomy [4]. Therefore, the aim of this study is to evaluate the anatomical and functional outcomes of revision surgery in eyes with idiopathic full-thickness MH that failed to close after primary surgery.

2. Methods

All consecutive patients that were operated for full-thickness MH surgery between 2014 and 2018 at the Centre Hospitalier Universitaire (CHU) de Québec-Université Laval, Québec, were identified. Patient records were systematically reviewed to identify patients with nonclosure in the postoperative follow-up period. Patients with a follow-up of less than four weeks after the first surgery were excluded. Only patients with idiopathic full-thickness MH were included in the analysis. Patients with stage 1 MH, lamellar MH, recurrent MH after an initially successful primary surgery, and MH secondary to other causes (i.e., trauma, AMD, type 2 macular telangiectasia, and retinal detachment) were also excluded.

The medical records of all patients included were systematically reviewed, and the data were recorded in an electronic data collection form. Preoperative data collected included age, sex, lens status, myopia, duration of symptoms prior to the primary surgery, and baseline VA and MH size on initial presentation. Operative data included surgical technique, method of tamponade, and internal limiting membrane peeling. Postoperative data included VA and MH size at 3 and 12 months postoperatively. Lens status was recorded at each visit. The VA originally reported on the Snellen scale was converted to ETDRS letters. All optical coherence tomography (OCT) scans were performed using the CIRRUS HD-OCT 5000 machine (Carl Zeiss Meditec, Jena, Germany). The MH size was determined as the minimum width of the MH at the narrowest point in the middle retina, as defined by the Vitreomacular Traction Study Group [5]. We also evaluated the time elapsed between initial symptoms and primary MH surgery and time to reoperation after the first unsuccessful surgery.

Our primary outcome was the rate of MH nonclosure after revision surgery. Our secondary outcomes included best-corrected visual acuity (BCVA) and MH size in eyes with failed primary surgery before and at 3 and 12 months after the revision surgery. MH closure was evaluated at 6 to 8 weeks of follow-up for patients with gas tamponade and after the removal of silicone oil for patients with silicone oil tamponade. Descriptive statistics using SPSS software were performed. The study was approved by the Research Ethics Committee of the Centre Hospitalier Universitaire (CHU) de Québec-Université Laval (2021-5371).

3. Results

During the study period, 1085 eyes were operated for MH. Of these, 159 eyes were excluded as per the exclusion criteria outlined in our methodology. Out of 926 eyes analyzed, 22 eyes had a failed primary surgery. Twenty eyes subsequently underwent revision surgery with successful closure in 17 of the 20 eyes (Figure 1). Therefore, the nonclosure rates of MH after primary surgery and revision surgery were 2.4% and 15%, respectively. Alternatively, the closure rates were 97.6% and 85% after primary and revision surgery, respectively.

The clinical and demographic characteristics of patients with unclosed MH upon initial presentation are shown in Table 1. The mean age of patients undergoing revision surgery was 73 ± 6 years and 68 ± 13 years for patients who did not attempt revision surgery. Among patients undergoing revision surgery, 7 (35%) patients were men and 13 (65%) were women. The two patients who did not attempt revision surgery were men. Eyes that underwent successful revision surgery had a shorter duration of symptoms at first presentation compared to those with an unsuccessful revision surgery (24 ± 21 ($n = 17$) vs. 46 ± 33 weeks ($n = 3$)). Eyes that underwent successful revision surgery had a smaller baseline MH size before the first surgery compared to those with an unsuccessful revision surgery ($630 \pm 237\,\mu$m ($n = 17$) vs. $781 \pm 174\,\mu$m ($n = 3$)). The baseline MH size in eyes that did not attempt revision surgery was larger ($790 \pm 170\,\mu$m ($n = 2$)). Eyes that underwent successful revision surgery had a smaller hole size after the first failed surgery compared to those with an unsuccessful revision surgery (559 ± 117 ($n = 17$) vs. $859 \pm 167\,\mu$m ($n = 3$)). The VA before the first surgery was 33 ± 27 letters ($n = 17$) for those with successful revision surgery, 33 ± 23 letters ($n = 3$) for those with failed revision surgery, and 41 ± 0 letters ($n = 2$) for those who did not attempt revision surgery.

Details of the revision surgery procedure are shown in Table 2. In successful revision surgery, techniques employed were 70% (12/17) vitrectomy with ILM peeling (peripheral extension of outer borders of ILM peeling ($n = 8$) or removal of a remnant ILM at foveal borders ($n = 4$)), 12% (2/17) changing tamponade with no complementary peeling, 12% (2/17) inverted flap technique (done with a remnant of ILM flap at the foveal border), and 6% (1/17) ILM transfer (free flap). For unsuccessful revision procedures, the surgery performed was vitrectomy with peeling of the remnant ILM (peripheral extension of outer borders of ILM peeling) ($n = 1$), changing tamponade with no complementary peeling ($n = 1$), and ILM transfer (free flap) ($n = 1$). Fifteen of 17 eyes (88%) with successful revision surgery and all eyes ($n = 3$) in unsuccessful revision surgery received C_3F_8 gas. Each patient was advised to position face-down after surgery for at least one week.

The VA after revision surgery is shown in Table 3. In eyes with failed primary surgery, the VA decreased slightly immediately after the first surgery (33 ± 26 letters to 21 ± 36 letters ($n = 20$)). At 3 months following revision surgery ($n = 16$), the mean VA was improved to 35 ± 32 letters with a mean change in VA compared to VA before the first surgery of $+3 \pm 33$ letters. VA increased greater than or equal to 0 letters in $n = 12$ eyes and greater than or equal to 15 letters in $n = 5$ eyes. At 12 months following revision surgery ($n = 6$), the mean VA was 55 ± 19 letters, and the mean change in VA compared to VA before the first surgery was $+16 \pm 17$ letters. VA increased greater than or equal to 0 letters in $n = 5$ eyes and greater than or equal to 15 letters in $n = 3$ eyes.

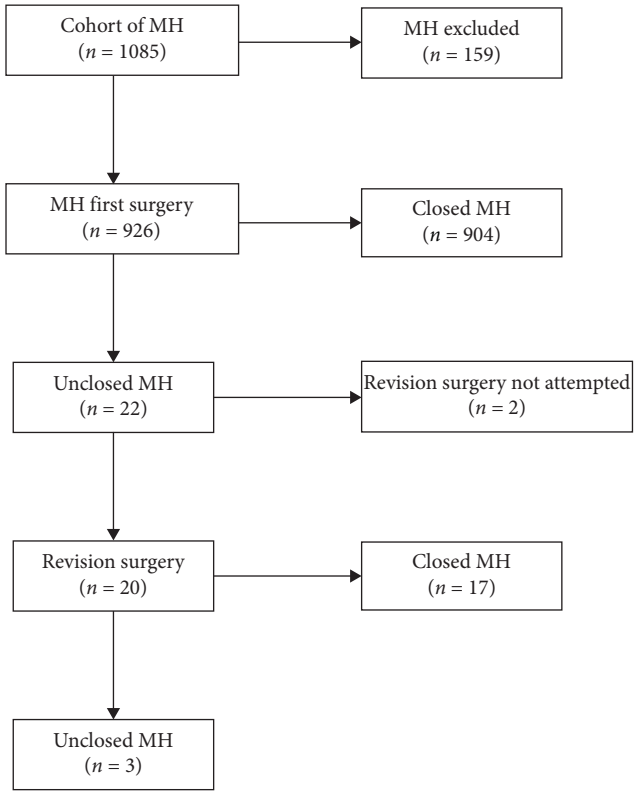


Figure 1: Flow chart showing the management process of eyes undergoing primary and revision surgery. MH: macular hole.

The evolution of the MH size after the revision surgery is shown in Table 4. Eyes with failed revision surgery ($n = 3$) had a width of 546 ± 156 ($n = 3$) and 849 ± 0 ($n = 1$) μm at 1 and 3 months, respectively, after revision surgery. The data at 12 months was missing.

In our study, 73% of eyes were phakic before the first surgery and 32% remained phakic 12 months after revision surgery.

4. Discussion

Despite the relatively high success rate following primary surgery, the persistence of MH remains a surgical challenge, affecting 8–44% of all operated MHs [6]. The optimal approach to failure-to-close cases, as well as the added value of reoperating, is still up for debate. In our study, 91% of all failed primary closure of MH underwent revision surgery. These patients typically had a worse preoperative acuity (21 ± 36 vs. 41 ± 0 letters) and larger holes (614 ± 169 vs. 539 ± 0 μm) following the initial surgery compared to those who did not attempt revision surgery. Furthermore, the duration of symptoms was shorter in those who had a successful revision surgery compared to those with an unsuccessful revision surgery (24 ± 21 vs. 46 ± 33 weeks). The failure MH size was also smaller in those who had a successful outcome (559 ± 117 vs. 859 ± 167 μm). Our findings for revision surgery are compatible with those of Fallico et al. [7] for primary surgery, which showed a better visual outcome in those with a shorter duration of symptoms and smaller MH size.

Patients who underwent revision surgery achieved a closure rate of 85%. This is consistent with a previous study by Yek et al. [3] which reported a success rate of 85% (45/53 eyes). At 12 months following revision surgery, we reported a mean BCVA of 55 ± 19 letters (6/24 with the Snellen chart) and a mean change in acuity of $+16 \pm 17$ letters compared to their initial presentation measures before the first surgery. VA also continued to improve over time. Indeed, a study suggests that VA improves up to 2 years after surgery for MH and stabilizes thereafter [8]. In our study, with only a 12-month follow-up, the BCVA was higher or equal to 6/12 on the Snellen chart in 29% of eyes that had revision surgery.

This is also congruent with a systematic review and meta-analysis by Reid et al. [4], which reported a range of revision surgery closure rates between 44% and 100% with a weighted mean of 75% ($n = 389$ of 520 eyes). The BCVA 12 months following revision surgery ranged from 26 to 65 letters with a weighted mean of 46 letters ($n = 213$ eyes). At 24-month follow-up, they showed that 15% of MHs that underwent revision surgery achieved a VA greater than or equal to 6/12 on the Snellen scale.

We also observed a reorganization of the foveal retina layers after the revision surgery (Figure 2). A larger preoperative MH size before the revision surgery has been associated with worse success in terms of anatomical closure and postoperative VA after the revision surgery [9, 10]. Our study supported these findings as the mean failure MH size was of 559 μm and 859 μm in successful and unsuccessful revision surgeries, respectively. Moreover, an enlargement of the hole is commonly observed after failed surgery. In the study by Yek et al. [3], the mean hole size increased from 426 to 524 μm following the primary failed surgery. This is in contrast to what we observed in our study, in which there was a reduction in the mean hole size from 653 to 614 μm postoperatively.

Our primary MH surgery employed standard methods such as pars plana vitrectomy, removal of posterior hyaloid, ILM peeling (after dye usage), and gas tamponade exchange. Surgical techniques used in the revision surgery included vitrectomy with ILM peeling (remnant peeling or peripheral extension), changing tamponade, inverted flap technique, and ILM transfer (free flap). At the revision surgery of one eye, we used a free flap technique and the MH closed anatomically. However, this eye showed no improvement in VA 6 months after revision surgery and BCVA was counting fingers. Morizane et al. [11] reported a closure rate of 90% (9/10 eyes) and the mean BCVA of 57 ± 67 letters at the 12-month follow-up using free flap technique for revision surgery in large MHs (>400 μm). At the revision surgery of another two eyes, we performed inverted flaps (since we had remnant ILM at the foveal border). These two MHs closed and the BCVA were, respectively, counting fingers and 35 letters at 3 months postoperatively. This method is particularly useful in large MHs but not always possible when complete peeling of ILM was previously done [12]. On the other hand, inverted flap in large MHs (>400 μm) at first surgery showed a closure rate of 95% (95% CI, 88 to 98% with 118 eyes) with BCVA of 51 ± 78 letters at a mean follow-up period of 10.18 ± 4.46 months [13].

Table 1: Clinical and demographic characteristics upon the first presentation.

	MH undergoing revision surgery $n = 20$	Successful revision surgery $n = 17$	Unsuccessful revision surgery $n = 3$	Revision surgery not attempted $n = 2$
Age				
Years, mean ± SD	73 ± 6	73 ± 7	73 ± 3	68 ± 13
Sex				
Male, *n* (%)	7 (35%)	6 (35%)	1 (33%)	2 (100%)
Female, *n* (%)	13 (65%)	11 (65%)	2 (67%)	0 (0%)
Pseudophakic *n* (%)	4 (20%)	2 (11%)	2 (67%)	1 (50%)
Duration of symptoms				
Weeks, mean ± SD	28 ± 24	24 ± 21	46 ± 33	25 ± 18
Baseline MH size				
μm, mean ± SD	653 ± 231	630 ± 237	781 ± 174	790 ± 170
Failure MH size				
μm, mean ± SD	614 ± 169	559 ± 117	859 ± 167	539 ± 0
VA (letters)				
Baseline, mean ± SD	33 ± 26	33 ± 27	33 ± 23	41 ± 0
Failure, mean ± SD	21 ± 36	24 ± 30	7 ± 63	41 ± 0

MH: macular hole. SD: standard deviation.

Table 2: Details of the revision surgery procedure.

Features	Successful revision surgery $n = 17$	Unsuccessful revision surgery $n = 3$
Surgery procedure		
Vitrectomy with extension of ILM peeling, *n* (%)	12 (70%)	1 (33%)
Changing tamponade with no complementary peeling, *n* (%)	2 (12%)	1 (33%)
Inverted flap technique, *n* (%)	2 (12%)	0 (0%)
ILM transfer (free flap), *n* (%)	1 (6%)	1 (33%)
Tamponade used		
C_3F_8, *n* (%)	15 (88%)	3 (100%)
Silicone, *n* (%)	2 (12%)	0 (0%)
Time to reoperation after MH failure		
Months, mean (range)	6 (0.5–57)	1 (1–2)

MH: macular hole. ILM: internal limiting membrane.

Large and persistent MHs remain surgical challenges, which is why new surgical methods continue to be developed. Modified autologous ILM translocation at revision surgery is also possible, but more challenging. Three studies have been published and showed a MH closure rate at revision surgery of 91%, 92%, and 100% with BCVA of 65 ± 71, 41 ± 69, and 35 ± 76 letters for a mean MH size of 512, 655, and 811 μm, respectively. The follow-up period was 8, 12, and 12 months, respectively [14–16].

Grafting with lens capsule is also a technique described by Chen and Yang [17] with closure rate at revision surgery of 67% (6/9 eyes) and BCVA of 37 ± 68 letters at 6 months postoperatively for a mean MH size of 805 μm. This technique is useful when there is a failure of MH closure with ILM peeling and where only minimal ILM is available as a graft.

Induced macular detachment is another technique consisting of injecting the subretinal balanced salt solution. Gurelik et al. [18] reported a closure rate at revision surgery of 100% (7/7 eyes) with subjective improvement in VA. Szigiato et al. [19] showed the same closure rate at revision surgery (8/8 eyes; mean MH size of 699 μm) with BCVA of 30 ± 66 letters at 6 months. In a study by Frisina et al. [20], the hole closure in revision surgery was 90% (9/10 eyes) in eyes with a mean MH size of 230 ± 117 μm at baseline, and BCVA improved to 57 ± 75 letters at 6 months postoperatively.

Macular graft has recently been described for large and refractory MHs. According to Mahmoud and Marlow [21], the macular graft should be considered for refractory MHs or large MHs (≥700 μm). Wu et al. [22] observed a closure rate at revision surgery of 67% (4/6 eyes) in eyes with a mean MH size of 979 ± 441 μm at baseline, and BCVA was 31 ± 59 letters at 12 months of follow-up. In another larger study by Grewal et al. [23], the closure rate at revision surgery was 88% (36/41 eyes) in eyes with a mean MH size at baseline of 825 ± 423 μm, and BCVA was 34 ± 60 letters at 11.1 ± 7.7 months postoperatively.

Table 3: VA after revision surgery.

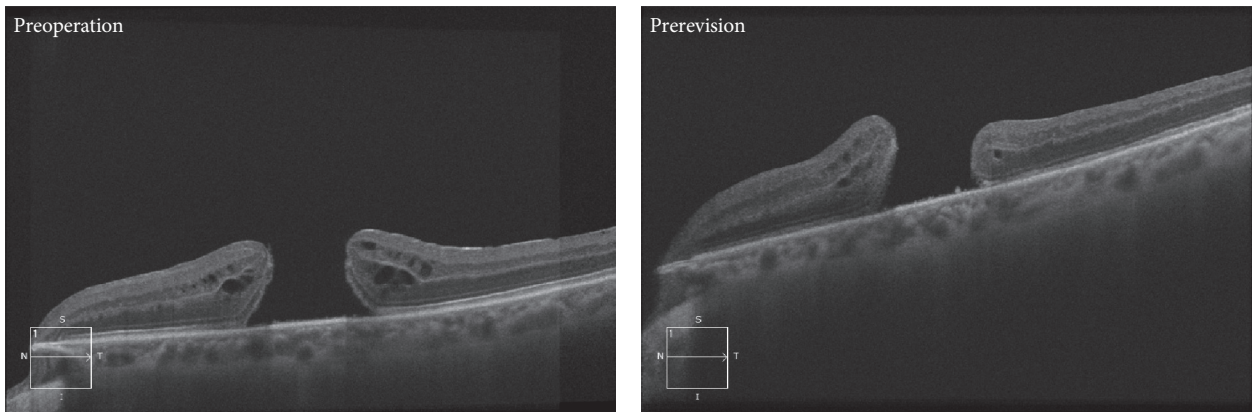
	MH undergoing revision surgery $n = 20$	Successful revision surgery $n = 17$	Unsuccessful revision surgery $n = 3$	Revision surgery not attempted $n = 2$
VA (letters)				
Before first surgery, mean ± SD	33 ± 26	33 ± 27	33 ± 23	41 ± 0
Failure, mean ± SD	21 ± 36	24 ± 30	7 ± 63	41 ± 0
3 months after revision surgery	35 ± 32, $n = 16$	37 ± 31, $n = 14$	18 ± 46, $n = 2$	—
Change in letter score, mean ± SD	+3 ± 33	+4 ± 31	−5 ± 64	—
≥0-letter increase, no. (%)	12 (75)	11 (79)	1 (50)	—
≥15-letter increase, no. (%)	5 (31)	4 (29)	1 (50)	—
12 months after revision surgery	55 ± 19, $n = 6$	55 ± 19, $n = 6$	N/A	—
Change in letter score, mean ± SD	+16 ± 17	+16 ± 17	N/A	—
≥0-letter increase, no. (%)	5 (83)	5 (83)	N/A	—
≥15-letter increase, no. (%)	3 (50)	3 (50)	N/A	—

VA: visual acuity. MH: macular hole. SD: standard deviation. N/A: not available.

Table 4: Evolution of MH size.

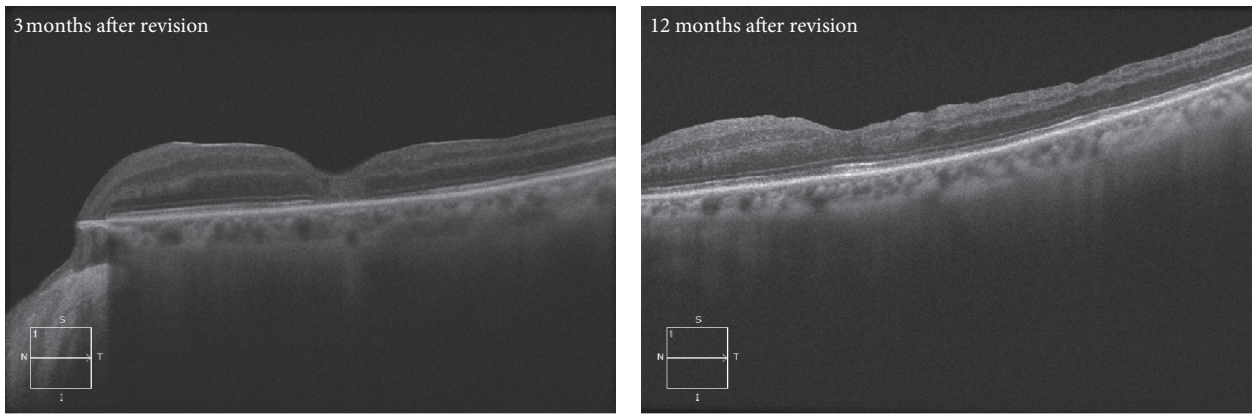
	MH undergoing revision surgery $n = 20$	Revision surgery successful $n = 17$	Unsuccessful revision surgery $n = 3$	Revision surgery not attempted $n = 2$
MH size before the first surgery μm, mean ± SD (n)	653 ± 231 (20)	630 ± 237 (17)	781 ± 174 (3)	790 ± 170 (2)
Failure MH size (before revision surgery) μm, mean ± SD (n)	614 ± 169 (11)	559 ± 117 (9)	859 ± 167 (2)	539 ± 0 (1)
MH size 1 month after revision surgery μm, mean ± SD (n)	102 ± 227 (16)	0 (13)	546 ± 156 (3)	—
MH size 3 months after revision surgery μm, mean ± SD (n)	71 ± 245 (12)	0 (11)	849 ± 0 (1)	—
MH size 12 months after revision surgery μm, mean ± SD (n)	0 (6)	0 (6)	N/A	—

MH: macular hole. SD: standard deviation. N/A: not available.



(a) (b)

Figure 2: Continued.



(c) (d)

Figure 2: Preoperative and postoperative OCT scans. (a) Preoperative OCT scan of an eye with a VA of 41 letters (6/45). (b) OCT scan of an eye prerevision surgery with a VA of hand motion. (c-d) OCT scans 3 and 12 months after successful revision surgery with a VA of counting fingers for both.

Finally, various adjuvants (autologous whole blood or serum, autologous platelet concentrate, and TGF-beta) have been used to facilitate hole closure. Functional improvement and closure rates vary greatly for these adjuvants and little data is available [24].

The main limitations of our study are the small sample size and the retrospective nature of the study with a follow-up of varying duration for different patients. Further randomized controlled trials with a larger sample size are necessary to better understand the value of these new surgical techniques.

In conclusion, there is limited evidence on the management of unclosed MHs after primary surgery. However, the postoperative results after revision surgery in terms of closure rate and improvement of VA lead us to consider revision surgery in the majority of cases. We demonstrated clear benefits in performing revision surgery, with 29% of unclosed MHs after primary surgery achieving BCVA higher or equal to 6/12 after revision surgery. An extension of the ILM peeling with an exchange of tamponade can often be attempted after a failed primary surgery with a fair success rate. Further work would be useful to further evaluate the role of unconventional surgical methods for refractory MH in revision surgery.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

AD conceptualized the project and oversaw the execution of the project. AL reviewed the proposal and collected the data. AD and AL analyzed, interpreted, and drafted the manuscript. EY, JG, SB, MC, and ET participated in drafting, reviewing, and editing the article. All coauthors reviewed the manuscript and approved the final manuscript.

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Research Article

Evaluation of the Morphology of Ganglion Cell Complex and Functional Outcomes after Internal Limiting Membrane Peeling with Macular Abrasion in Idiopathic Macular Hole

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Aim. This study aims to evaluate the morphology of ganglion cell complex (GCC) along with functional outcomes in patients undergoing vitrectomy with ILM peeling and macular abrasion with Tano diamond dusted membrane scrapers (DDMS) for three different stages of the idiopathic macular hole (IMH). *Methods*. This retrospective study was conducted between April 2019 and December 2019. 33 patients with IMH were included and divided into three groups: stage I, stage II, and stage IV. All patients were subjected to vitrectomy with ILM peeling. Gentle and vigorous macular abrasion was additionally performed for stage II and stage IV patients, respectively. The best-corrected visual acuity (BCVA), GCC thickness (measured by spectral domain-optical coherence tomography (SD-OCT)), and photopic contrast sensitivity (Rodenstock CV 900 Chart Panel) were determined before surgery and at 1- and 3-month follow-ups. *Results*. Closure of MH was achieved in all the patients. The difference between the preoperative and one- and three-month postoperative values of BCVA was statistically significant in the three groups ($P < 0.01$). Contrast sensitivity progressively improved in all patients and was statistically significant ($P < 0.01$). The reduction in GCC thickness during follow-up was 34%–42% of the preoperative measurements. On comparing the mean GCC thickness of the operated and healthy eyes, it was not statistically significant in stage I patients. However, the same when done in stage II and IV was statistically significant with P value < 0.05 and $P < 0.01$, respectively. *Conclusion*. Combining ILM peeling with macular abrasion in advanced stages of MH may facilitate its closure without significantly affecting the functional outcome.

1. Introduction

Idiopathic macular holes are full-thickness defects in the neurosensory retina, which usually results in moderate to severe central vision loss [1, 2]. Pathogenesis of macular holes is due to anomalous vitreomacular traction and incomplete posterior vitreous detachment (IC-PVD). It often leaves remnants of the vitreous cortex on the internal limiting membrane (ILM) surface [3, 4]. ILM is the basal lamina of inner retina. It is formed by the footplates of Muller cells. The structural interface between the retina and the vitreous is composed of collagen fibers, glycosaminoglycans, laminin, and fibronectin.

Kelly and Wendel in the late 80 s performed a pilot study of vitrectomy with ILM peeling as a possible solution to relieve traction over the macula in full thickness macular holes (FTMH). Prior to this, there was no definitive treatment for idiopathic macular holes (IMH) [5].

With the evolution in surgical techniques such as small gauge vitrectomy, epiretinal membrane peeling (ERM), ILM peeling, and inverted flap technique, the percentage of hole closure approached 90–100%, with a low recurrence rate

[6–8]. It is proposed that ILM peeling is an adjuvant therapy for inducing controlled gliosis, which helps in hole closure [9]. An inverted flap technique has improved the prognosis of large holes (>500 μm in diameter) from an anatomical point compared with the classic ILM peeling vitrectomy [7]. However, the restoration of the photoreceptor layer (IS/OS junction) and the external limiting membrane (ELM) is not achieved in all patients. Hence, this method may be associated with a poor functional result [10].

ILM peeling itself can lead to visible changes of the inner retinal surface. It may lead to thinning of ganglion cell complex (GCC) [11]. The retinal nerve fiber layer (RNFL) may provide the appearance of "dissociated optic nerve fiber layer" (DONFL) [12, 13]. These changes are linked to a decrease in retinal sensitivity and increase the incidence of microscotomas [12, 14]. Initial studies suggested that DONFL appearance does not affect the retinal function [15, 16]. However, a recent study points toward decreased retinal sensitivity on microperimetry in the area of the DONFL [14].

In recent years, the development of spectral domain-optical coherence tomography (SD-OCT) has allowed detailed study of the retinal layers [17]. The functional potential of the inner retina and recovery of vision is linked to GCC thickness and integrity of the IS/OS junction and ELM [18, 19]. Mahajan et al. [20] proposed macular abrasion technique aiming to eliminate tangential traction. This may aid closure of holes by facilitating approximation of its edges and also allow reconstitution of the IS/OS junction and ELM [21].

The purpose of this study is to evaluate the morphological and functional changes in GCC, in patients undergoing vitrectomy with ILM peeling and macular abrasion with Tano diamond dusted membrane scrapers (DDMS) for IMH.

2. Materials and Methods

2.1. Study Design. This is a nonrandomized retrospective study carried out on 33 patients (33 eyes) with IMH. All cases were examined and treated between April 2019 and December 2019 in San Marino State Hospital, Istituto per la Sicurezza Sociale, Department of Ophthalmology, Republic of San Marino. All patients underwent 25-gauge vitrectomy (E.V.A D.O.R.C, NE) with ILM peeling using Tano DDMS with or without macular abrasion. All patients were informed about risks and benefits of the surgery, giving written informed consent. The study was conducted in accordance with the tenets of the Helsinki Declaration.

Thirty-three patients (33 eyes) with IMH in different clinical stages were recruited. The MHs were staged by a modified Gass [22] classification, after analyzing fundus images, OCT, medical records, and operative notes.

Consequently, the macular hole patients were classified as stages I, II, and IV. The hole size was calculated on the OCT scans by drawing a horizontal line connecting its two narrowest points, with the line being parallel to the retinal pigmented epithelium. All patients' demographic information was collected from the database. All of them underwent a complete ocular examination before and after surgery, including measurements of best-corrected visual acuity (BCVA), slit-lamp examination, applanation tonometry, fundus examination, photopic contrast sensitivity curve (CS), and SD-OCT evaluation (Spectralis OCT; Heidelberg Engineering GmbH, Heidelberg, Germany).

Pseudophakic patients with IMH with recent onset of diminution of vision (DOV) (less than 3 months) were included. Exclusion criteria were the presence of cataract that represents a bias for the preoperative study of visual acuity and contrast sensitivity, as well as comorbidity affecting visual functions (ERM, diabetic retinopathy, age-related macular degeneration, vascular occlusions, myopic degeneration, inflammatory diseases, trauma, etc.). Follow-up was in the first and third postoperative months.

2.2. Surgical Technique. The surgical procedure was a 25-gauge, 3-port pars plana vitrectomy (PPV) performed by experienced surgeons (A.I. and M.F.). A posterior vitreous detachment (PVD) was induced if not already present. A complete vitrectomy was performed. Cases with an evident ERM were excluded to avoid the effect of ERM peeling on retinal tissue. The ILM was stained with Membrane Blue-Dual™ (MBD), consisting of a sterile combination of trypan blue (0.15%), brilliant blue G (0.025%), and 4% polyethylene glycol (PEG). The dye was allowed to stay inside only for the short period required for removing the cannula and inserting the next instrument. After staining, defect was created at the temporal quadrant with the Tano DDMS (Synergetics Inc., O'Fallon, MO, USA) and then peeling flap with Eckardt forceps. The ILM was removed over the entire macular area, with an extension of approximately 2 disc diameters. Before performing the fluid-air exchange, macular abrasion was performed. This entailed soft massage of the edges of the hole within an area of 1 disc diameter with the Tano DDMS, in a radial and centripetal manner (Video 1–link shared in Annexure).

The type of abrasion strokes performed was different as per stage and size of the hole. For stage I, no massage was given. For stage II, gentle strokes were given, whereas for stage IV, relatively vigorous strokes were applied. The aim of macular abrasion was to reduce the size of the hole and facilitate its closure.

Subsequently, the fluid-air exchange and air-gas exchange were performed, using 20% sulfur hexafluoride (SF6). Postoperatively, all patients were instructed to maintain strict prone position for first 3 days and 3-4 hours per day for subsequent 4 days.

During the follow-up, following outcomes were recorded:

SD-OCT was performed to assess anatomical closure of the macular hole. It also allowed evaluation of GCC morphology. GCC thickness was measured in an 8×8 mm square centered on the fovea, analyzing the thickness values of the perifoveal quadrants of the three single layers constituting the GCC (RNFL, GCL, and IPL). The reproducibility of the measurement of GCC was confirmed by multiple observations. The preoperative and postoperative

GCC thickness map of the affected eye was also compared with that of the contralateral healthy eye, using it as a reference for a normal value of our sample regarding GCC thickness.

Further functional improvement was assessed by noting 2 or more line improvement in BCVA on ETDRS chart. Contrast sensitivity (CS) was evaluated during the follow-up under photopic condition (85 candela/m^2) using sine-wave gratings, according to Michelson contrast [23] (Rodenstock CV 900 Chart Panel, Germany). The test allows determining the patient's contrast sensitivity curve using circular graphic stimuli containing sinusoidal gratings of different spatial frequencies and different levels of contrast sensitivity. Five spatial frequency levels from A to E, each of this consisting of 8 contrast sensitivity levels, were checked. For each stimulus, the patient must recognize the inclination of the grating, responding with the following 4 possibilities: right, left, vertical, or unrecognized. At the end of the examination, the contrast sensitivity curve of each patient is obtained, indicating the sensitivity value for each spatial frequency. We obtained 5 sensitivity values (between 0 and 8) for the 5 spatial frequency levels from *A* to *E*.

2.3. Statistical Analysis. Statistical analysis was performed using Minitab, version 15.1.0.0, statistical software (Minitab Inc., State College, PA, USA). Changes in visual acuity, contrast sensitivity, and GCC thickness were analyzed using the Student paired data test (Student's *t*-test). *P* values less than 0.01 were considered statistically significant.

3. Results

The MH was closed in all cases after the initial surgery (Figures 1 and 2). No intraoperative or postoperative complications were noted. Mean age of patients was 68.57 ± 8.05 years (range 48–81). Twenty patients (60.6%) were females, whereas remaining 13 (39.4%) were males. Seven patients had stage I MH, 9 patients (27.3%) had stage II MH, and remaining 17 patients (51.5%) had stage IV MH. The mean hole diameter was $187.00 \pm 65.07\,\mu$m for stage I MH, $304.33 \pm 81.10\,\mu$m for stage II MH, and $533.65 \pm 80.26\,\mu$m for stage IV MH. Table 1 shows demographic data and mean preoperative hole diameter values.

BCVA improved in all patients after the surgery (Table 2, Figure 3). Preoperative BCVA was 17.14 ± 10.38 letters for stage I MH, 15.11 ± 8.23 letters for stage II MH, and 6.29 ± 3.05 letters for stage IV MH. Postoperative BCVA progressively improved during the follow-up. After 1 month, BCVA improved to 30.71 ± 6.65 letters for stage I MH, 30.11 ± 7.02 letters for II stage MH, and 25.29 ± 8.35 letters for IV stage MH. At third postoperative month, BCVA was 42.57 ± 5.19 letters for stage I MH, 39.22 ± 6.85 letters for II stage MH, and 33.88 ± 8.35 letters for IV stage MH. The difference between the preoperative and one- and three-month postoperative values of BCVA was statistically significant in the three groups ($P < 0.01$).

During the follow-up, the average visual acuity recovery was similar in all stages. Stage I MH patients had an average gain of 26 letters (from 17.14 ± 10.38 to 42.57 ± 5.19) at the final follow-up. Similarly, stage II MH had an average final gain of 24 letters (from 15.11 ± 8.23 to 39.22 ± 6.85). In patients with stage IV MH, VA improved from 6.29 ± 3.05 in the preoperative to 33.88 ± 8.35 letters in the final follow-up with an average final gain of 27 letters at the ETDRS.

Contrast sensitivity (CS) was evaluated in 5 levels, from A to E, each of which has a specific spatial frequency and a different contrast value. Preoperative and postoperative CS are presented in Table 3 for all examined groups. Preoperative CS was *A*: 3.57; *B*: 3.28; *C*: 2.00; *D*: 0.71; and *E*: 0.28 for stage I MH, whereas it was *A*: 1.77; *B*: 1.66; *C*: 0.33; *D*: 0.00; and *E*: 0.00 for stage II MH; and it was *A*: 0.94; *B*: 0.47; *C*: 0.05; *D*: 0.00; and *E*: 0.00 for stage IV MH.

After 1 month, CS was improved, that is, *A*: 4.42; *B*: 4.85; *C*: 3.42; *D*: 1.57; and *E*: 0.85 for stage I MH. For stage II MH, it increased to *A*: 3.88; *B*: 3.22; *C*: 1.66; *D*: 0.77; and *E*: 0.11; and *A*: 3.17; *B*: 3.00; *C*: 1.35; *D*: 0.52; *E*: 0.05 for stage IV MH. At the third postoperative month, CS was *A*: 5.42; *B*: 5.85; *C*: 3.71; *D*: 2.14; and *E*: 1.28 for stage I MH; for II stage MH, it was *A*: 5.00; *B*: 4.66; *C*: 2.77; *D*: 1.33; and *E*: 0.33; and *A*: 4.23; *B*: 4.05; *C*: 2.47; *D*: 1.23; *E*: 0.35 for stage IV MH.

Contrast sensitivity improved during the follow-up in all three groups (Figure 4). The difference between the preoperative and postoperative contrast sensitivity values was statistically significant ($P < 0.01$) in both the first and third month.

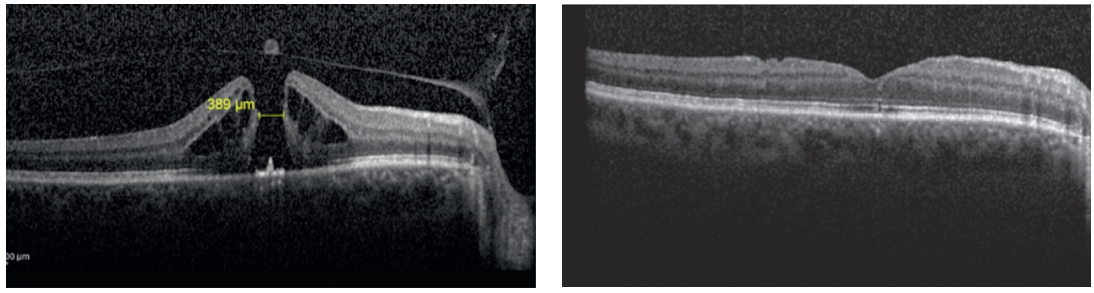
The total GCC thickness gradually decreased during the follow-up (Table 4, Figure 5). After the first month, it was $126.25 \pm 23.75\,\mu$m for stage I MH, $106.50 \pm 25.17\,\mu$m for stage II MH, and $97.57 \pm 14.88\,\mu$m for stage IV MH. At the third-month follow-up, the thickness further decreased to $109.96 \pm 16.38\,\mu$m for stage I MH, $92.94 \pm 20.99\,\mu$m for stage II MH, and $89.10 \pm 14.37\,\mu$m for stage IV MH. The difference between the preoperative and postoperative average thickness values was statistically significant ($P < 0.01$) in both the first and third month.

The analysis of the GCC thickness of the perifoveal quadrants also showed a progressive reduction in thickness in the third month after surgery and was statistically significant (*P* value <0.01) (Table 5, Figure 6). The reduction in thickness of the singular perifoveal quadrants during follow-up was between 34% and 42% of the preoperative values (Figure 7).

Finally, mean GCC thickness values of the operated eyes was compared with that of the contralateral healthy eyes, using them as a reference value for our sample (Table 6, Figure 8). Mean total GCC thickness of the fellow healthy eyes was $115.57 \pm 8.29\,\mu$m for stage I MH, $106.72 \pm 10.28\,\mu$m for stage II MH, and $105.94 \pm 8.83\,\mu$m for stage IV MH.

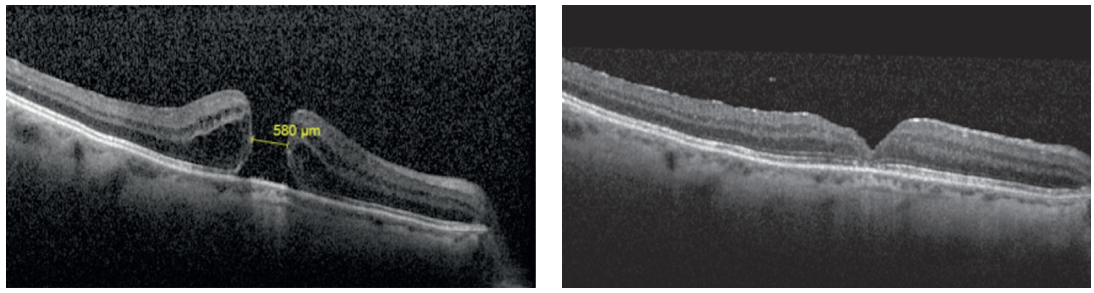
In stage I MH, there was no statistically significant difference between the mean thickness values of the GCC of the operated and healthy eyes, with an average thickness difference between the two groups being $5\,\mu$m ($P > 0.01$).

In stage II and IV MH, there was a statistical significant difference between the average GCC thickness of the operated eyes and healthy eyes with *P* value < 0.05 and $P < 0.01$. The average thickness difference between the two groups was $13\,\mu$m and $16\,\mu$m, respectively.



(a) (b)

Figure 1: (a) OCT image showing stage II macular hole with a diameter of 389 μm preoperatively. (b) OCT at 3-month follow-up showing closed MH with restored ELM and IS/OS junction integrity.



(a) (b)

Figure 2: (a) OCT image showing stage IV IMH with a diameter of 580 μm preoperatively. (b) Follow-up OCT scan at 3 months showing closed macular hole with restored ELM and IS/OS junction integrity.

Table 1: Demographic characteristics and preoperative values.

Parameter	Values	Percentage
Eye		
Right	16	48.49
Left	17	51.51
Macular hole stage		
I	7	21.2
II	9	27.3
IV	17	51.5
Hole diameter		
I	187.14 ± 65.07 μm	
II	304.33 ± 81.10 μm	
IV	533.65 ± 80.26 μm	

Table 2: Preoperative and postoperative best-corrected visual acuity.

Best-corrected visual acuity (BCVA)–N° letters (ETDRS)			
Stage	Mean N°	St Dev	SE mean
Preoperative values			
I	17.14	10.38	3.92
II	15.11	8.23	2.74
IV	6.29	3.05	0.74
1-month postoperative values			
I	30.71	6.65	2.51
II	30.11	7.02	2.34
IV	25.29	8.35	2.02
3-month postoperative values			
I	42.57	5.19	1.96
II	39.22	6.85	2.28
IV	33.88	8.35	2.02

Preoperative and postoperative best-corrected visual acuity (BCVA) N° letters (ETDRS). St dev: standard deviation; SE: standard errors.

4. Discussion

ILM is the inner most layer of retina constituting the basement membrane and originates from the Muller cells. The outer surface of ILM is continuous with Muller cell end-feet and is adherent to the retinal nerve fiber layer and ganglion cell layer. The etiopathogenesis of MH formation is not clearly understood. Multiple factors such as tangential and anteroposterior traction and degenerative and cellular changes have been speculated. Removal of ILM ensures elimination of residual cortical vitreous, ERMs, and vitreous-derived cells that may be left on the retinal surface [24, 25]. It has been postulated that ILM peeling could activate Muller cells to secrete collagen, basement membrane components, and inflammatory factors. This stimulates glial cell-mediated closure of macular holes. This may explain the modestly higher closure rates observed with ILM peeling compared with vitrectomy alone [26]. In addition, more recent data suggest that MHs may reopen at lower rates when the ILM is peeled [27].

Our results showed that all the IMHs included in the study were closed after 25G PPV with ILM peeling and macular abrasion (wherever indicated). SD-OCT showed restoration of the foveal profile with integrity of the ELM and the photoreceptor layer in all patients. Sabater et al. [28]

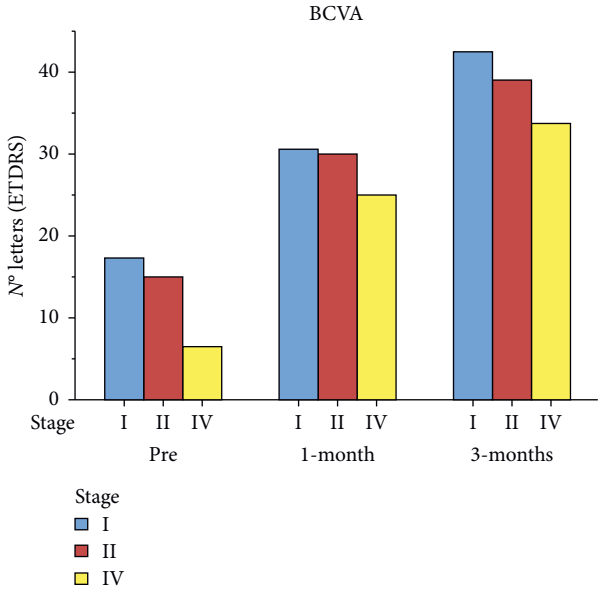


Figure 3: Preoperative and postoperative BCVA.

Table 3: Mean preoperative and postoperative contrast sensitivity (CS) for all groups.

CS	Stage I MH	Stage II MH	Stage IV MH
Preoperative values (mean ± St dev)			
A	3.57 ± 1.51	1.77 ± 0.97	0.94 ± 1.02
B	3.28 ± 2.13	1.66 ± 1.41	0.47 ± 0.62
C	2.00 ± 2.16	0.33 ± 0.50	0.05 ± 0.24
D	0.71 ± 1.25	0.00 ± 0.00	0.00 ± 0.00
E	0.28 ± 0.75	0.00 ± 0.00	0.00 ± 0.00
1-Month postoperative values (mean ± St Dev)			
A	4.42 ± 1.27	3.88 ± 1.26	3.17 ± 1.28
B	4.85 ± 1.06	3.22 ± 1.20	3.00 ± 1.36
C	3.42 ± 0.97	1.66 ± 0.86	1.35 ± 0.86
D	1.57 ± 1.61	0.77 ± 1.09	0.52 ± 0.62
E	0.85 ± 1.46	0.11 ± 0.33	0.05 ± 0.24
3-Month postoperative values (mean ± St Dev)			
A	5.42 ± 0.78	5.00 ± 0.50	4.23 ± 1.20
B	5.85 ± 0.69	4.66 ± 1.11	4.05 ± 1.24
C	3.71 ± 0.75	2.77 ± 0.83	2.47 ± 0.94
D	2.14 ± 0.69	1.33 ± 0.50	1.23 ± 0.75
E	1.28 ± 0.95	0.33 ± 0.50	0.35 ± 0.60

and Baba et al. [11] also had a 100% MH closure rate on OCT evaluation in 25 and 28 study eyes, respectively.

Visual acuity progressively improved throughout the follow-up in the three groups. All patients had an average gain of more than 4 lines at the ETDRS, with a statistically significant difference between the preoperative and postoperative values ($P < 0.01$).

Contrast sensitivity progressively increased in all stages. The highest mean contrast sensitivity values were found, at the end of the follow-up, in patients with stage I MH, followed by stage II and IV MH. The greatest increase in CS for stage I MH and stage II MH was for levels C, D, and E. For stage IV MH, the greatest gain was for levels A and B.

MBD dye was used to stain the ILM and facilitate peeling. Some dyes, such as indocyanine green, have been associated with retinal toxicity and may be responsible for reducing the GCC. MBD, on the other hand, has been shown to be cytoprotective against retinal nerve cells [29]. Baba et al. [30] showed its influence on GCC reduction to be minimal. Similarly, Sevim and Sanisoglu [31] showed no significant decrease of average superior and inferior GCC thickness after BBG-assisted ILM peeling. Additionally, we ensured bare minimum dye retina contact time by quick aspiration of the dye.

The presence of ganglion cells on the surgically excised ILM, demonstrated by immunohistochemistry, confirms mechanical removal of ganglion cells during peeling, which is suggestive of iatrogenic damage [32]. This damage can be assessed by measuring average GCC thickness after ILM peeling and macular abrasion.

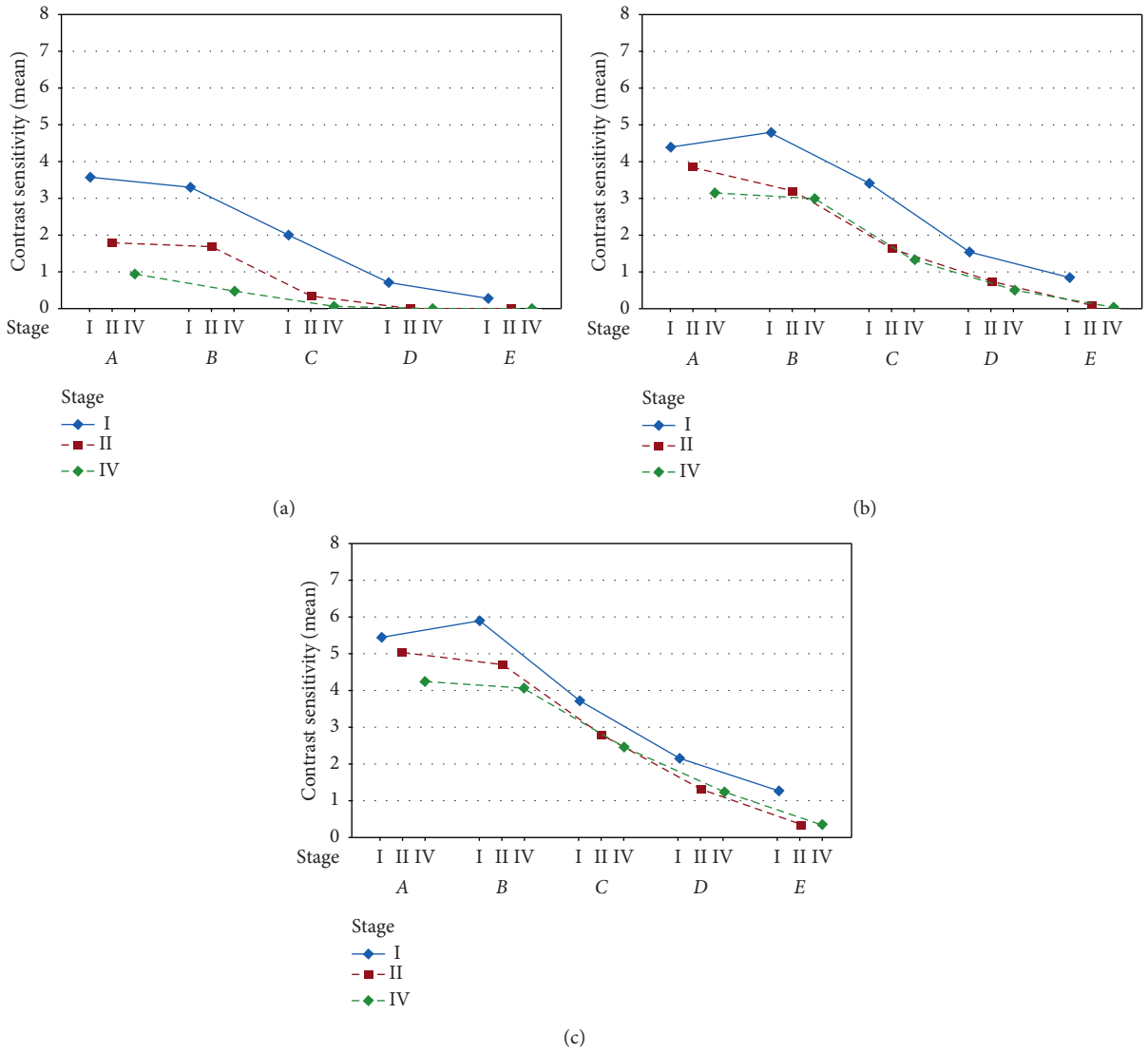


Figure 4: Mean preoperative and postoperative contrast sensitivity (CS) for all groups: (a) preoperative, (b) 1-month follow-up, and (c) 3-month follow-up.

In our study, the mean GCC thickness showed a reduction in all stages during follow-up. The major reduction occurred in the first month after surgery and continued with a low progression till the third month. The sharp reduction in thickness during the first month could be linked to the removal of ILM and resolution of intraretinal edema; the minimum reduction that occurred in the third month may be attributed to iatrogenic damage.

According to some reports, the GCC thickness in normal eyes, as measured by RTVue-100, ranged from 93.7 to 95.1 mm. [33–35] In our study, GCC thickness of unaffected fellow eyes was 108.66 ± 4.6 mm. The postoperative GCC thickness in our study was 96.66 ± 8.8 mm at 3 months, and it was thinner than normal GCC thickness by approximately 11.33 mm.

We compared the mean GCC thickness of the operated eyes with that of the healthy contralateral eyes. In stage I MH, the difference between the two thicknesses was not statistically significant ($P > 0.05$). Thus, it can be concluded that there was not much iatrogenic damage in this group. Stage II MH patients showed statistically significant difference between the two thickness values (P value <0.05). In stage IV MH, statistical difference was highly significant (P value <0.01).

We also compared the GCC thicknesses of the individual perifoveal quadrants preoperatively and postoperatively. We noticed uniform reduction of the GCC in all 4 quadrants in all stages. The reduction was between 34 and 42% compared with the preoperative values. The higher reduction in thickness at the end of the follow-up was detected in the temporal quadrant. Similar findings were also noted by Baba et al. [30]. Sabater et al. [28] also noted significant reduction of retinal ganglion cell inner plexiform layer (GCIPL) thickness more at the temporal quadrants during analysis. It was done with newer ganglion cell analysis (GCA) software of the Cirrus HD-OCT at 6 months after BBG-assisted ILM peeling vitrectomy.

Table 4: Mean preoperative and postoperative GCC thickness values in the three groups.

Ganglion cell complex thickness (μm)			
Stage	Mean	St Dev	SE mean
Preoperative values			
I	175.85	32.18	6.08
II	144.08	36.84	6.14
IV	144.58	31.91	3.87
1-Month postoperative values			
I	126.25	23.75	4.48
II	106.50	25.17	4.19
IV	97.57	14.88	1.80
3-Month postoperative values			
I	109.96	16.38	3.09
II	92.94	20.99	3.49
IV	89.10	14.37	1.74

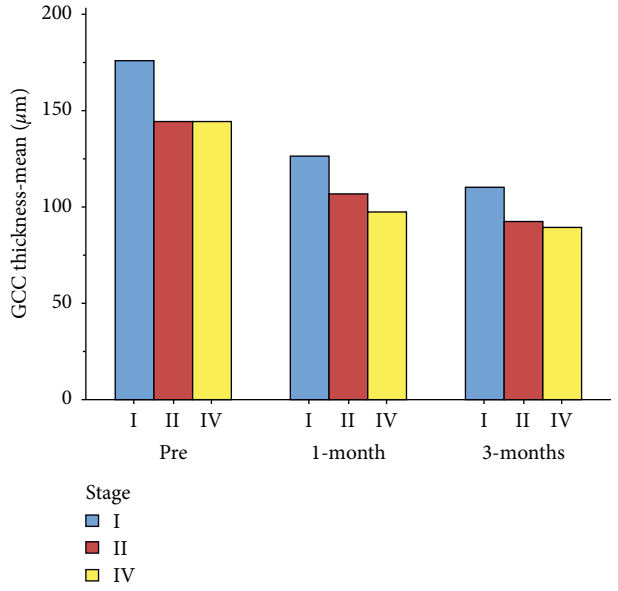


Figure 5: Mean preoperative and postoperative GCC thickness values in the three groups.

Table 5: Mean preoperative and postoperative GCC thickness of the perifoveal quadrants of three groups.

Quadrant	Stage I MH	Stage II MH	Stage IV MH
Preoperative values (mean ± St Dev)			
Temporal	165.57 ± 24.95	141.78 ± 33.60	140.52 ± 35.93
Superior	180.14 ± 41.44	149.22 ± 45.35	146.18 ± 30.98
Nasal	178.86 ± 34.29	140.22 ± 35.60	146.17 ± 35.13
Inferior	178.86 ± 31.28	145.11 ± 37.83	145.52 ± 27.51
3-Month postoperative values (mean ± St Dev)			
Temporal	103.28 ± 16.21	88.11 ± 13.95	81.29 ± 9.89
Superior	114.42 ± 13.80	96.44 ± 20.42	93.17 ± 14.71
Nasal	108.00 ± 15.05	92.55 ± 28.56	92.41 ± 17.77
Inferior	114.14 ± 20.67	94.66 ± 21.36	89.52 ± 11.88

This could be because of mechanical manipulation of the ILM that always started from the temporal quadrant of the retina. We feel safer to initiate ILM peeling starting from the temporal quadrant because the terminals of retinal nerve fibers exist at the temporal retina. This could have altered the temporal GCC thickness more than that in other quadrants. Contrary to our rationale, Nukada et al. [36] noted similar temporal GCC loss even though initial ILM flap was created at the superior or inferior quadrant.

The nerve fiber layer is physiologically thinner in the temporal quadrant. The density of the ganglion cells in the temporal retina is less than that of its nasal counterpart [37].

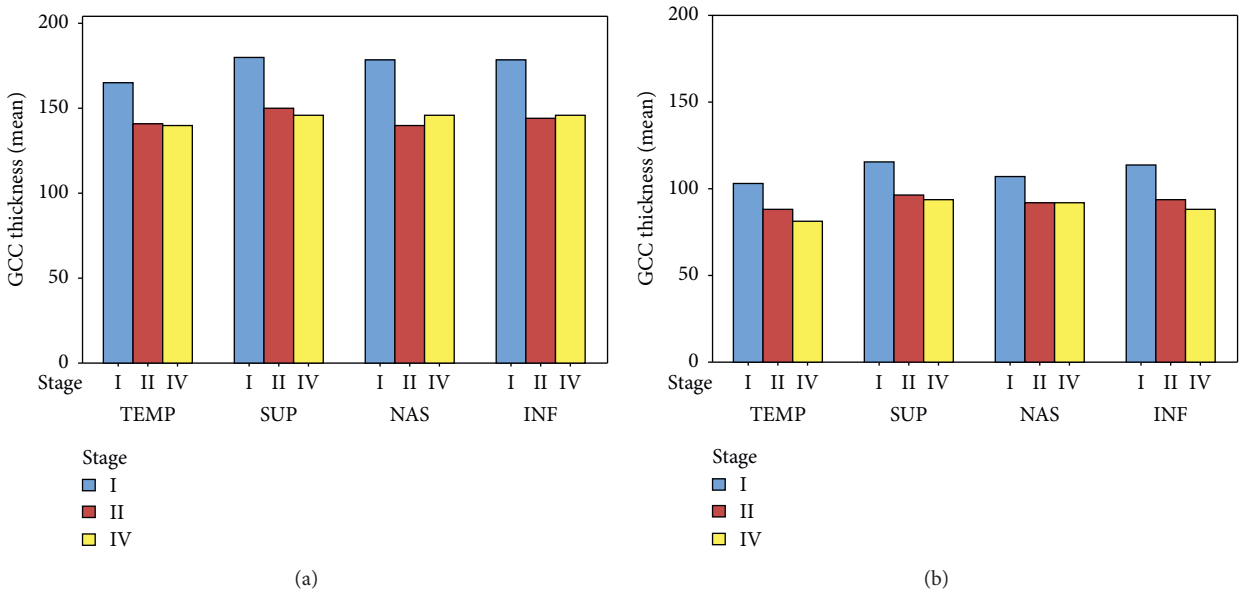


Figure 6: Mean preoperative and postoperative GCC thickness of the perifoveal quadrants of three groups: (a) preoperative GCC thickness of perifoveal quadrants and (b) 3-month GCC thickness of perifoveal quadrants.

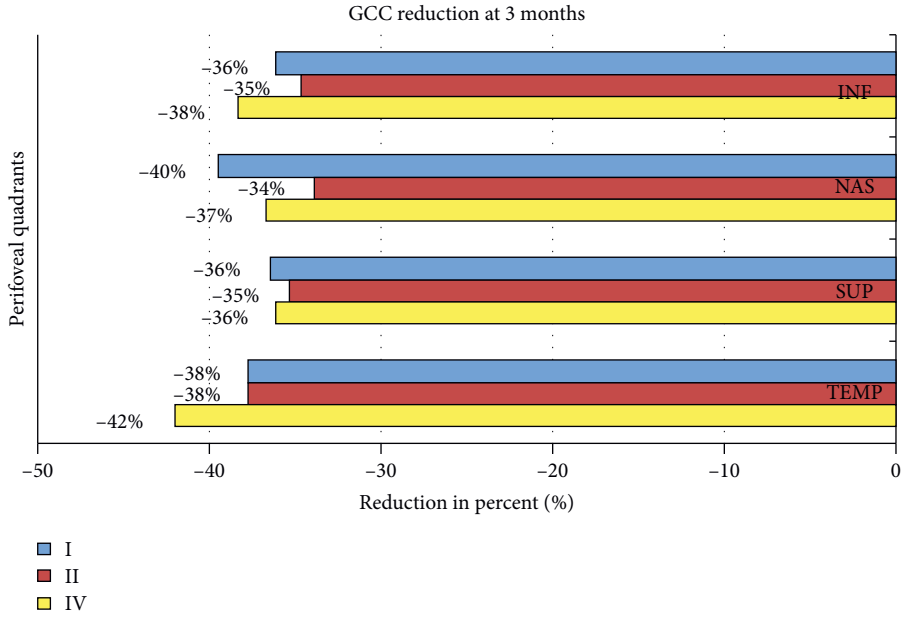


Figure 7: Reduction in thickness of the singular perifoveal quadrants during follow-up.

These aspects may also be contributing to its iatrogenic damage.

The Tano DDMS is a safer instrument since it only removes the cell membranes and surface layer of the ILM. The abrasion of the MH edge is performed to reduce the size of the large holes and facilitate the reconstitution of IS/OS junction and ELM and possibly stimulate proliferation of glial cells. Michalewska et al. [7] hypothesized that the proliferation of glial cells leads to relocation of adjacent photoreceptors to the fovea, thus explaining the improvement of functional results. However, the improvement in visual acuity and contrast sensitivity confirm the functional success of this technique [21]. Moreover, the use of the Tano DDMS could be beneficial in recurrent patients previously treated with ILM peeling alone.

Table 6: Comparison between GCC thickness of the operated eye and contralateral healthy eye in the three groups at three-month follow-up.

GCC thickness of stage I MH at 3-month follow-up					
	Mean		St Dev		SE mean
Operative eye	109.96		14.04		5.68
Fellow eye	115.57		8.29		3.13
Estimation for paired difference					
Mean	St Dev	SE mean	95% CI for μ_d	*T* value	*P* value
−5.607 μm	9.500	3.591	(−14.393; 3.179)	−1.56	<0.1694
GCC thickness of stage II MH at 3-month follow-up					
	Mean		St Dev		SE mean
Operative eye	92.94		18.99		6.33
Fellow eye	106.72		10.28		3.42
Estimation for paired difference					
Mean	St Dev	SE mean	95% CI for μ_d	*T* value	*P* value
−13.778 μm	13.689	4.563	(−24.300; −3.255)	−3.02	<0.0166
GCC thickness of stage IV MH at 3-month follow-up					
	Mean		St Dev		SE mean
Operative eye	89.10		11.10		2.69
Fellow eye	105.94		8.83		2.142
Estimation for paired difference					
Mean	St Dev	SE mean	99% CI for μ_d	*T* value	*P* value
−16.838 μm	10.214	2.477	(−24.074; −9.603)	−6.80	<0.0001

St Dev: standard deviation; SE mean: standard error of mean; CI: confidence interval.

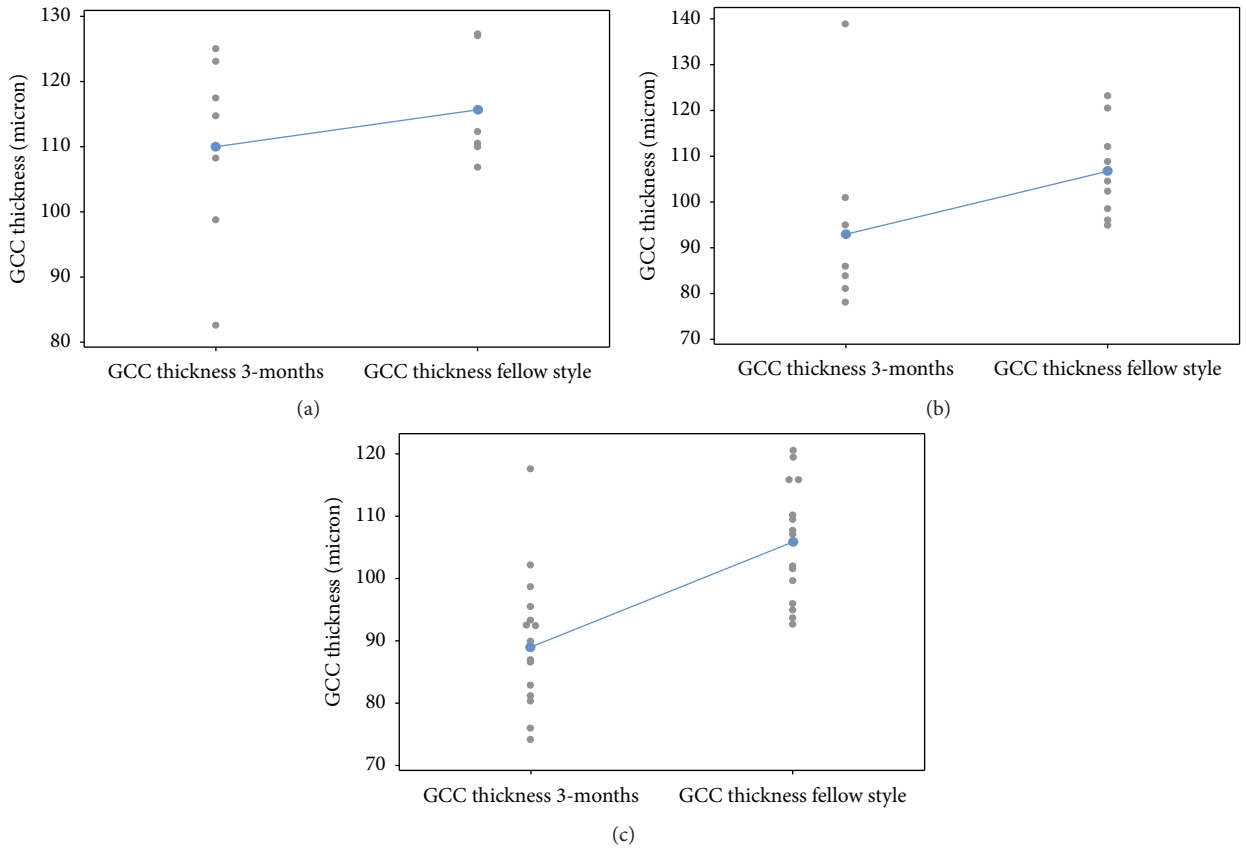


Figure 8: Comparison between GCC thickness of the operated eye and contralateral healthy eye in the three groups at three-month follow up: (a) macular hole stage I, (b) macular hole stage II, and (c) macular hole stage IV.

5. Conclusion

To conclude, we studied an alternative method of MH surgery that appears to preserve the retinal function. Although our current practice continues to perform complete ILM peels, the additional macular abrasion technique when selectively applied seems to improve functional outcomes.

The major limitation of this study is the retrospective design with a short observation period and limited subjects. Functional postoperative evaluation could possibly be more accurate with microperimetry and also multifocal electroretinographic evaluations. However, the results are encouraging. Further prospective studies with longer follow-up may be needed to exclude any long-term iatrogenic damage.

Data Availability

The data are available on request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Video 1 showing vitrectomy with MBD assisted ILM peeling with macular abrasion for stage IV MH. Video attached. . (*Supplementary Materials*)

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Research Article

Surgical Treatment of Idiopathic Macular Hole Using Different Types of Tamponades and Different Postoperative Positioning Regimens

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Purpose. To compare the effect of different types of intraocular tamponade and different types of postoperative positioning on the closure of idiopathic macular hole (IMH). *Methods*. Prospective randomized clinical trial enrolling 104 eyes of 100 patients (age, 57–87 years) undergoing MH surgery. All patients were operated on by an experienced surgeon using 25-gauge pars plana vitrectomy (PPV) and internal limiting membrane (ILM) peeling. Patients were randomized according to the type of intraocular tamponade and postoperative positioning into the following four groups: SF6 + nonsupine reading position ($n = 26$) (group 1), air + nonsupine reading position ($n = 25$) (group 2), air + prone position ($n = 26$) (group 3), or SF6 + prone position ($n = 27$) (group 4). The follow-up period was 6 months. *Results*. MH closure was achieved in 87 eyes (83.7 %) in the overall sample after the first surgery, with closure rates of 100%, 56%, 84.6%, and 92.6% in groups 1, 2, 3, and 4, respectively. The group 2 was significantly less successful compared to the other three groups ($p < 0.05$). MH of sizes ≤400 μm was closed in 97.2% of cases after the first surgery, with no significant differences between groups ($p = 0.219$). MH with sizes over 400 μm was closed in 70.9% of cases after the first surgery, with both groups with air tamponade being significantly less successful than group 1. The nonsupine reading position was subjected to a better subjective evaluation in terms of postoperative comfort and quality of sleep, with no differences between air and SF6 tamponade tolerance. *Conclusion*. PPV with ILM peeling, intraocular tamponade, and positioning remains the basic surgical approach in the treatment of IMH. For MH ≤ 400 μm, a high closure rate can be achieved by combining air tamponade and nonsupine reading position. For macular holes >400 μm, the greatest anatomical success can be achieved by using the SF6 tamponade in combination with the nonsupine reading position.

1. Introduction

The macular hole (MH) represents a defect of the fovea center in its full thickness from the internal limiting membrane (ILM) to the outer segments of photoreceptors. This pathological condition is characterized by painless decline in visual acuity, metamorphopsia, and central scotoma [1]. The idiopathic macular hole (IMH) is the most common presentation, being considered as incurable until 1991, when Kelly and Wendel published their successful

results in 52 patients (58% of holes closed) after vitrectomy surgery and gas tamponade [2]. During the following years, the surgical procedure underwent a number of modifications in order to increase its success and safety.

Perioperative removal of ILM around the macular hole to increase the anatomical and functional success of the MH surgery was first described by Eckardt et al. in 1997 [3]. Subsequently, different authors confirmed the importance of ILM peeling for MH closure [4, 5]. Although the ILM peeling increases the anatomical and functional success of the MH surgery, it can also negatively affect the function and structure of the retina [6]. After the surgical release of the posterior vitreous, vitrectomy, and subsequent ILM peeling, the infusion fluid is routinely exchanged for air and subsequently for expansion gas [2]. The duration of the gas charge varies depending on the gas used and its concentration, ranging from 2 to 11 weeks (2–2.5 weeks for SF6, 4–6 weeks for C2F6, and 8–11 weeks for C3F8) [7]. A prone position is traditionally recommended for patients undergoing this surgical procedure, which is very uncomfortable and can cause some complications, such as back pain, sinusitis, or paralysis of the ulnar nerve [8]. The most optimal duration for this recommended positioning remains unclear and is very variable among published studies. The most recommended option is to maintain the prone position at least 8 hours a day for at least 5–7 days in order to maximize the contact of the bubble with the macular landscape [7, 9].

There is a close relationship between the type of tamponade chosen and the postoperative patient positioning regimen, to ensure that the tamponade bridges the MH. Even in the upright position, the gas bubble still bridges the hole, provided that the gas fills more than 50% of the vitreous space. Furthermore, long-lasting gas tampons fill more than 50% of the vitreous space in a longer period than short-acting gases or air. However, it is still unclear how long the gas must bridge the MH to close it. The initial size of the MH is the most relevant risk factor for the surgical success, being this apparently a key factor in the choice of the tamponade and the need for specific postoperative patient positioning [10]. The aim of this work was to compare the effect of combinations of different types of intraocular tamponades (air or SF6 gas) and different types of postoperative patient positioning on IHM closure (prone or nonsupine reading position). This article is of high clinical relevance although new advances have suggested that postoperative positioning may be not mandatory for MH closure considering that new techniques of hole closure seem to adequately relieve the tangential traction and some even to provide a scaffold for possible regeneration. However, it should be considered that these techniques, such as the ILM flap technique, are used by some surgeons primarily for large MH, not routinely for all MH.

2. Methods

2.1. Patients. This prospective, randomized, clinical series enrolled a total of 104 eyes with IMH of 100 patients with ages ranging from 57 to 87 years that underwent MH surgery at the Department of Ophthalmology of the University Hospital Kralovske Vinohrady in Prague (Czech Republic). All patients were informed about the nature and risks of the study and signed a written informed consent to be enrolled in it according to the tenets of the Declaration of Helsinki. Likewise, the protocol of the study was approved by the ethics committee of the Royal Vinohrady University Hospital on March 1, 2016. Inclusion criteria were diagnosis of IMH stage 2 to 4 according to Gass [1] and signing informed consent. Exclusion criteria included the following conditions: previous pars plana vitrectomy (PPV), eye injury, myopia ≥6 diopters, any intraocular or periocular infection or active intraocular inflammation (infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, or uveitis) in the evaluated eye on the day of surgery and other macular diseases that could affect the surgical outcome (wet form of age-related macular degeneration, central serous chorioretinopathy, macular telangiectasia, diabetic macular edema, or edema in retinal vein occlusion).

Patients enrolled in the study were divided into 4 groups according to the intraocular tamponade used in the MH surgery and the type of patient positioning recommended in the postoperative period using a randomization generator (https://www.sealedenvelope.com/simple-randomiser/v1/lists):

Group 1: SF6 tamponade + nonsupine reading position (Figure 1)

Group 2: tamponade air + nonsupine reading position

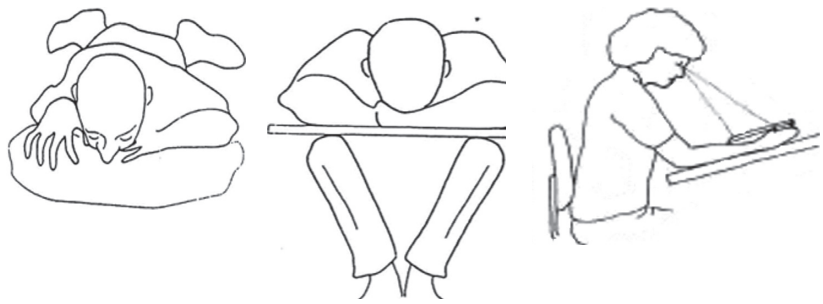
Group 3: tamponade air + prone position (Figure 1)

Group 4: SF6 tamponade + prone position

The assignment to the relevant group was performed just before the start of the surgical procedure in the operating room.

2.2. Clinical Examinations. In all patients, a complete preoperative examination was performed including anterior segment slit lamp examination, including biomicroscopy of the posterior segment of the eye under artificial mydriasis, air tonometry, measurement of uncorrected (UCVA) and best-corrected visual acuity (BCVA) using the ETDRS (Early Treatment Diabetic Retinopathy Study) optotypes in decimal values, manifest refraction, and analysis of the retinal structure confirming the diagnosis of MH by spectral domain optical coherence tomography (OCT) (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). The first postoperative examination was performed the day after surgery, with additional postoperative examinations at 1, 3, and 6 months after surgery. The same spectrum of examinations as before surgery was also performed on all these postoperative examinations, with the exception of the first examination in which no OCT examination was included. If there was significant cataract development or progression in the postoperative period, patients underwent standard phacoemulsification cataract surgery with implantation of a posterior chamber intraocular lens.

2.3. Surgical Procedure. All patients were operated on by the same experienced surgeon (MV) using the 25-gauge PPV of the Constellation surgical system (Alcon, Fort Worth, TX,



(a) (b)

Figure 1: Drawing scheme showing the configuration of the two types of positioning recommended in the current study: (a) prone position; (b) nonsupine reading position.

USA). The area around the eye and the conjunctival sac was disinfected with a 5% povidone-iodine solution, the operating field was covered with a sterile drape, and a dilator was placed. After oblique transconjunctival insertion of trocars through the pars plana at 3.5–4 mm from the limbus, vitrectomy was initiated. In the case of fixation of the ZSM to the posterior pole of the eye, it was released by suction of the vitrectomy approximately at the equator region. ILM peeling was performed using Eckardt forceps and a contact macular lens. Brilliant blue (Ocublue Plus, Aurolab) was used to facilitate the identification of the membranes for their safe and complete removal. The ILM peeling area covered approximately 2 PD (papilla diameter). Afterwards, a complete exchange of fluid for air and, if necessary, instillation of expansive gas 20% SF6 was performed following the protocol defined according to the preoperative randomization. After extraction of the trocars, the tightness of the sclerotomies was checked, and in case of leakage, they were sutured with Vicryl 8–0 absorbable sutures. All surgeries were performed under retrobulbar anesthesia (3 ml of Marcain + 2 ml of Supracain).

After surgery, the following recommendations were given to patients depending on the group of randomization assigned (Figure 1):

Groups 3 and 4: to keep the head as much as possible in the prone position for 3 days, with the greatest emphasis on maintaining this position for the first 24 hours after surgery

Groups 1 and 2: to keep looking during the daily activities as if reading for 3 days, not laying on the back at night (recommendation of sleeping on the stomach or side at night)

Furthermore, each patient also received a questionnaire with three questions to evaluate the severity of the recommended postoperative regimen.

2.4. Statistical Analysis. Statistica version 9 from Statsoft was used for statistical analysis. Normality of quantitative data samples was evaluated using the Kolmogorov–Smirnov test in order to confirm if parametric or nonparametric statistical tests had to be used. Contingency table analysis and Pearson's chi-square test were used to determine the difference in macular hole closure success rates between the four groups of patients evaluated and also between pairs of groups. Fisher's exact test was used in the case of the comparison of small sample sizes. A paired Student's t-test (Wilcoxon test if the sample was not normally distributed) was used to compare the visual acuity before and after surgery for the whole sample as well as for each group separately. The unpaired Student's t-test (Mann–Whitney test if the sample was not normally distributed) was used to compare postoperative intraocular pressure values between individual operated groups. A p value of less than 0.05 was considered as statistically significant.

3. Results

A total of 104 eyes of 100 patients (76 women and 24 men) were included in the study. Both eyes were operated in two women and two men. Mean age of patients was 70.8 years (range, 57 to 87 years). A total of 74 eyes were phakic at the time of IMH diagnosis, whereas 30 eyes were pseudophakic. The preoperative mean value of decimal BCVA was 0.15 in the whole sample, with a range of variation from 0.05 to 0.50. The average size of the MH at its narrowest point in the hole sample was 408.5 μm (range, 133 to 741 um). In 44 eyes (42.3%), an epiretinal membrane (ERM) was also present. In 89 eyes (85.6%), the posterior vitreous membrane was attached, being then necessary to release it perioperatively. The main characteristics of the patients enrolled in each individual group are summarized in Table 1. The follow-up period was 6 months.

3.1. MH Closure Rate Analysis. Full MH closure was achieved in 87 eyes (83.7%) from the whole group after the first surgery. The MH closure success rates after primary surgery in each group are displayed in Table 2. A flattening and complete closure of the edges of the MH was considered as an anatomical success. The group with air tamponade and nonsupine reading position (group 2) was statistically significantly less successful compared to the other three groups (group 2 vs. 1, $p < 0.001$; 2 vs. 3, $p = 0.025$; 2 vs. 4, $p = 0.003$). The differences in the MH closure success rates between the other three groups (1, 3, and 4) were not statistically significant (group 1 vs. 3,

Table 1: Preoperative characteristics of the operated patients in each individual group.

	Group 1 (SF6 + nonsupine reading position)	Group 2 (air + nonsupine reading position)	Group 3 (air + prone position)	Group 4 (SF6 + prone position)
Number of eyes	26	25	26	27
Mean age (range) (years)	70.2 (63–80)	71.3 (57–86)	69.2 (59–79)	72.4 (61–87)
Mean decimal BCVA (range)	0.11 (0.05–0.33)	0.10 (0.05–0.33)	0.19 (0.05–0.50)	0.18 (0.01–0.50)
Mean IMH size (range) (μm)	426.7 (178–612)	446.4 (178–711)	405.4 (148–741)	358.7 (133–652)
Number of phakic eyes (%)	16 eyes (61.5)	20 eyes (80.0)	21 eyes (80.8)	17 eyes (63.0)
Eyes with ERM (%)	9 eyes (34.6)	10 eyes (40.0)	15 eyes (57.7)	10 eyes (37.0)
Eyes with posterior vitreous membrane attached (%)	24 eyes (92.3)	20 eyes (80.0)	20 eyes (76.9)	25 eyes (92.6)

BCVA, best-corrected visual acuity; IMH, idiopathic macular hole; ERM, epiretinal membrane.

Table 2: Macular hole closure success rates after primary surgery in each individual group.

	Group 1 (SF6 + nonsupine reading position) (%)	Group 2 (air + nonsupine reading position) (%)	Group 3 (air + prone position) (%)	Group 4 (SF6 + prone position) (%)
MH closure success of whole sample	100	56.0	84.6	92.6
MH closure success of IMH $\leq 400\,\mu$m	100	88.9	100	100
Successful closure of IMH $> 400\,\mu$m	100	37.5	71.4	77.8

IMH, idiopathic macular hole.

$p = 0.110$; 1 vs. 4, $p = 0.255$; and 3 vs. 4, $p = 0.316$). MH with a size of $\leq 400\,\mu$m closed after the first surgery in 97.2% of cases, with no statistically significant difference in closure success rates between the individual-operated groups ($p = 0.219$). Macular holes of more than $400\,\mu$m in size closed in 70.9% of cases after the first operation. Both groups with air tamponade (2 and 3) were statistically significantly less successful compared to the SF6 + nonsupine reading position group (group 1) (1 vs. 2, $p < 0.001$; 1 vs. 3, $p = 0.037$). No statistically significant differences in the closure success rates were found between the two groups with air tamponade ($p = 0.081$), as well as between the two groups with gas tamponade SF6 ($p = 0.120$).

A second PPV with gas tamponade due to a not complete closure of the MH after primary PPV was needed in 16 eyes. Only in 1 eye, a third PPV with a silicone oil tamponade was required. Furthermore, one patient with an open MH refused a second operation after primary PPV. In the last follow-up visit, the MH was closed in a total of 103 eyes (99.0%).

3.2. Visual Outcome Analysis. At the end of the follow-up period, mean decimal BCVA in the whole group improved to 0.56 (range from 0.16 to 1.0) ($p < 0.001$). BCVA worsened in one eye (patient number 9 from group 4, worsening by 2 ETDRS lines) and remained at the preoperative level in another eye. In the rest of cases, BCVA improved (98.1%). BCVA improved by 3 ETDRS lines or more in 92 eyes (88.5%). At the end of the follow-up period, 15 of the 17 eyes (88.2%) not achieving a MH closure after primary surgery also improved by more than 3 ETDRS lines. At the last postoperative visit, no significant differences in the level of BCVA between individual were found ($p > 0.05$).

3.3. Questionnaire Outcomes. Concerning the first question performed (was the postoperative positioning uncomfortable for you?), patients rated the prone position statistically significantly worse than the nonsupine reading position ($p = 0.010$). In the second question (did you experience impaired sleep quality due to positioning?), patients with the recommendation of the prone position reported a more significant impairment of sleep quality than patients with the recommendation of the nonsupine reading position ($p = 0.001$). Regarding the third question (did the air/gas tamponade bother you with its duration?), patients rated air tamponade as significantly worse ($p = 0.028$).

3.4. Complications. All sclerotomies were sufficiently sealed, not being necessary to suture them. On the first postoperative day, mean IOP was 16.0 mm Hg (range, 6 to 40 mm Hg) in the overall sample, not observing hypotension below 6 mm Hg in any operated eye. Mean IOP values on the first postoperative day were 18.6, 12.5, 14.9, and 17.9 mm Hg in groups 1, 2, 3 and 4, respectively. Differences in IOP the first day after surgery were statistically significant among groups 1 and 2 ($p < 0.001$), 1 and 3 ($p = 0.011$), 2 and 4 ($p < 0.001$), and 3 and 4 ($p = 0.035$). In the postoperative period, IOP ≥ 25 mm Hg was observed in 4 eyes (3.8%) that were quickly resolved with local antiglaucoma therapy.

The frequency of complications was relatively low. Small retinal tears at the end of the procedure during the peripheral retinal examination were detected in 10 cases (9.6%). Likewise, peripheral vitreoretinal traction and

malignant degeneration were observed in 20 eyes (19.2%) that were successfully treated with laser photocoagulation or cryopexy. Cataract surgery was performed in 28 of 74 phakic eyes (37.8%) due to a progress in the opacification of the crystalline lens after MH surgery. No other postoperative complications, such as retinal detachment or endophthalmitis, were recorded in this cohort.

4. Discussion

Many authors have confirmed the relevance of ILM peeling for a successful closure of MH, considering as a standard step in MH surgery. In 1997, Eckardt et al. reported a successful closure of MH in 92% of cases using this surgical procedure [3]. Subsequently, many other authors have confirmed the positive effect of ILM peeling on MH closure. Kwok et al. [11] reported an anatomical success rate of the operation of 89% in patients with MH grades 3 and 4, in which ILM peeling was performed compared to a rate of 59% in patients operated on without ILM peeling. In another study enrolling 127 patients, Lois et al. [4] detected a closure of MH in 84% of undergoing surgery with ILM peeling, whereas in eyes undergoing surgery without ILM peeling, the MH closure was only achieved in 48% of cases ($p < 0.001$). In the current study, ILM peeling was performed in all patients. Although ILM peeling has been shown to rise the anatomical success of the MH surgical procedure, it should be also mentioned that the ILM peeling can also lead to defects of the retinal architecture, atrophy of the macular area (especially in the temporal part), and significant defects of retinal sensitivity when measured with microperimetry [12–14].

Besides ILM peeling, the type of intraocular tamponade chosen as well as the mode of postoperative patient positioning have a fundamental influence on the closure of the MH. Kelly and Wendel's surgical procedure using a gas tamponade and subsequent face-down patient positioning has become a standard in the treatment of MH [2]. Several studies have demonstrated the excellent effect of gas tamponade in combination with patient face-down positioning on the closure of MH. Almeida et al. [15] found that MH (stages 1–3) was successfully closed with SF6 tamponade and patient pronation position for three days in 49 of 50 eyes (98%) [15]. Our research group published in 2015 a study showing the results of MH surgery using either SF6 or C3F8 as gas tamponade and recommending a prone position for three days to all patients [16]. In this previous series, a successful outcome was obtained after the first operation in 92.5% of eyes [16]. In the current series, a similar MH closure rate (92.6%) was found in the SF6 + pronation group. The effect of long-term gas tamponade using C3F8 and C2F6 is similar to that found for a shorter tamponade using SF6. In 2008, a comparison of the effect of different types of gas tamponade in combination with the patient prone position was performed, confirming that 90% and 91% of MH were closed using SF6 and C3F8, respectively ($p = 0.91$). [17] Modi et al. [18] also compared the effect of SF6 and C3F8, not detecting a statistically significant difference in the effect of both gases and obtaining MH closure rates of 86.4% and 86.5% using SF6 and C3F8, respectively ($p = 0.98$). However, a lower incidence of cataract and postoperative ocular hypertension were observed with the use of SF6.

The gas bubble contributes to the closure of the MH by several mechanisms, being essential for the maintenance of a dry macula and its isolation from vitreous fluid [19, 20]. The duration of the gas tamponade varies depending on the gas used and its concentration, ranging from 2 to 11 weeks [7]. During this period, the patient loses the binocular vision, with the impossibility of driving or travelling by plane. Approximately 60% of patients rate gas tamponade as uncomfortable or very uncomfortable [21]. Gas tamponade also accelerates the development and progression of cataracts [22]. In contrast, air is absorbed more rapidly in the eye, with an acceleration of the recovery and the return of the patient to normal life. In our cohort, patients were asked by means of a questionnaire to evaluate the duration of the tamponade, with no more favorable perception of the air tamponade compared to SF6. In phakic eyes, the half-life of air is 1.3 days [23]. In pseudophakic eyes, the air filling of the eye is larger, with an average time of complete air absorption of 10 days [24]. When a pronation position is recommended, the air bubble keeps the macula sufficiently isolated from the vitreous fluid, and therefore, excellent surgical results can be achieved. Sato and Isomae [25] reported a MH closure rate of 91.3% after surgery with ILM peeling in patients in which the prone position was recommended for one day during air tamponade. Hejsek et al. [26] reported a MH closure rate of 93.1% using air tamponade. Hasegawa et al. [27] achieved a similar MH closure rate (92.3%) in a group of eyes with air tamponade, whereas the MH closure rate was 90.1% in another group of eyes with SF6 tamponade (the difference did not reach statistical significance, $p = 0.132$). Similarly, Usui et al. [28] compared the effect of air tamponade and SF6 in MH with sizes up to 500 μm, being successful in 100% of cases in both groups, but using a significantly shorter positioning time in the air tamponade group. In another study, similar success rates were also reported, with a closure of 30 from a sample of 33 MHs after 3 days of positioning with air (90.9%) [29]. In our series including 57.7% of MH with sizes ≥ 400 μm, 84.6% of MH was successfully closed in the group of eyes using air tamponade and prone position, with no significant differences compared to the group of eyes using SF6 tamponade and prone position ($p = 0.316$).

The success of the MH closure when using prone positioning was very high, even regardless of the type of the tamponade used. However, many patients referred that the maintenance prone positioning was difficult or very difficult [30]. It should be considered that the MH typically develops in elderly patients that commonly have physical obstacles, such as obesity or spinal problems to maintain this position. The prone position represents a significant source of discomfort for the patient. In some patients, the prone position may be also the cause of some complications, such as ulnar nerve palsy or ulnar pressure ulcer [8]. For this reason, the need for a prone position is still currently a matter of debate. In our cohort, patients perceived the nonsupine reading position significantly better than the prone position in terms of both comfort and sleep quality. Many authors have

confirmed that a high anatomical success can be also achieved with other modes of patient positioning (nonsupine reading position). Iezzi and Kapoor [31] reported the results of MH surgery using ILM peeling (8000 μm wide), SF6 tamponade, and reading position for 3–5 days in 68 eyes showed a successful MH closure in 100% of the eyes. In another study, a MH closure was obtained in 203 of 204 eyes (99.5%) undergoing surgery with ILM peeling, SF6 tamponade, and recommendation to patients of maintaining a reading position [32]. Other authors reported nonsignificant differences in the MH closure success rate using gas tamponade between recommending to patients postoperatively the reading position or the pronation position (91.2%–97.1%) [21, 33, 34]. These authors did not observe a difference between reading and pronation position groups, even for MH larger than 400 μm. In our series, the MH was closed in all cases after the first operation in the group of eyes in which the SF6 tamponade was used and the patient nonsupine reading position was recommended.

Forsaa and Krohn [24] used a combination of reading position and air tamponade in an attempt to increase the postoperative comfort. In the group of MH $\leq$ 400 μm, a successful closure was reached in 95% of cases, whereas only a successful closure was achieved in 57% of eyes in the group of MH > 400 μm. This study only enrolled pseudophakic eyes in which a larger air filling can be achieved, with sufficient coverage of the MH and an efficient isolation from vitreous fluid. It should be considered that the air bubble occupies an average of 59% of the vitreous space on the first postoperative day, which seems to be sufficient to close MH with sizes up to 400 μm. Previously published study groups have shown that up to 96% of MH closes within the first 24 hours [29, 31, 35]. On the third postoperative day, only an average of 39% of air is present in the vitreous space [24]. MH of more than 400 μm therefore seems to require a longer isolation time from vitreous fluid to heal than smaller MH, which is in line with the observations of other authors [29, 36]. In the group of eyes of the current series using air tamponade and patient nonsupine reading position, MH closure was only achieved in 56% of eyes, being a significantly worse result than those obtained in the air + prone position group and in the SF6 gas + nonsupine reading position. However, MH closure was achieved in 88.9% of eyes with MH with sizes up to 400 μm, which is worse outcome than that obtained by Forsa and Krohn [37]. Two main factors may have accounted for this: the inclusion of phakic eyes in our sample and a better postoperative cooperation of patients in the study of Forsa and Krohn [37] in which the tennis ball technique was used to eliminate the supine position.

Finally, it should be acknowledged that air tamponade is also safer than gas due to the possible elevation of IOP in the postoperative period. After PPV with gas tamponade, up to 35.6% of patients may have IOP above 30 mm Hg [38]. In a previous study of our research group, 28.5% of patients with detached retina and treated with PPV and gas tamponade had IOP $\geq$ 25 mmHg on the first postoperative day group of patients [39]. In contrast, eyes with air tamponade have shown the lowest risk of IOP elevation (cumulative risk of 11.5% for IOP elevation $\geq$ 30 mmHg after 48 hours) [40]. In our series, the mean values of IOP on the first postoperative day in the groups using air tamponade were 12.5 and 14.9 mmHg, whereas mean values of 18.6 and 17.9 mm Hg were found in the group of eyes using SF6 tamponade, being the differences statistically significant. According to this, the use of air tamponade should be especially considered in patients with preexisting glaucoma.

In conclusion, PPV with ILM peeling, intraocular tamponade, and positioning remains the basic surgical approach in the treatment of IMH. The type of tamponade and positioning should be chosen based on the size of the macular hole, the condition of the crystalline lens, and the overall condition of the patient. For MH $\leq$ 400 μm, their closure can be achieved with high success by combining an air tamponade with a patient's nonsupine reading position, especially in pseudophakic eyes. For MH > 400 μm, the greatest anatomical success can be achieved using SF6 gas tamponade in combination with the nonsupine reading position. Patients tolerated the nonsupine reading position better than the prone position. The duration of the SF6 tamponade versus the shorter air tamponade does not seem to be perceived as a benefit by patients.

Data Availability

The data used to support the findings of this study are available upon request to the first author.

Disclosure

The authors do not have proprietary or commercial interest in the medical devices that are involved in this manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Multiple Therapy Approach for Stage 3 Coats Disease: Long-Term Follow-Up

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Purpose. To assess long-term efficacy of a multiple therapy approach in the treatment and management of unilateral stage 3 Coats disease with exudative retinal detachment. *Methods*. 2 eyes of 2 young patients suffering from unilateral stage 3 Coats disease underwent a multiple therapy approach consisting of surgical drainage of exudative subretinal fluid + one simultaneous and up to one subsequent intravitreal injection of bevacizumab + multiple (up to 3) laser photocoagulation sessions of retinal nonperfusion areas and leaking Coats vasculature. *Results*. Complete reabsorption of SRF and retinal reattachment were observed in both cases over the follow-up. In no cases, we observed progression to phthisis bulbi. No bevacizumab-related complications were observed. Epiretinal membrane onset was detected in one eye at the end of follow-up. *Conclusion*. The management and treatment of this rare and degenerative disease in young subjects are still a challenge. The described technique is less invasive than conventional intraocular surgery and may be preferable to halt the devastating progression of the disease.

1. Introduction

Coats disease remains a progressive and devastating retinal vascular disorder with an estimated population incidence in the United Kingdom of 0.09 per 100,000 people, mainly in young males aged from 8 to 16 years, although adult-onset has been rarely reported [1, 2].

In 2001, Shields et al. proposed a detailed classification for this rare disease based on clinical features: stage 1 (retinal telangiectasia only), stage 2A (telangiectasia and extrafoveal exudation), stage 2B (telangiectasia and foveal exudation), stage 3A1 (subtotal extrafoveal exudative retinal detachment), stage 3A2 (subtotal exudative retinal detachment involving the fovea), stage 3B (total exudative retinal detachment), stage 4 (total exudative retinal detachment with secondary glaucoma), or stage 5 (end-stage disease, phthisis bulbi) [3].

Unfortunately, the exact pathogenesis of Coats disease is unknown, and its diagnosis is often delayed due to its great variability in appearance. Several treatment options based on stages have been proposed: for stages 1 and 5, observation; for stage 2, retinal laser photocoagulation as a first-line; and for stages 3 and 4, many options described starting from sclerotomy and drainage of subretinal fluid, buckling or encirclement, vitrectomy with gas or silicone oil tamponade [4].

A new treatment approach for stage 3 Coats disease was described by Stanga et al. [5], combining three different procedures such as transscleral drainage of SRF, intravitreal anti-VEGF injection, and retinal nonperfusion area laser photocoagulation. They reported their successful experience in 8 eyes of children with a variable follow-up from 9 to 60 months.

The aim of our case series was to assess long-term efficacy of a multiple therapy approach in the treatment and management of unilateral stage 3 childhood-onset Coats disease with exudative retinal detachment.

2. Methods

2.1. Study Participants. In this retrospective interventional case series, 2 eyes of 2 children suffering from unilateral stage 3 Coats disease received a successful multiple therapy approach as described below.

The affected eyes were classified according to Shields' classification as stage 3B (Case 1: total exudative retinal detachment) and stage 3A1 (Case 2: subtotal extrafoveal exudative retinal detachment, not involving the fovea).

Inclusion criteria were as follows: (i) children with a diagnosis of unilateral Coats (stage 3, according to Shields' classification) and (ii) no history of previous ocular surgery or other treatments including laser or cryotherapy.

Exclusion criteria were as follows: (i) evidence or history of other ocular conditions; (ii) evidence or history of systemic disorders; and (iii) other stages of Coats disease.

For both cases, a complete ophthalmological evaluation, best-corrected visual acuity (BCVA) assessment, and OCT were performed before surgical procedure and at all follow-up visits.

2.2. Surgical Procedure. In one case (Case 1), a triple therapy approach was performed as previously described by Stanga et al [5]: under general anesthesia, exudative subretinal fluid was drained transclerally by a 27-gauge needle mounted on a 5 ml syringe with the plunger removed. In order to avoid retinal damage, the needle was inserted perpendicularly to the sclera in the area having the higher amount of fluid (previously identified with binocular indirect ophthalmoscopy). An anterior chamber maintainer was used to keep an adequate eye pressure during the drainage. Thereafter, an intravitreal injection of bevacizumab and laser photocoagulation of retinal nonperfusion areas and leaking Coats vasculature were performed. Another bevacizumab injection and 2 more sessions of laser photocoagulation were performed during the follow-up.

In the other case (Case 2), no drainage procedure was performed because of the exudative retinal elevation appeared to be a retinoschisis as described below in detail. Both patients received injection of 1.25 mg intravitreal Avastin® (30 G needle) combined with binocular indirect argon laser photocoagulation of microaneurysms, telangiectatic vascular changes, and areas of nonperfusion. Imaging wide-field fundus fluorescein angiography treatment guidance Optos® was used in the two eyes. No intraoperative complications were observed.

3. Results

A total of 2 eyes of 2 children aged between 16 and 17 and affected by unilateral stage 3 Coats disease were considered in the study. Case 1 required only 1 episode of drainage of SRF. The second case (Case 2) with significant elevation of the retina did not require drainage since the exudative retinal elevation appeared to be a retinoschisis rather than a full-thickness exudative retinal detachment. This became apparent during laser treatment when laser burns applied to the bed of the elevated retina showed "whitening of the outer leaf," indicating a thin layer of the retina was still in contact with the RPE and was, therefore, a schisis (Figure 1).

Demographic and clinical features of the two patients enrolled are reported in Table 1.

Family history was negative in both cases.

Reabsorption of SRF and total retina reattachment were observed in all two cases during the follow-up (Table 1 and Figure 1).

In Case 1, BCVA remained stable (light perception) after surgery and for whole follow-up without recurrence of SRF and retinal detachment (Table 1). In Case 2, a significant improvement in terms of BCVA was assessed (from 0.10 LogMAR to 0.0 LogMAR), even though an initial epiretinal membrane onset was found at the end of follow-up.

No bevacizumab-related complications were observed. No further disease progression was observed in all cases.

4. Discussion

Coats disease is a sporadic, nonhereditary retinal vascular disorder mainly affecting young males. Adulthood-onset disease is very rare and has been described as less aggressive with a slow development and a more favorable treatment outcome [2].

A definitive gold standard treatment for Coats disease has not been established yet [3].

Indeed, the management and treatment of such a rare and degenerative disease in young subjects are still a challenge. Ideally, the least invasive approach would be preferable to halt the devastating progression of the disease. The choice of follow-up and treatment depends on disease staging [6]. In spite of treatment, many advanced Coats disease-related complications have been reported in previous studies, such as rubeosis iridis, neovascular glaucoma, phthisis bulbi, and ocular pain leading to enucleation [7].

The external SRF drainage has previously been described to successfully prevent neovascular glaucoma onset [8].

Intravitreal anti-VEGF injections have showed a temporary efficacy in the reduction of capillary leakage and the consequent exudation that eventually leads to exudative retinal detachment [9–11]. Retinal laser photocoagulation has been reported to be effective in ablating the abnormal peripheral retinal vasculature that characterizes this pathology [12].

Other more invasive surgical procedures have been performed such as pars plana vitrectomy with silicone oil or gas tamponade or scleral buckling in order to solve the exudative retinal detachment and to halt progression of advanced-stage Coats disease [13].

In 2016, Stanga et al. [5] were the first to propose a new treatment multiple approach for stage 3 Coats disease combining three different procedures: transscleral drainage of SRF, intravitreal anti-VEGF injections, and laser photocoagulation of the nonperfused area of the retina.

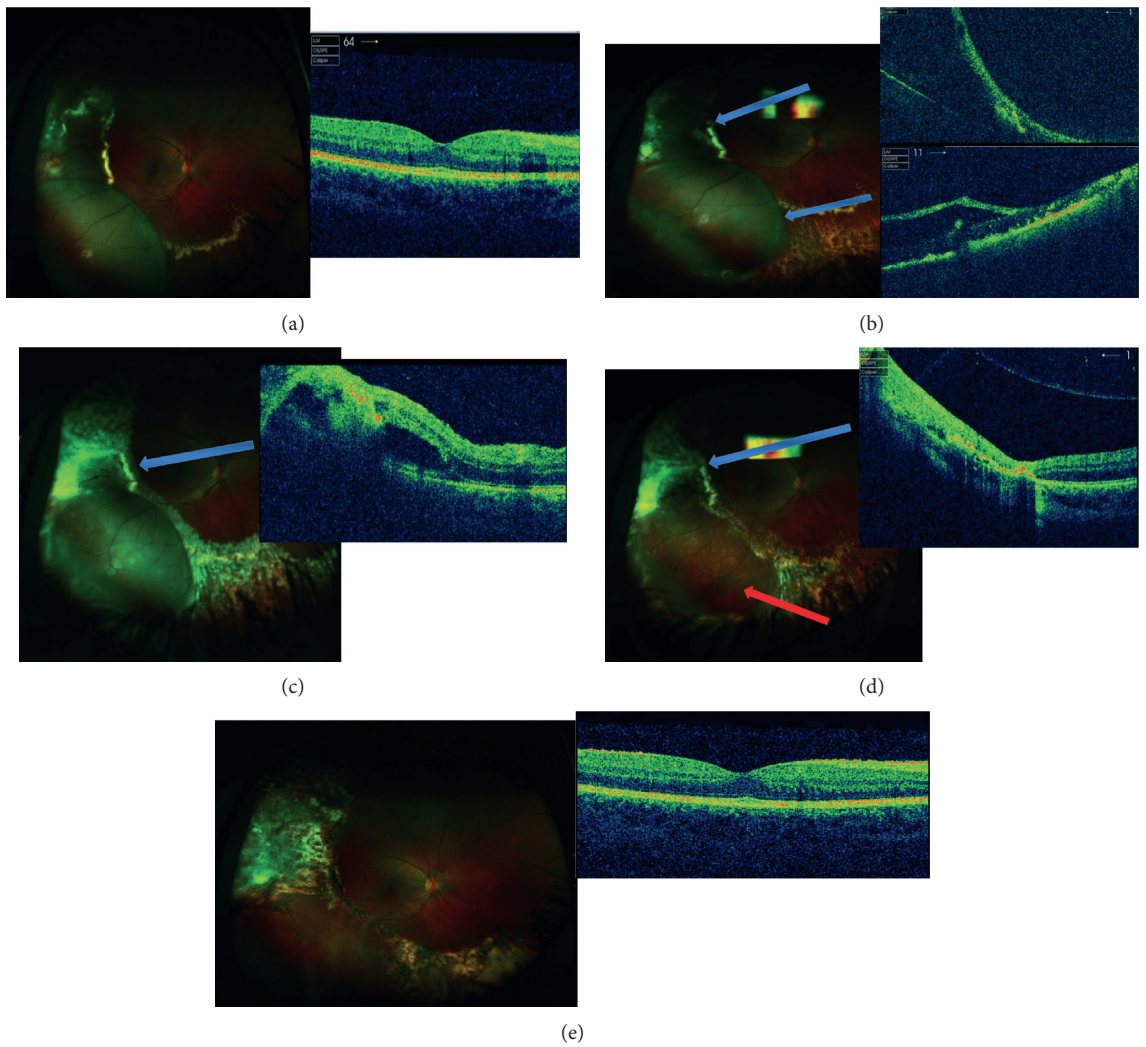

Figure 1: Case presentation of a 16-year-old patient treated with multiple therapy approach for Coats disease. (a) At presentation, the patient had a stage 3A Coats disease with the macula spared from exudation (VA 0.10 LogMAR). (b) 1 month after surgical treatment: note the laser scars and the persistence of SRF temporally, whereas the inferotemporal area appears at the OCT as a retinoschisis (arrows). The patient underwent a second treatment. (c) 1 week after the second session of laser. *Note.* The fresh scarring tissue and the gradual reabsorption of SRF at the OCT (arrow). The patient received a third treatment. (d) 1 month after the last treatment. *Note.* The total reabsorption of SRF (blue arrow). The red arrow shows the presence of laser scars, which confirms the diagnosis of retinoschisis. (e) 8 months after the first treatment. The SRF is completely reabsorbed and the clinical picture is stable. *Note.* The development of a mild and asymptomatic ERM at the OCT (VA 0.0 LogMAR).

Table 1: Demographic and clinical features of the patients enrolled.

Case	Eye	Age	Stage B	SRF drainage	No. of bevacizumab injections	No. of laser sessions	F up	Preop VA	Postop VA	Complications
1	RE	17	3	Y	2	3	35	LP	LP	None
2	RE	16	3	N	3	3	22	0.10	0.0	ERM

Preop: preoperative; postop: postoperative; VA: visual acuity (expressed in LogMAR scale); F up: follow-up; SRF: subretinal fluid; Y: yes; N: no; LP: light perception; RE: right eye; ERM: epiretinal membrane.

Similarly, our work reported anatomical and functional outcomes of 2 eyes with a diagnosis of unilateral stage 3 Coats disease: one case was treated with the triple approach consisting of external SRF drainage, consecutive bevacizumab intravitreal injections, and multiple wide-field image-guided photocoagulation laser sessions and the other case was treated with laser + anti-VEGF treatments alone because of the schisis.

In the case with total exudative retinal detachment (Case 1), the SRF drainage procedure was essential to allow

apposition of the retina against the RPE in order to allow uptake of the laser by the detached retina. When the SRF is sufficiently drained, scleral indentation during the indirect argon laser treatment allows more complete laser photocoagulation of the ischemic areas and telangiectatic vessels. Care must be taken during lasering to not allow too much heat to accumulate in one spot; otherwise, the resulting "pop" could potentially inadvertently convert the exudative detachment into a rhegmatogenous detachment. The intravitreal anti-VEGF injection is designed to halt the ongoing leakage from retinal vessels while the laser takes effect over the subsequent weeks. Further laser treatment is usually carried out after the first session as the anti-VEGF will temporarily dry the subretinal space, further allowing better uptake of a laser at the second session. If sufficient photocoagulation of the leaking areas has occurred, this prevents recurrence of leakage and subretinal fluid accumulation when the anti-VEGF injection wears off. The indirect laser technique may need to be modified with the application of longer duration burns in order to achieve uptake and complete coagulation of the abnormal vasculature. As mentioned above, care must be taken to avoid too much laser energy being concentrated at one spot. Our results showed an excellent anatomical outcome with a total reabsorption of SRF and a complete retinal reattachment without relapses during long-term follow-up. Of note, a second case (Case 2) showed an excellent BCVA (0.0 LogMAR), which was maintained over the follow-up. This is probably related to the staging (3A) differently from the other case enrolled who was classified as more advanced (3B). Interestingly, this second case had an exudative retinoschisis rather than a full-thickness retinal detachment and developed an ERM during the follow-up as ate complication, possibly due to the multiple sessions of laser treatment and/or breakdown in the blood-retinal barrier secondary to the primary pathology. Despite the ERM, we observed an excellent BCVA restoration presumably because it was early without a significant traction. This positive visual outcome was quite unexpected but very welcoming when considering the usual visual outcomes of patients affected by advanced Coats.

As reported by Shields in their classification of 2001, 74% of patients with stage 3 Coats have a poor visual outcome of 20/200 or worse. Moreover, they state that visual acuity goes parallel with staging of patients [1].

Shields et al. thoroughly described possible predictors of enucleation that represent often the final step of Coats management failure, considering age category and degree of subretinal fluid [1]. A younger age is strongly associated with a worse disease presentation and final functional outcome [1].

In our two cases, similarly to Stanga et al., a multiple therapy approach including at least 2 consecutive intravitreal injections of anti-VEGF was performed. The role of VEGF in the pathogenetic mechanisms of Coats disease, particularly in vascular abnormalities and capillary exudation, is already known. The two main factors that have a key role in Coats pathogenesis are retinal vessel endothelial changes responsible for the breakdown of blood-retinal barrier and the presence of abnormal pericytes causing telangiectatic vessels, with the typical appearance of "light bulb telangiectasias," due to the terminal shape of peripheral vasculature and yellow exudation [2].

Nevertheless, much caution should be taken when using anti-VEGF due to the possible risk of fibrosis and consequent tractional retinal detachment [5].

In their retrospective case note review, Stanga et al. [5] reported that this new therapeutic and less invasive multiple approach was safe and long-term effective in 8 eyes of children, avoiding the need for vitrectomy. Unfortunately, 3 of them developed cataract as a late complication. We did not observe any complication, apart from 1 case of early epiretinal membrane that is not yet significantly affecting the visual outcome. A strict follow-up is necessary to evaluate ERM development. Our work has some limitations such as the small case series of children considered, the relatively short follow-up, and the lack of a genetic workup, even if Coats disease is sporadic and nonhereditary in its strict definition.

Obviously, further cases and a wider follow-up are required to make these data consistent. It should be remembered that many patients with Coats disease are often undiagnosed until advanced stages. A prompt diagnosis, an accurate management, and treatment of such a rare disease affecting very young subjects are still challenging.

Other retinal pathologies can simulate an "exudative retinopathy" including branch retinal occlusion, ocular toxoplasmosis, familiar exudative retinopathy, retinal capillary hemangiomatosis, etc., confounding the final diagnosis [3].

A less invasive approach and a more conservative staged treatment regime, particularly in childhood-onset Coats, may be preferable to halt the devastating progression of the disease, aiming to minimize the possible recurrence of exudation and subretinal fluid formation.

In conclusion, our case series have shown promising results in controlling and stabilizing this blinding condition, confirming the previous findings presented by Stanga et al. in terms of safety and long-term efficacy of SRF drainage, followed by anti-VEGF intravitreal injections and laser photocoagulation in stage 3 Coats disease and without SRF drainage in stage 3 Coats associated with schisis.

Data Availability

The data are available upon request from the corresponding author.

Additional Points

Summary. A multiple therapy approach in unilateral stage 3 Coats disease is less invasive and very effective in long-term follow-up.

Conflicts of Interest

All authors declare that they do not have conflicts of interest.

Authors' Contributions

Rodolfo Mastropasqua and Rossella D'Aloisio contributed equally to this work and should be considered as co-first authors.

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Research Article

Limited Vitrectomy versus Complete Vitrectomy for Epiretinal Membranes: A Comparative Multicenter Trial

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Purpose. To evaluate whether limited vitrectomy is as effective as complete vitrectomy in eyes with epiretinal membrane (ERM) and to compare the surgical times and rates of complications. *Methods*. In this multicentre European study, data of eyes with ERM that underwent vitrectomy from January 2017 to July 2018 were analyzed retrospectively. In the limited vitrectomy group, a posterior vitreous detachment (PVD) was induced up till the equator as opposed to complete PVD induction till the vitreous base in the comparison group. Incidence of iatrogenic retinal breaks, retinal detachment, surgical time, and visual outcomes were compared between groups. *Results*. We included 139 eyes in the analysis with a mean age being 72.2 ± 6.9 years. In this, sixty-five eyes (47%) underwent limited vitrectomy and 74 eyes (53%) underwent complete vitrectomy. Iatrogenic retinal tears were seen in both groups (5% in limited vitrectomy versus 7% in complete vitrectomy, $p = 0.49$). Retinal detachment occurred in 2 eyes in the limited vitrectomy group (3%) compared to none in the complete vitrectomy group ($p = 0.22$). Best-corrected visual acuity (BCVA) and central macular thickness improved significantly with no intergroup differences ($p = 0.18$). Surgical time was significantly shorter in the limited vitrectomy group with 91% surgeries taking less than 1 hour compared to 71% in the complete vitrectomy group ($p < 0.001$). *Conclusion*. A limited vitrectomy is a time-efficient and effective surgical procedure for removal of epiretinal membrane with no additional complications.

1. Introduction

The role of the posterior vitreous face has been established in the pathogenesis of many macular diseases such as macular hole, epiretinal membranes (ERM), and vitreomacular traction disorders [1, 2]. During surgical management of macular diseases, it is imperative to remove the posterior hyaloid face to gain access to the ERM and internal limiting membrane. Removal of the hyaloid also ensures relief from the anteroposterior tractional forces postulated to be causative in many of these diseases. Though the role of the postequatorial face of the posterior hyaloid is well established, the role of the peripheral hyaloid and vitreous cortex, including the firmly adherent vitreous base, is not fully understood in cases with macular pathologies.

Traditional vitreoretinal surgical teaching emphasizes that the entire vitreous must be removed while attempting any form of vitreoretinal surgery [3]. Though this may be true in cases of rhegmatogenous retinal detachment and other pathologies where the peripheral vitreous cortex is

causative, this may not be true for eyes with predominantly macular pathologies. Performing a complete vitrectomy with base dissection can be time-consuming, requires panoramic wide-angled systems for proper visualization, is dependent on a skilled assistant for bringing the extreme peripheral cortex and ora serrata into view, and is associated with increased risk of lens touch and subsequent cataract formation in phakic eyes, especially in lesser-skilled surgeons and those with relatively lesser experience in these maneuvers. Since the peripheral vitreous cortex and vitreous base are challenging to excise thoroughly and are unlikely to be associated with most macular pathologies, it may be prudent not to attempt base excision and perform a limited vitrectomy alone in these cases [4].

However, leaving the preequatorial residual vitreous skirt may increase the risk of retinal tears and may predispose to a retinal detachment in these vitrectomised eyes. Bonfiglio et al. [5] have suggested limited vitrectomy for phakic eyes in cases with rhegmatogenous retinal detachment (RRD) without macular pathology with excellent results. Though minimal vitrectomy up to the equator was proposed almost a decade back by Boscia et al. [6], there have been no follow-up studies to establish the safety of this technique. We performed this multicentre study to primarily compare the efficacy of limited vitrectomy versus complete vitrectomy with base excision in eyes with ERM. The surgical time required and complication rates were secondary outcomes considered for analysis.

2. Methods

This retrospective study was carried out as per the tenets of the declaration of Helsinki. All patients had been well informed regarding the surgical procedure. Written informed consent was obtained from all patients. Data was obtained from the Institute of Ophthalmology, University of Modena and Reggio Emilia, Modena, Italy, Department of Ophthalmology, "S. Maria delle Croci" Hospital, Ravenna, Italy, and Department of Ophthalmology, University of Bari, Italy. The patient's identity was kept anonymous during data analysis and manuscript preparation. The study was carried out between January 2017 and July 2018. All patients with idiopathic ERMs who underwent standard 3-port pars plana vitrectomy (PPV) with or without combined phacoemulsification and intraocular lens implantation and having a minimum of 6-month follow-up were included in the data analysis. Eyes with other coexistent ocular pathologies such as corneal opacities, uveitis, and ERMs occurring secondary to other retinal pathologies such as trauma, previous retinal detachment, and retinal vascular disorders were excluded. Diabetics with any sign of retinopathy or maculopathy were excluded from the study.

All files of eligible patients were drawn from the electronic medical records from all the four participating centers using the ICD-9 coding system. The operating room registers were also used to identify eligible patients so that all consecutive patients operated for ERM during the study period were identified. Patient demographics, history of previous laser procedure, coexistent ocular pathology, baseline visual acuity, intraocular pressure, peripheral retinal degenerations, high-definition optical coherence tomography (HD-OCT) (Carl Zeiss Meditec, Inc., Dublin, CA)-based central macular thickness, presence of macular pucker, and the lens status were recorded from the case files. BCVA was measured by early treatment diabetic retinopathy study (ETDRS) charts and then converted into a logarithm of the minimum angle of resolution (logMAR) for statistical analysis.

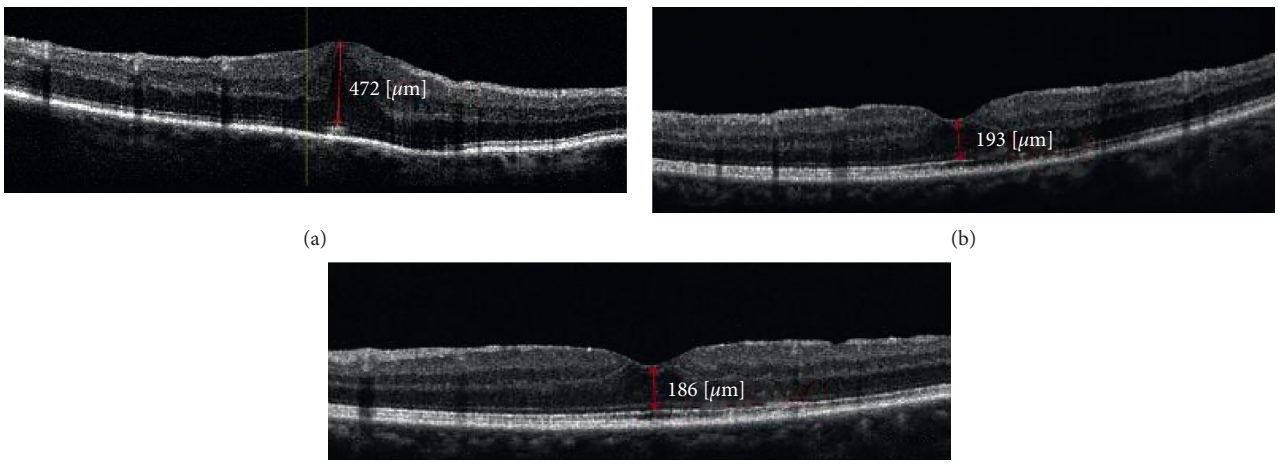
Intraoperative parameters such as the gauge of instrumentation used, limited versus complete vitrectomy, peeling of ERM alone or combined with internal limiting membrane peeling (ILM), the stain used to delineate the ERM and ILM, and tamponade used at the end of surgery were noted. Intraoperative complications, especially the occurrence of peripheral retinal tears and the need for any laser photocoagulation, were also noted. The duration of surgery was recorded in 5 categories as 30–45 minutes, 46–60 minutes, 61–90 minutes, 91–120 minutes, and > 120 minutes. Data from follow-up visits at 1 week, 6 months, and the last follow-up was noted. It included BCVA, central macular thickness, and any complications, especially retinal detachment (Figures 1 and 2).

3. Surgical Procedure

The standard three-port pars plana vitrectomy (PPV) was carried out under local anesthesia. In eyes with coexistent cataract routine phacoemulsification via a clear corneal temporal incision with an intraocular lens (IOL), implantation was done. In eyes that underwent limited vitrectomy alone, after creating 3 standard ports at the pars plana, a PVD was induced up till the equator and the limited vitrectomy was completed without disturbing the peripheral cortical vitreous and vitreous base (Figure 3). In a complete vitrectomy, the PVD was propagated till the vitreous base and the entire vitreous body, including the peripheral cortex and base, was removed to the extent possible (Figure 4). In phakic eyes, under scleral indentation, the entire peripheral vitreous was visualized and removed. After vitrectomy, the ERM was stained with the preferred dye and peeled using microforceps. The ILM was then stained with a brilliant blue or dual dye and peeled around the center of the fovea for approximately 2 disc diameters (Figure 5). Ports were removed after using tamponade. The eye was filled with either saline or another tamponade as per the surgeons' choice. The gauge of vitrectomy, limited versus complete vitrectomy, type of stain used, and the type of tamponade were at the surgeon's discretion.

4. Statistical Analysis

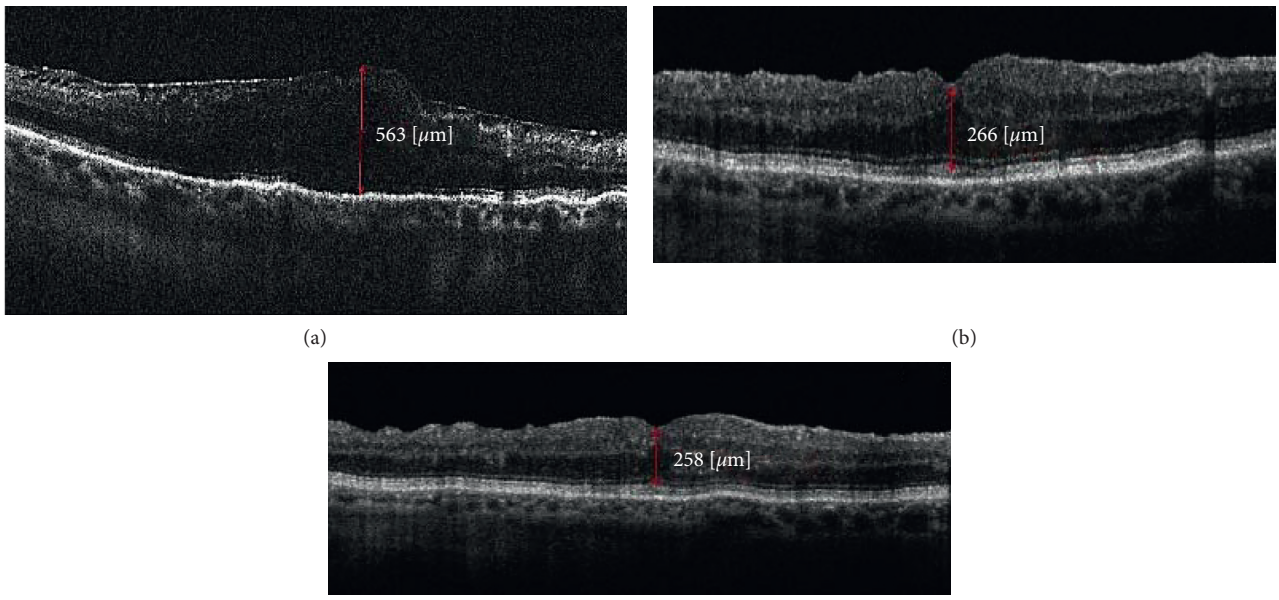
All continuous variables were expressed as mean with standard deviation or median with interquartile range and group differences were analyzed using the Student *t*-test or Wilcoxon's rank-sum test for variables with the nonparametric distribution. Categorical variables were expressed as proportions (*n*%) and group differences were analyzed using the chi-square or Fisher's exact test. All data were entered in



(a) (b)

(c)

Figure 1: OCT scan of patient with limited vitrectomy with ERM removal. ((a)) Preoperative scan showing ERM with CMT of 472 μ with BCVA measuring 0.5 logMAR. ((b)) A one-month postoperative scan showing reduced CMT of 193 μ with BCVA improving to 0.8. ((c)) Yearly follow-up scan showing CMT 186 μ with normal foveal contour and vision improving to 0.9 logMAR.



(a) (b)

(c)

Figure 2: OCT scan of the patient with complete vitrectomy with ERM removal. ((a)) Preoperative scan showing ERM with loss of foveal contour, CMT measuring 563 μ, and BCVA measuring 0.5 logMAR. ((b)) The one-month postoperative scan showing a reduction in CMT to 266 μ with BCVA measuring 0.8. ((c)) After a year, CMT was 258 μ and BCVA improved to 0.9 logMAR.

Microsoft Excel and analyzed using STATA 12.1 I/c (Fort Worth, Texas, USA), and p value of less than 0.05 was considered statistically significant.

5. Results

One hundred and thirty-nine eyes of 139 patients were included in the analysis. The mean age was 72.2 ± 6.9 years. Of these, 52% (73) were men and 66 were females. Diabetes was seen in 38 (27%) subjects and 63 (45%) were hypertensive on systemic medications. Sixty-five eyes (47%) underwent limited vitrectomy prior to ERM removal, whereas 74 eyes (53%) underwent complete vitrectomy with peripheral base excision to the extent possible. A comparison of baseline characteristics between these groups is shown in Table 1. Patients undergoing limited vitrectomy were marginally younger and more eyes in this group were phakic compared to those in the complete vitrectomy group. All other preoperative parameters including BCVA and central macular thickness were comparable between groups.

A comparison of the intraoperative characteristics between groups is shown in Table 2. About two-thirds of surgeries were performed using 25G instrumentation in the limited vitrectomy group compared to a significantly higher

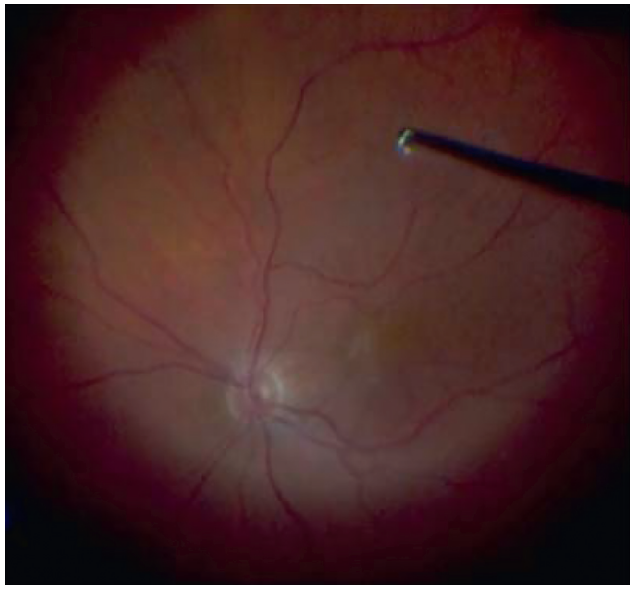


Figure 3: Limited vitrectomy: posterior vitreous detachment induction with "core vitrectomy."

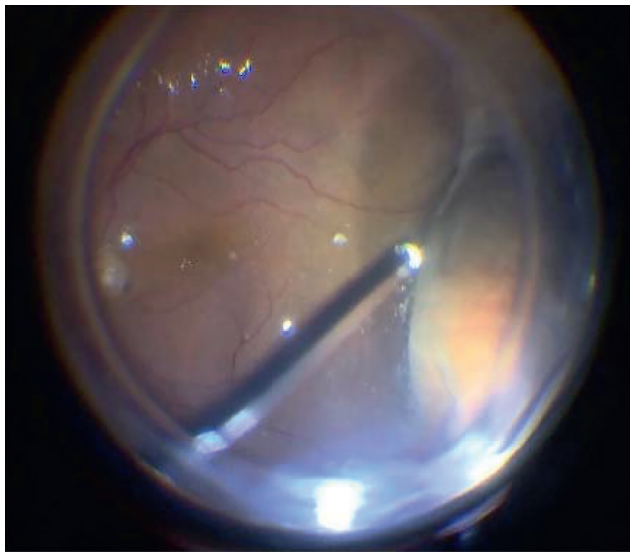


Figure 4: Complete vitrectomy: peripheral vitreous removal with vitreous base shaving using dynamic preequatorial scleral indentation.

proportion of 23G in the complete vitrectomy group. A combination of ERM and ILM was peeled in significantly more eyes in the complete vitrectomy group. Similarly, a dual dye staining technique was used more often in the complete vitrectomy group while brilliant blue dye with negative ERM staining was more often used in the limited vitrectomy group. The air was the commonest tamponade used in the complete vitrectomy group compared to significantly greater use of nonexpansile gases and saline in the limited vitrectomy group. Iatrogenic peripheral retinal tears occurred in 8 eyes overall (6%) with no intergroup differences and all tears received prophylactic barrage laser intraoperatively. The surgical time was significantly reduced

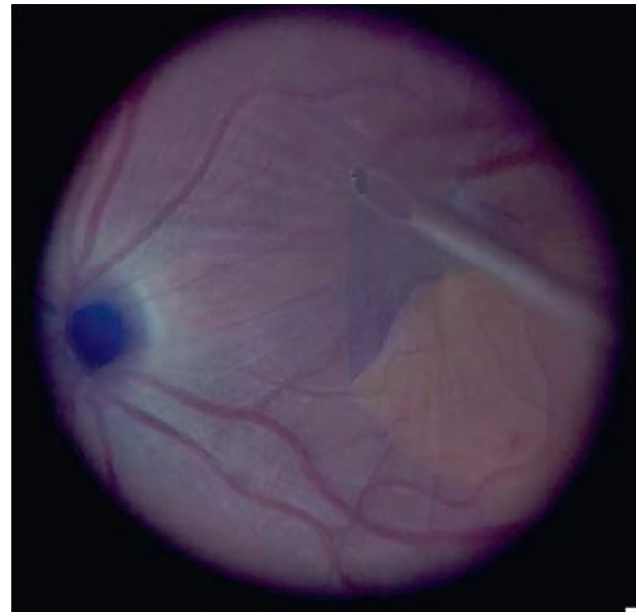


Figure 5: Internal limiting membrane peeling after brilliant blue staining after ERM removal.

in the limited vitrectomy group with more than 90% of the surgeries completed in less than 1 hour compared to only 70% in the complete vitrectomy group.

After adjusting for possible confounders influencing the duration of surgery such as the operating surgeon, gauge of PPV used, lens status, and PVD status, we found that performing phacoemulsification along with PPV required 3.4 minutes more (95% confidence interval = 1.8 to 6.9 minutes) compared to PPV alone ($p = 0.04$). Table 3 shows a comparison of surgical time in both groups.

A comparison of outcomes and complications between the groups is shown in Table 4. The mean follow-up was 14.3 ± 2.3 months. At a 1-week follow-up, BCVA had improved to 0.5 ± 0.2 logMAR in the limited vitrectomy group and 0.43 ± 0.2 logMAR in the complete vitrectomy group ($p = 0.21$). BCVA improved further in both groups compared to preoperative vision and there was no difference in vision between groups at 6 months. The central macular thickness was marginally lower in the limited vitrectomy group but this difference did not reach statistical significance. Retinal detachment was seen in two eyes (3%) in the limited vitrectomy group and in none of the eyes in the complete vitrectomy group. None of the retinal detachments occurred in eyes that had experienced iatrogenic retinal tears during surgery. One detachment occurred 10 months after surgery and the other occurred 2 months after surgery. Both underwent successful retinal reattachment surgery with silicone oil tamponade. Self-limiting cystoid macular edema was the commonest complication seen in fewer than 10% of the patients in both groups.

6. Discussion

In this multicentric retrospective European study, we found that performing a limited vitrectomy along with ERM peeling yielded equivalent results compared to a complete

Table 1: Baseline demographic and clinical characteristics of eyes in limited versus complete vitrectomy group.

Variable	Limited vitrectomy ($n = 65$)	Complete vitrectomy ($n = 74$)	p value
Age (years)	71.03 ± 5.6	73.2 ± 7.8	0.06
Gender (% men)	35 (54%)	38 (51%)	0.77
Eye (% right eye)	38 (58%)	43 (58%)	0.96
BCVA (logMAR)	0.6 ± 0.1	0.5 ± 0.2	0.13
Central macular thickness (μ)	428 ± 93	454 ± 100	0.14
Previous h/o retinal laser	9 (14%)	8 (11%)	0.22
Lens status: clear lens	7 (11%)	6 (8%)	
Cataractous lens	41 (63%)	29 (39%)	0.01
Pseudophakia	17 (26%)	39 (53%)	
Coexistent glaucoma (%)	3 (5%)	6 (8%)	0.40
Coexistent retinal pathology (%)			
Peripheral degenerations	3 (5%)	0	
Diabetic retinopathy	2 (3%)	1 (1.3%)	0.34
High myopia	0	2 (2.7%)	
Polypoidal choroidal vasculopathy (PCV)	1 (1.3%)	0	

Table 2: Comparison of intraoperative characteristics in limited versus complete vitrectomy group.

Variable	Limited vitrectomy ($n = 65$)	Complete vitrectomy ($n = 74$)	p value
Gauge used			
23G	19 (29%)	29 (40%)	<0.001
25G	43 (66%)	32 (43%)	
27G	3 (5%)	13 (17%)	
Peeling			
ERM only	17 (26%)	2 (3%)	<0.001
ERM + ILM peeling	48 (74%)	72 (97%)	
Stain used			
Dual staining	9 (14%)	61 (82%)	
Brilliant blue dye	39 (60%)	3 (4%)	<0.001
Triamcinolone	11 (17%)	9 (12%)	
Others	6 (9%)	1 (1%)	
Phacoemulsification combined	39 (60%)	44 (59%)	0.95
Peripheral retinal breaks	3 (5%)	5 (7%)	0.49
Tamponade used			
Gas	9 (14%)	5 (7%)	<0.001
Air	43 (66%)	68 (92%)	
Saline	13 (20%)	1 (1%)	

Table 3: Comparison of duration of surgery of ERM + ILM peeling groups in limited versus complete vitrectomy groups.

Duration of surgery (mins)	Limited vitrectomy	Complete vitrectomy	Total	p value
30–45 min	2 (3.5%)	15 (20%)	17 (12%)	
46–60 min	58 (89%)	37 (50%)	95 (68%)	
61–90 min	3 (4%)	17 (23%)	20 (15%)	<0.0001
91–120 min	2 (3.5%)	4 (5.5%)	6 (4.3%)	
>120 min	0 (0%)	1 (1.5%)	1 (0.7%)	
Total	65 (100%)	74 (100%)	139 (100%)	

Table 4: Complications and outcomes of limited versus complete vitrectomy at the end of a 6-month follow-up.

Variable	Limited vitrectomy ($n = 65$)	Complete vitrectomy ($n = 74$)	p value
BCVA (logMAR)	0.3 ± 0.2	0.22 ± 0.2	0.18
Central macular thickness (μ)	286 ± 87	358 ± 75	0.09
Complications			
Retinal detachment	2 (3%)	0	0.22
Cystoid macular edema	5 (8%)	8 (11%)	0.45
Macular hole	1 (1.5%)	0	

vitrectomy with base excision. Though both groups experienced the same number of iatrogenic retinal tears during surgery, there are chances of retinal detachment occurring in the limited vitrectomy group; however, the incidence was not statistically significant compared to the complete vitrectomy group. Limited vitrectomy was significantly faster with the majority of surgeries being completed in less than one hour.

Boscia et al. [6], in a noncomparative design, suggested limited vitrectomy for ERM and vitreomacular traction syndrome. They performed the same in 176 eyes using 25G vitrectomy systems. At a mean follow-up of 15 months, they found excellent visual and anatomical results and retinal detachment seen only in 2 eyes (1%). Similarly, Ozkaya et [4] performed limited vitrectomy with membrane peeling for ERM and IMH (idiopathic macular hole) in fifty-two eyes. They found a transient rise of intraocular pressure (IOP) in 3 (5.9%), endophthalmitis in 1 (2.0%), and retinal detachment in 1 patient (2.0%) during the follow-up.

In our comparative study, we found similar results in the cohort of eyes that underwent limited vitrectomy alone. Likewise, we also noticed retinal detachment in 2 eyes only. Spaide [7] has suggested a minimal vitrectomy by dissecting the connection between the vitreous and the retina. This was done under OCT guidance with a newly designed microspatula knife. The posterior vitreous was not stripped from the retinal surface. Limited vitrectomy over the hole was performed to create a space for a gas bubble. They reported successful results from 3 patients, without any significant complications. In another study, Kim et al. [8] performed posterior hyaloid separation slightly beyond the temporal vascular arcade in 59 eyes with macular disorders and compared it with 57 eyes that underwent complete vitrectomy. The incidence of iatrogenic peripheral retinal breaks was significantly lower in eyes with the partial vitrectomy (3.4%), compared to complete vitrectomy (16%). In our study, we observed peripheral breaks in 5% and 7% eyes undergoing limited and complete vitrectomy, respectively.

The main concern with performing a limited vitrectomy for macular pathologies is the possibility of condensation and contraction of the residual peripheral vitreous cortex. This may further lead to an increased risk of retinal tears with subsequent retinal detachment. The incidence of retinal detachment varies from 1 to 18% in previously reported studies [9–12]. In a large multicentric study from France, involving 474 eyes with macular pathologies, Matoni et al. [9] reported that iatrogenic retinal breaks were seen in 1.7% cases and an additional 2.7% experienced retinal detachment. In another large study on more than 1600 eyes using an ultrahigh-speed 25G cutter, Mura et al. [10] reported that the risk of iatrogenic breaks (1.8%, $n = 25$) is higher when a PVD is induced intraoperatively. Tarakcioglu et al. [13] postulated that induction and extension of PVD or performing peripheral vitreous shaving could be a cause of iatrogenic peripheral retinal tears. Another mechanism could be sclerotomy-associated breaks. Rahman et al. [12] reported a much higher incidence of iatrogenic retinal breaks (18%) in eyes with macular pathologies and attributed this to more adherent posterior hyaloid. Hence, it may be prudent to not induce a PVD beyond the equator while performing vitrectomy for macular pathologies. Thus, the vital step before concluding the surgery is to do a detailed examination of the periphery with indentation and prompt laser treatment whenever needed.

We found that performing a limited vitrectomy along with peeling the ERM and ILM was significantly faster than performing a complete vitrectomy in most instances. Reducing surgical time may improve surgical performance, especially in a high volume surgical setup. Additionally, the patient's subjective experience may also be better with a shorter surgical time. We did not find any other significant differences between eyes that underwent limited versus complete vitrectomy in terms of BCVA, macular thickness, or other postoperative complications such as cystoid macular edema.

The merits of this study are its multicentric nature and the presence of a comparison group. The drawbacks are the retrospective nature, relatively small sample size, and fewer cases of retinal tears and detachments making safety assessment difficult using statistical tools. So, we analyzed the rate of complications. Different surgeons and different settings could have had an influence on our results. The findings of our study may have limitations in cases of complex ERMs, where the surgical time may be prolonged.

7. Conclusion

In conclusion, we found that performing a limited vitrectomy is at least as effective as a complete vitrectomy in the management of macular pathologies. Limited vitrectomy also reduces the operative time, without increasing the rate of complications. Further prospective, randomized studies with larger sample sizes are required to confirm these observations.

Data Availability

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Supplementary Materials

Video 1: limited vitrectomy with ILM peeling. Video 2: total vitrectomy + ILM peeling with peripheral base shaving with endolaser. (*Supplementary Materials*)

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Research Article

Traumatic Macular Hole: Clinical Management and Optical Coherence Tomography Features

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The complex and uncertain prognosis of traumatic macular hole (TMH) makes it a difficult and challenging problem in clinical management. The features of spontaneously closed TMH and the time of vitrectomy remain unclear. This retrospective study aimed to demonstrate the optical coherence tomography (OCT) features of TMH, explore the relationship between OCT parameters and visual outcomes, and further evaluate the therapeutic effect of surgical management. Seventeen TMH patients were included in this study. 13 eyes of TMH received vitrectomy surgery and 4 eyes of TMH were closed spontaneously. Baseline patient characteristics, surgical details, and 6-month postoperative follow-up clinical assessment were recorded prospectively. There was a moderate rate (4/17 eyes, 23.5%) of spontaneous closure. The mean time of hole closure was 9.5 ± 9.9 weeks, and 75% occurred within three months. In the spontaneously closed TMH eyes ($n = 4$), an intact ellipsoid band was observed in all four patients with a mean age of 12.0 ± 1.6 years and a smaller preoperative basal diameter of $418.0 \pm 283.6\,\mu$m. Small basal diameter of the macular hole at baseline ($p = 0.02$) was associated with spontaneous closure of TMH acuity. In the vitrectomy surgery group ($n = 13$), an intact ellipsoid band was observed in four patients (4/13) with a mean age of 27.0 ± 12.7 years and a larger preoperative basal diameter of $943.0 \pm 444.2\,\mu$m ($p = 0.02$). Vitrectomy results in a better closure rate (11/13 eyes, 84.6%). Combined with the spontaneously closed TMH eyes, the overall hole closure rate was 88.2% (15/17 eyes). After 6-month treatment for all patients, the best-corrected visual acuity (BCVA) increased to 0.59 ± 0.40 (logMAR) compared to baseline 1.01 ± 0.50 (logMAR) ($p < 0.001$). The ellipsoid band integrity was found to be closely correlated with visual acuity ($p = 0.03$). In conclusion, vitrectomy is an effective treatment for TMH. Surgical management for TMH achieved better anatomical closure and improved visual outcomes. Observation for 3 months may be considered before deciding if surgical intervention is suitable.

1. Introduction

Macular holes are full-thickness defects of the neuroretina that disrupt the foveal contour. They are commonly idiopathic or age-related but may be traumatic due to blunt injury to the eye. The first case of traumatic macular hole (TMH) was described by Knapp [1] in 1869. The incidence of TMH is 1.4% in closed-globe trauma and 0.15% in open-globe injuries [2]. Due to its rarity, studies on TMH are limited [3].

Idiopathic macular hole (IMH) occurs more generally among women over 65 years of age. However, TMH occurs most often in young people and is caused by a sudden extrinsic force, which creates dynamic forces within the sclera and vitreous. The forces lead to a wide range of retinal pathologies, including commotio retinae, diffuse retinal edema, retinal hemorrhage, retinal tears, vitreous hemorrhage, choroidal rupture, and photoreceptor and retinal pigment epithelium (RPE) damage [4]. All these pathological changes will eventually result in severe vision loss. Due to the low incidence of TMH, currently, there are no standard clinical guidelines for the clinical characteristics, treatment, and prognosis of TMH.

According to the follow-up reports on TMH cases, the rate of spontaneous closure of TMH is reported to range from 10% to 67% [5–9]. A meta-analysis of surgical

outcomes of vitrectomy for TMH revealed a successful closure rate of 83% [1]. In the observation of TMH prognosis and follow-up, there have been relatively few studies on the correlation between optical coherence tomography (OCT) and prognosis of TMH. Herein, we present a follow-up case series of consecutive patients with TMH. By retrospection of both initial and follow-up OCT data, we analyzed the clinical and OCT characteristics and effects of operation in detail in order to provide valuable information regarding the treatment and prognosis of TMH.

2. Materials and Methods

This is a retrospective case series of 17 patients diagnosed with TMH who were evaluated at our hospital outpatient clinic from 2014 to January 2017. The study was approved by the Ethics Committee of the No. 4 Xi'an Hospital. The study adhered to the tenets of the Declaration of Helsinki.

Baseline assessment included age, sex, laterality, nature of blunt ocular trauma, and time lapse between trauma and first presentation. Baseline best-corrected visual acuity (BCVA) was recorded in decimal notation and converted to a logMAR value for statistical analysis. All cases were subjected to detailed ophthalmic examination, including BCVA, slit lamp of the anterior segment, OCT examination, fundus slit-lamp biomicroscopy, and color fundus photography. These cases were followed up for at least 6 months.

2.1. Inclusion and Exclusion Criteria. Inclusion criteria were a clear traumatic history with diagnosis of full-thickness MH, which was confirmed by indirect ophthalmoscopy, color fundus imaging, and OCT. Exclusion criteria were patients with any other eye diseases that affect vision and prognosis, or with open-globe injuries, severe cataract or vitreous hemorrhage, and retinal detachment. Those patients who had received laser or surgical treatment before or who could not be reached for regular follow-up also were excluded.

2.2. Spectral Domain OCT Examination. Spectral domain (SD) OCT is the key technique in the management of TMH. It allows for a detailed assessment of the macular hole parameters, vitreoretinal interface, and other associated macular changes at each presentation. In our study, OCT scans were performed using one of the two SD-OCT versions: the Topcon 3D OCT-2000 (Topcon, Tokyo, Japan) or the Heidelberg Spectralis (Heidelberg Engineering, Inc., Heidelberg, Germany). Several SD-OCT parameter measurements were recorded, including height (internal limiting membrane (ILM) to RPE) and the minimum and basal diameter of the hole (Figure 1).

During the follow-up, if the OCT examination revealed a persistent open hole for three months or increased basal diameter, observation was stopped and vitrectomy was performed. For patients presenting signs of hole basal diameter decreasing, OCT was reexamined weekly to observe hole size, especially in the first month. During subsequent follow-up, OCT was reexamined monthly or every 2 months.

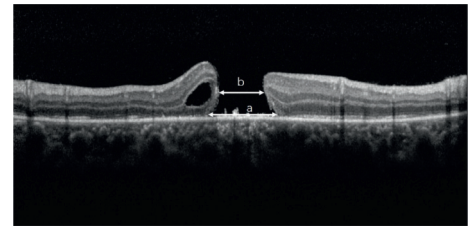

Figure 1: The hole basal diameter (a) was measured as the hole diameter at the level of the retinal pigment epithelium. The hole minimum diameter (b) was measured as the minimum inner diameter of the hole.

Finally, observation was stopped once the hole was completely closed.

2.3. Surgical Method. The surgical procedure was explained to all patients or their relatives, and written consent was obtained. A standard 23 G three-port pars plana vitrectomy (PPV) was conducted, followed by induction of posterior vitreous detachment if not already detached. After ILM staining with indocyanine green dye, the ILM around the hole was peeled at least 2 disc diameter areas in order to release the traction. ILM was not completely lifted off the retinal surface; rather, peeling was stopped at the edges of the hole, creating a free-floating flap that was left attached all around the edges of the hole. Then, fluid-air exchange was conducted followed by injection of air, perfluoropropane (C3F8), or hexafluoroethane (C2F6). Based on the literature review, [10] we improved the surgical technique by using autologous serum to promote the healing of the hole in three patients with a large macular hole. Sclerotomy ports were removed, and their sites were tested for any leakage. Postoperatively, combined antibiotic-steroid drops (Tobradex eye drops, Alcon, Fort Worth, USA) were used four times daily for 4 weeks. For gas-filled eyes, the patients were instructed to maintain a face-down position whenever possible for 1 week or until 50% of the gas bubble was absorbed.

2.4. Pattern of Hole Closure. According to previous literature studies [11, 12], there are different types of hole closure for postoperative anatomical outcome of IMH and TMH. In Grade A, the macular hole is closed with a bridge-like closure. In Grade B, the macular hole is completely closed with a foveal morphology appearance. In Grade C, the macular hole is poorly closed, with an absence of foveal-area neurosensory retina. For unclosed macular holes, the edge of the macular hole was attached to the RPE.

2.5. Postoperative Follow-Up. After operation, follow-up occurred at postoperative day 1, week 1, month 1, month 3, and month 6. BCVA was recorded at each visit. The follow-up period, pattern of TMH closure, and grade of ellipsoid zone recovery were observed using SD-OCT, especially for the outer retinal layers, including the external limiting

membrane and the inner segment/outer segment photoreceptor junction layers.

2.6. Statistical Analysis. Comparisons of means were analyzed using the unpaired Mann–Whitney U test or paired t-test. All statistical tests were two-tailed, and significance was defined as $p < 0.05$. GraphPad Prism 8.0 (GraphPad Software, California, USA) was used for all statistical analyses.

3. Results

3.1. General Data. Seventeen patients (17 eyes) with TMH were included during the study period, including 15 males and 2 females. The age of TMH patients ranged from 12 to 45 years (mean: 23.5 ± 12.5 years). All cases were caused by incidents of closed-globe trauma, including boxing, ball sports, firecrackers, and laser pen injury (Table 1). Among these 17 patients, 13 cases (76.5%) received vitrectomy, while 4 cases (23.5%) demonstrated spontaneous closure. The mean age of the spontaneous closure group was 12.0 ± 1.6 years (range: 10–14 years), whereas the mean age the vitrectomy group was 27.0 ± 12.7 years (range: 12–45 years) ($p = 0.009$) (Figure 2(a)).

3.2. Hole Closure. Four (23.5%) of the TMHs closed spontaneously, and the meantime of hole closure was 9.5 ± 9.9 weeks (range: 2–24 weeks). Two of these spontaneous closures occurred between 2 and 4 weeks, one occurred at 8 weeks, and one occurred more than 24 weeks after presentation. Thirteen patients underwent vitrectomy; of these, 11 patients (84.6%) had successful closure. The median time from trauma to intervention was 2.5 ± 0.8 months. Patients presented with three grades of anatomical outcomes: one case was Grade A, seven cases were Grade B, and five cases were Grade C. Two cases of TMH were not closed. OCT shows the absence of foveal-area neurosensory retina, but the edge of the macular hole was attached to the RPE.

3.3. OCT Characteristics at Presentation. In OCT examination, preexisting posterior vitreous detachment (PVD) and intraretinal cysts have a relation with TMH formation. In our study, two of the 17 eyes were found to have PVD. Intraretinal cysts were found in one of the four patients (25%) in the spontaneous closure group and four of the eleven patients (36.6%) in the vitrectomy group.

During the follow-up, OCT showed a significantly smaller basal diameter of $418.0 \pm 283.6\,\mu$m in the spontaneous closure group compared with $943.0 \pm 444.2\,\mu$m in the vitrectomy group ($p = 0.02$) (Figure 2(b)). Additionally, in the spontaneous closure group, the smaller minimum diameter and height of hiatus were $220.0 \pm 129.3\,\mu$m and $424.0 \pm 237.1\,\mu$m, respectively, and in the vitrectomy group, the smaller minimum diameter and height of hiatus were $520.0 \pm 129.3\,\mu$m and $471.0 \pm 218.3\,\mu$m, respectively ($p = 0.05$). The basal diameter of patients with hole closure is significantly smaller than that of not closed ($754.8 \pm 475.4\,\mu$m vs. $1204.5 \pm 132.2\,\mu$m, $p = 0.02$) (Figure 2(c)).

The ellipsoid band integrity was found to be closely correlated with visual acuity. In our study, the average BCVA was logMAR 0.38 ± 0.20 in the eight cases that retained ellipsoid band integrity. However, in the nine patients with incomplete ellipsoidal bands, an average BCVA was logMAR 0.78 ± 0.48. Greater ellipsoid band attenuation was found in eyes with worse postoperative visual acuity ($p = 0.03$) (Figure 2(d)).

A complete ellipsoid band could be seen in all OCT images of patients in the spontaneous closure group (Figures 3 and 4), while only 30.7% of patients (4/13) in the vitrectomy group retained the integrity of the ellipsoid band. A Fisher analysis confirmed that the integrity of the ellipsoid band was significantly correlated with visual acuity prognosis (Table 2).

3.4. Visual Outcome. For all 17 eyes in our study, the BCVA improved from logMAR 1.01 ± 0.50 to 0.59 ± 0.40 at the final follow-up visit ($p < 0.001$) (Figure 5(a)). In the 15 hole closure eyes, the BCVA improved from logMAR 0.98 ± 0.49 to 0.55 ± 0.39 ($p = 0.01$). In the four eyes with spontaneous hole closure, the BCVA improved from logMAR 0.86 ± 0.32 to 0.30 ± 0.25 ($p = 0.03$). In the 13 eyes with vitrectomy, the BCVA improved from logMAR 1.05 ± 0.54 to 0.68 ± 0.41 ($p = 0.06$). Preoperative basal diameter was positively correlated with preoperative ($r = 0.07$ and $p = 0.2$) and postoperative ($r = 0.02$ and $p = 0.5$) logMAR visual acuity (Figures 5(b) and 5(c)).

Complication: two gas-treated cases had a postoperative day 1 high intraocular pressure that was medically controlled for 1 week. None of the cases in the study developed serious complications, such as endophthalmitis, choroidal hemorrhage, or retinal detachment.

4. Discussion

Previously, very few studies reported the clinical and OCT features of TMH due to its low prevalence. Thus far, no clinical guidelines for TMH have been established. Therefore, it is necessary to explore the mechanism, examination, treatment, and prognosis of TMH.

4.1. Mechanism of TMH and Risk Factors. Many studies reported uncertain mechanism of TMH [3, 7, 9] with many hypotheses and speculations been put forward. The early-onset TMH is thought to be as a result of anteroposterior compression caused by blunt trauma, followed by a rebound contrecoup resulting in vitreofoveal traction [8]. During the rebound process, the tangential traction force between the vitreous and retina played an important role in the formation of the macular hole. We speculated that patients with preexisting posterior vitreous detachment (PVD) might have a lower risk of TMH formation. We all know that TMH patients are typically younger and have stronger vitreofoveal adhesion, which increases the risk of foveal avulsion. In China, a maximum sample size of 73 TMH eyes without

Table 1: All patient's details, surgery, and outcome.

Case	Age/ gender	Eye	Type of trauma	Initial visual acuity	Macular hole size	Final visual acuity	Time from trauma to PPV	Surgical details	Adjunct	Outcome and complication
1	24/M	Right	Laser	20/63	1057	20/50	6 m	PPV + ILM peeling + C3F8	—	Closed
2	38/F	Right	Firecracker	20/200	1129	20/160	1 m	PPV + ILM peeling + C3F8	—	Closed
3	14/F	Right	Firecracker	20/125	231	20/32	—	—	—	Closed spontaneously
4	45/M	Right	Firecracker	20/100	1111	20/63	7 m	PPV + ILM peeling + C3F8	—	Not closed
5	12/M	Right	Racket	20/63	663	20/20	—	—	—	Closed spontaneously
6	19/M	Left	Bump	20/800	1298	20/50	3 m	PPV + ILM peeling + C2F6	—	Not closed (choroid rapture)
7	12/M	Left	Racket	20/80	498	20/40	2 m	PPV + ILM peeling + air	—	Closed
8	40/M	Right	Belt	20/100	732	20/400	5 m	PPV + ILM peeling + air		Closed
9	12/M	Left	Blunt	20/400	658	20/50	—	—	—	Closed spontaneously
10	10/M	Right	Racket	20/125	120	20/80	—	—	—	Closed spontaneously
11	45/M	Left	Laser	20/200	1242	20/63	2 w	PPV + ILM peeling + C3F8	ILM flap + serum	Closed
12	40/M	Right	Firecracker	20/80	451	20/50	3 w	PPV + ILM peeling + C3F8		Closed
13	17/M	Left	Football	20/500	475	20/125	1 m	PPV + ILM peeling + C3F8	—	Closed (subretinal hemorrage)
14	12/M	Right	Racket	20/80	627	20/50	3 m	PPV + ILM peeling + air	—	Closed
15	16/M	Right	Fist	20/500	1781	20/100	1 m	PPV + ILM peeling + air	ILM flap + serum	Closed
16	26/M	Right	Fist	20/500	540	20/500	3 w	PPV + ILM peeling + C3F8	ILM flap + serum	Closed (hemorrage; choroid rapture; orbit fracture)
17	17/M	Right	Racket	20/200	579	20/63	1 m	PPV + ILM peeling + C3F8	—	Closed

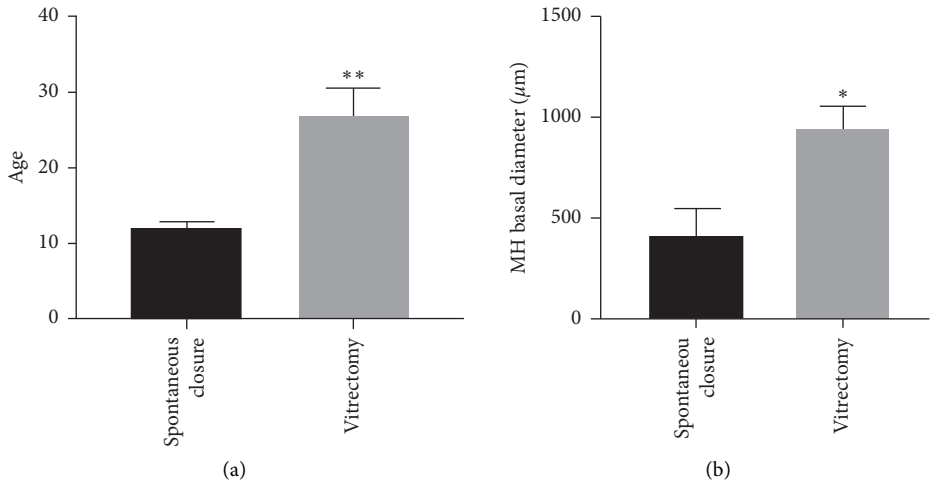

Figure 2: Continued.

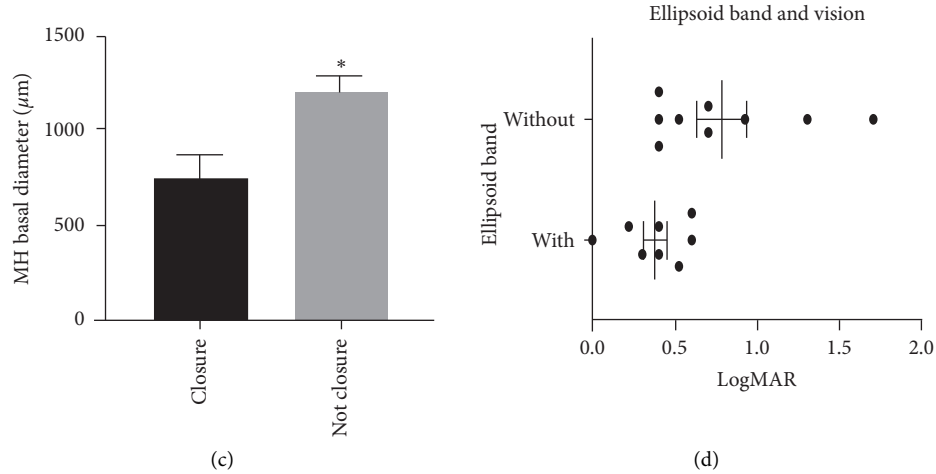

Figure 2: (a) Patients' mean ages for both groups. The mean age was 12.0 ± 1.63 years in the spontaneous closure group and 27.0 ± 12.7 years in the vitrectomy group ($p = 0.009$). (b) In the spontaneous closure group, the basal diameter was 418.0 ± 283.6 μm, whereas the diameter was 943.0 ± 444.2 μm in the vitrectomy group ($p = 0.02$). (c) The preoperative basal diameter was 754.8 ± 475.4 μm in the eyes with successful macular hole closure and 1204.5 ± 132.2 μm in the eyes without macular hole closure ($p = 0.02$). (d) The relationship between ellipsoidal band and postoperative BCVA. The eight cases with ellipsoid band integrity demonstrated better average BCVA than those without ellipsoid band integrity ($p = 0.03$).

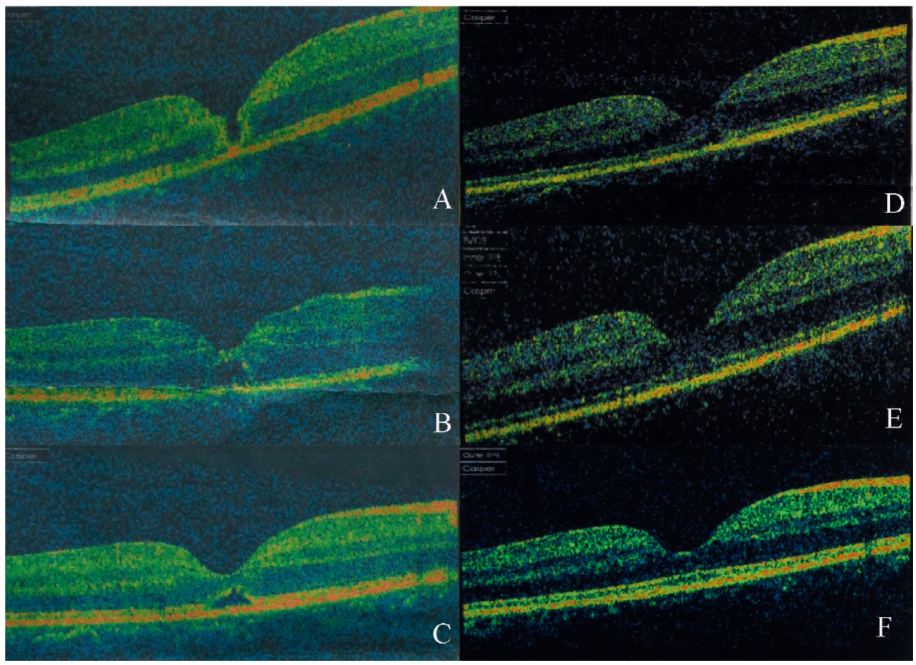

Figure 3: Case 3: a 14-year-old female patient with spontaneous macular hole closure. The patient sustained blunt trauma to the right eye from a firecracker. Her BCVA was 20/125 at initial and improved 120/200 after treatment. (a) OCT image 2 days after trauma showing FTMH. (b) OCT image 1 week, (c) 1 month, (d) 2 months, and (e) 3 months after trauma showed that a bridge connection has formed in the middle of the hole. (f) OCT image of 6 months after trauma, showing the neurosensory retina had almost connected, and the ellipsoid band had regained integrity.

PVD was recorded through careful clinical examination or by SD-OCT [13]. In a study of 20 patients with TMH, PVD was only found in three eyes (15%), and the vitreous was detached from the macula in only one eye (5%) [14]. In our study, only two of the 17 TMH eyes were found with PVD. The differentiation of PVD may be related to different methods of detecting PVD and examination time. Since PVD is generally detected during the patient evaluation, for some of these case reports, PVD could have been a result of injury rather than an antecedent event.

For delayed-onset TMH, ILM rupture and disruption in the retinal layers with secondary vitreous fluid accumulation may cause intraretinal cysts and swelling, which is also the reason for TMH formation [15]. Chen et al. [16] found that

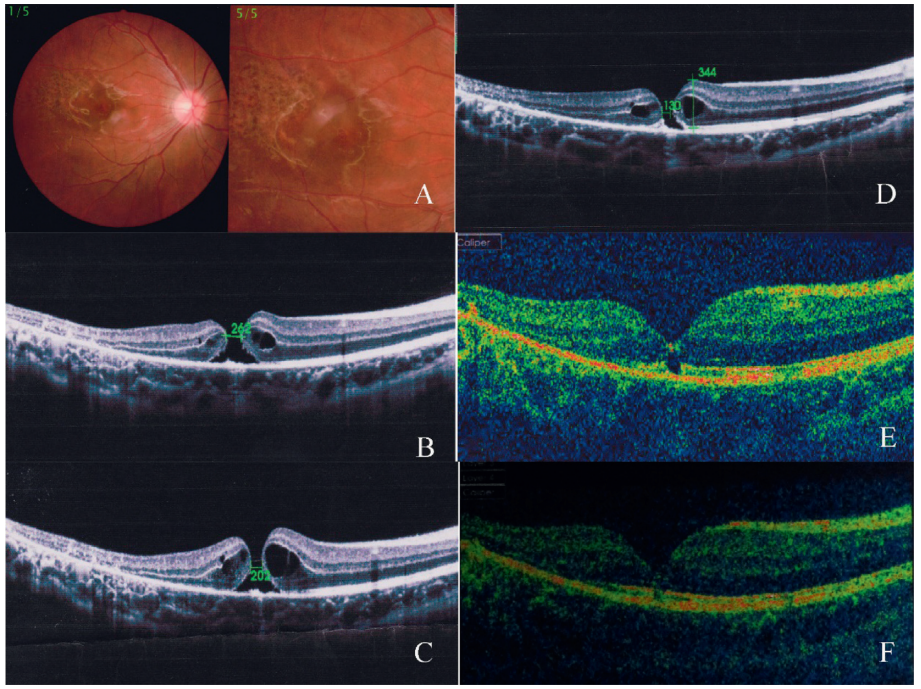

Figure 4: Case 5: a 12-year-old male patient with spontaneous macular hole closure. The patient sustained blunt trauma to the right eye from a racket. His BCVA was 20/63 at initial and improved 20/20 after treatment. (a) Color photo of the same eye 20 days after trauma showing retinal edema. (b) OCT image 20 days after trauma showing FTMH with narrowest diameter of 262 μm. (c) OCT image 1 month after trauma; narrowest diameter decreased to 202 μm. (d) OCT image 3 months after trauma; narrowest diameter decreased to 130 μm. (e) OCT image 6 months after trauma; part of the ellipsoid band had not regained integrity. (f) OCT image 12 months after trauma; neurosensory retina and ellipsoid band had almost completely regained integrity.

Table 2: The relationship between ellipsoid zone and visual acuity prognosis.

Ellipsoid band zone	Spontaneous closure group	Vitrectomy group	Fisher's exact test
With	4	4	$p = 0.029$
Without	0	9	

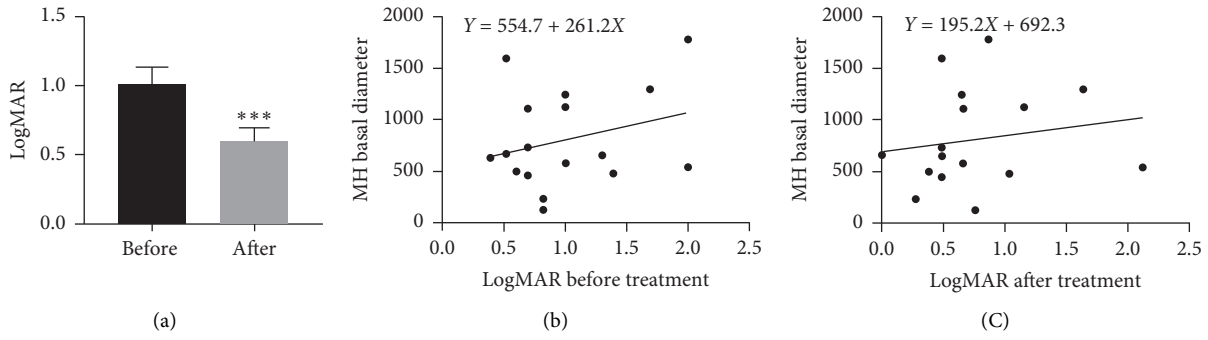

Figure 5: BCVA before and after treatment. (a) For all 17 eyes in our study, BCVA improved from median logMAR 1.01 ± 0.50 to 0.59 ± 0.40 at the final follow-up visit ($p < 0.001$). Preoperative macular hole basal diameter was positively correlated with (b) preoperative ($r = 0.07$, $p = 0.2$) and (C) postoperative ($r = 0.02$, $p = 0.5$) logMAR visual acuity.

holes with spontaneous closure were less likely to have intraretinal cysts compared to holes that did not close spontaneously (10% versus 76.5%). They suggested that an absence of intraretinal cysts was the only independent predictive factor for spontaneous closure of TMH. Similar results were found in this study, with intraretinal cysts found in one of the four patients (25%) in the spontaneous closure group and in four of the thirteen patients (30.8%) in the

vitrectomy group. However, there was not a statistically significant difference between the two groups.

4.2. Spontaneous Closure of TMH. In this study, we found that four eyes (23.5%) underwent spontaneous closure of TMH and the mean time of hole closure was 9.5 ± 9.9 weeks (range: 2–24 weeks), which is consistent with the literature report of 10–50% [7, 9, 16–18]. We also observed that the diameters of the holes in the spontaneous closure group were smaller than those in the vitrectomy group. Yamashita et al. [8] reported spontaneous closure in eight out of 18 (44.4%) TMH cases after a mean follow-up of 8.4 months. Li et al. [19] reported spontaneous closure in three out of 28 (10.7%) TMH cases after a mean follow-up of 18 months. Faghihi [7] reported six cases of spontaneous closure after 1 to 6 months of follow-up. Chen et al. [16] reported a 37.0% rate of spontaneous closure and found that those macular holes that closed spontaneously had a small minimum diameter and few intraretinal cysts. Therefore, Miller et al. [2] advised a 2- to 3-month observation period after TMH presentation. Although spontaneous hole closure can occur after another 3 months, this is less likely. Furthermore, extended observation beyond 3 months can lead to diminishing returns on successful hole closure via vitrectomy. Therefore, the experience of spontaneous closure of TMH suggests that a period of observation before surgical intervention may be recommended for the management of TMH. Based on our data, observation for 3 months may be considered before deciding if surgical intervention is suitable.

The mechanism of spontaneous closure of TMH is not clearly known. Lewis et al. [20] outlined that formation of the epiretinal membrane results in constriction of the hole. Takahashi and Kishi [21] suggested that reattachment of the operculum to the hole edge and bridging of the protruding retinal tissue over the hole can result in closure of the hole. On the contrary, Imai et al. [22] and Yamada et al. [9] observed no clear operculum during follow-up OCT and they supported that proliferation of glial cells and RPE cells from the edges of holes results in the filling of holes. Ishida et al. [23] noted that a complete detachment of the posterior hyaloid leads to a reduction in anteroposterior tractional forces and thus closure of the hole.

Our study identified two factors associated with spontaneous closure of TMH. The first factor was the small basal diameter of the macular hole at baseline, which may allow for easy migration of glial cells. The other associated factor was the integrity of the ellipsoid in the retina. In this study, OCT revealed that the ellipsoid band was intact in all patients with spontaneous closure of TMH, yet only four of the 13 eyes in the operation group had an intact ellipsoid band. The ellipsoid band is located in the photoreceptor layer of the retina, which is closely related to the RPE cell layer. During the repair process, glial cells and RPE at the edge of the hole proliferate and repair the hole, alleviating the edema of the photoreceptor layer and restoring the ellipsoid band (Figures 3 and 4).

4.3. Ellipsoid Band and Basal Diameter of OCT. OCT plays an important role in the follow-up of TMH to delineate the anatomic details of the defect, determine associated retinal pathology, and assess its progression objectively on a weekly or monthly basis. Our study revealed that the visual acuity was closely related to the integrity of the ellipsoid band. Miller [18] analyzed macular morphology on the OCT of 13 TMH eyes and concluded that there was a positive trend of better final acuity in both surgically managed eyes and those with spontaneous closure with the presence of an intact ellipsoid band. OCT showed that basal diameter was also a factor for TMH prognosis. Our study also confirmed that preoperative basal diameter was positively correlated with preoperative and postoperative logMAR visual acuity. Additionally, in our study, the preoperative BCVA of three eyes was very poor, and postoperative visual did not have obvious improvement which accompany on serious complications, including choroid rupture and subretinal hemorrhage.

OCT also allows for evaluation of the changes in the macular hole and guides surgical intervention. In the follow-up of cases with an aggravating tendency, it was observed through OCT that the basal diameter of holes increased in size from presentation to the last follow-up, which indicates a poor prognosis and merits further surgical intervention. Our results reported that the median time from clinical presentation to the operation was 2.3 ± 0.8 months. Therefore, an OCT observation period of 2–3 months after trauma was recommended.

4.4. Hole Closure of TMH. At present, the surgical treatment of choice for TMH is controversial. Kelly and Wendel [24] and Wendel et al. [25] reported on the surgical treatment of IMH for the first time. Most of the studies revealed that vitrectomy with or without ILM peeling remains an effective method for closing holes and improving vision for TMH [1, 26]. Our results showed that vitrectomy combined with ILM peeling is an optimal choice and the closure rate of holes after vitrectomy was 84.6%. A meta-analysis of surgical outcomes in all published reports of vitrectomy for TMH found a successful closure rate of 83% [1]. The multicenter trial by Johnson et al. [26] found successful closure in 24 of 25 cases (96%) of TMH undergoing vitrectomy. The reason for this difference in the hole closure rate may be the different criteria for evaluating hole closure. Kuhn et al. [27] defined macular hole closure as the disappearance of subretinal fluid and flattening of the hole edges. Ghoraba et al. [28] defined W-pattern closure as when the edges of the macular hole flatten against the RPE, though with a persistent full-thickness defect in the neurosensory retina. However, in our study, we defined not closure as a persistent full-thickness defect in the neurosensory retina, though the edge of the macular hole is attached to the RPE, which is the same as a W-pattern closure. Therefore, the percentage of holes closed was lower compared to other studies.

Another reason for the differences in closure rates could be surgery management in terms of whether or not adjunctive is used during the operation. Macular hole closure via vitrectomy involves the stimulation of glial cell proliferation in the hole [29]. TGF-beta 2, platelet concentrate, and serum have been described as surgical adjuvants for the closure of IMH [24, 25]. These adjuvants can also be used in

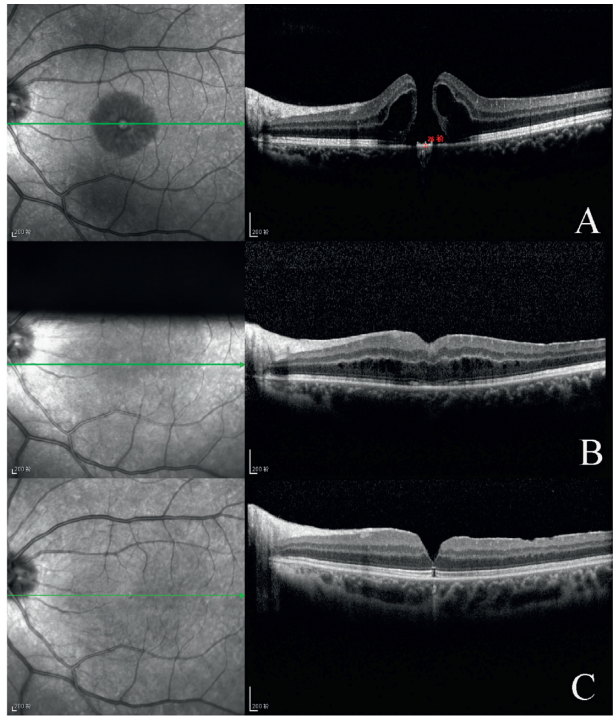

Figure 6: Case 11: a 45-year-old male patient with macular holes closed by vitrectomy combined with ILM peeling and C3F8 tamponade. The patient's left eye was damaged by a laser. His BCVA was 20/200. at initial and improved 20/63 after surgery. (a) Preoperative OCT image showing FTMH with intraretinal cyst. (b) OCT image 2 weeks postoperative showing the closed hole and intraretinal edema. (c) OCT image 4 months postoperative showing closed hole, but ellipsoid band had not regained integrity. His BCVA was now 20/63.

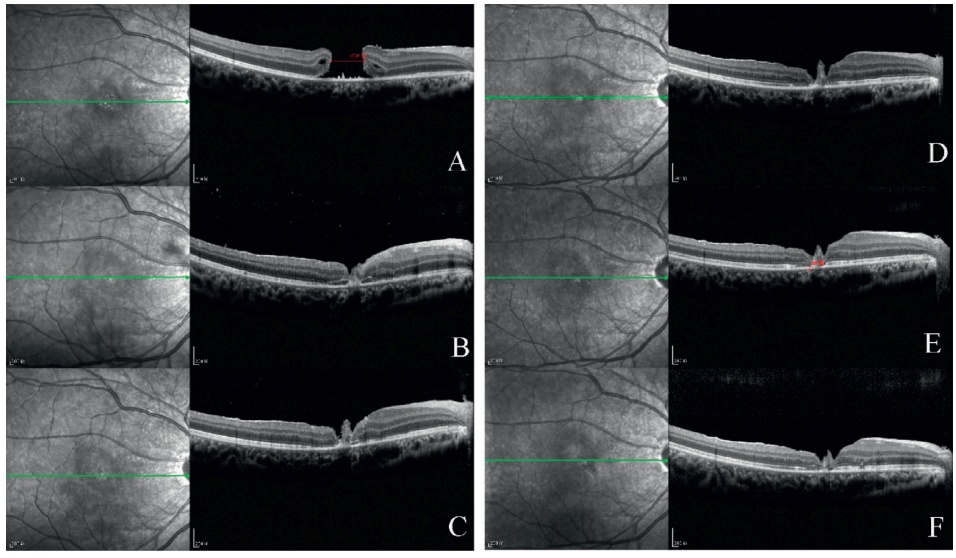

Figure 7: Case 15: a 16-year-old male patient with macular holes closed by vitrectomy. The patient sustained blunt trauma to the right eye from a fist. His BCVA was 20/500 at initial and improved 20/100 after surgery. (a) Preoperative OCT image showing FTMH with basal diameter of 1781 μm. (b) OCT image 2 weeks after vitrectomy combined with ILM peeling and ILM flap and air tamponade. Retinal connection is visible, but part of the neuroretina and ellipsoid band has not regained integrity. OCT image (c) 1 month, (d) 4 months, (e) 9 months, and (f) 12 months postoperative.

the repair of TMH. In our study, the standard surgical procedure was vitrectomy, followed by ILM peeling combined with gas tamponade, and then ILM flap and serum tamponade. We speculated that these adjuvants and the ILM flap may act as a scaffold, which could induce proliferation and migration of glial cells and assist in the formation of chorioretinal adhesion, thus enabling macular hole closure (Figures 6 and 7).

4.5. Treatment of TMH: Silicone Oil versus Gas. Silicone oil has also been used for TMH closure in some cases. Brasil and Brasil [30] reported a case of a nine-year-old boy with a TMH who was treated with ILM peeling and silicone oil tamponade and who gained better vision. In our study, none of the patients were treated with silicone oil. We believe that the gas is sufficient to facilitate the closure of the macular hole. The surface tension of silicone oil is lower than that of gas, and silicone oil will not increase the success rate of hole closure. In addition, silicone oil can cause burdens for the patient, such as the need for a second operation, increased risk of cataract, high intraocular pressure, and other surgical complications.

4.6. Limitations. This study had several limitations. Firstly, its retrospective design inevitably carries biases inherent in such studies. For example, the follow-up schedule was not consistent, and OCT scan was not performed on a regular basis. Secondly, the sample size was limited, and the results may not be generalizable to all populations. Thirdly, the most important limitation may be the method of OCT image acquisition. Different OCT instrument models were used for the same patient, and the image quality was variable. This may have affected the accuracy of measurement of ellipsoid band attenuation. Lastly, we did not have a comparative study on adjuvant serum use in vitrectomy management, which is mainly due to the low incidence of TMH. Therefore, the use of serum to promote the closure of TMH may lead to biased conclusions.

5. Conclusion

In conclusion, our study showed there is a moderate rate (23.5%) of spontaneous closure after the occurrence of TMH, while vitrectomy can result in an even better closure rate (84.6%). The mean time for the spontaneous closure of the hole was 9.5 ± 9.9 weeks, and 75% of the hole closure occurred within three months. Intraretinal cystic edema on the edge of the hole may be an unfavorable factor for the spontaneous closure of TMH. The basal diameter was smaller in the spontaneous closure group than that in the vitrectomy group. The ellipsoid band integrity was found to be closely correlated with visual acuity. Greater ellipsoid band attenuation was found in eyes with worse postoperative visual acuity. In all TMH patients, BCVA after treatment was significantly improved compared with that occurrence of TMH. Preoperative basal diameter was positively correlated with preoperative and postoperative logMAR visual acuity, yet there are no significant differences. In treatment, vitrectomy is an effective treatment for TMH, and the gas is sufficient to facilitate the closure of the macular hole.

Data Availability

The data used to support the findings of this study are included within the supplementary information files.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Research Article

Comparison of 27-Gauge and 25-Gauge Microincision Vitrectomy Surgery for the Treatment of Vitreoretinal Disease: A Systematic Review and Meta-Analysis

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Background. We performed a systematic review and meta-analysis to evaluate the safety and effectiveness of 27-gauge (27-G) microincision vitrectomy surgery (MIVS) compared with 25-guage (25-G) MIVS for the treatment of vitreoretinal disease. *Methods*. A systematic electronic search was conducted in March 2020 in PubMed, Embase, and the Cochrane library. Eligible criteria for including studies were controlled trials comparing 27-G vitrectomy with 25-G vitrectomy in patients with vitreoretinal disease. The main outcomes included operation time; best corrected visual acuity (BCVA) in logMAR; postoperative intraocular pressure (IOP); primary anatomical success rate for rhegmatogenous retinal detachment (RRD) cases and postoperative central macular thickness (CMT) for idiopathic epiretinal membrane (ERM) cases; intraoperative/postoperative complications. Odds ratio (OR) and mean difference (MD) were synthesized under fixed or random effects models. *Results*. Eleven studies enrolling 940 eyes were identified. Among those 11 studies, six studies were on the treatment of RRD and five studies were on the treatment of ERM, so subgroup analyses were conducted. The total pooled results indicated that 27-G surgery system had obvious advantages in improving BCVA at six months after the vitrectomy ($P = 0.004$) and reducing intraoperative/postoperative complications ($P = 0.03$). However, the mean operation time was significantly longer by three minutes for 27-G compared with 25-G vitrectomy ($P = 0.002$). In subgroup analyses, for the treatment of ERM cases, 27-G group was associated with less complications and longer operation time. However, for the treatment of RRD cases, 27-G groups and 25-G groups were comparable in operation time, postoperative BCVA, postoperative IOP, and primary anatomical success rate. *Conclusions*. This meta-analysis confirmed that 27-G MIVS was an effective and safe surgical system compared with 25-G MIVS for the treatment of RRD and ERM cases, even though 27-G system needs a longer surgical time.

1. Introduction

Microincision vitrectomy surgery (MIVS) was first introduced by Machemer in the early 1970s [1], and this technique represented a new era in ophthalmology. Since that moment, 20-gauge (20-G), 23-G, and 25-G surgery system were applied to vitrectomy [2–4]. There was no doubt that current MIVS with 25-G or 23-G instruments had simplified vitrectomy procedure and had provided numerous potential advantages over traditional 20-G surgery [5–10]. It was confirmed that smaller wounds could reduce the intraocular inflammation [9, 11], shorten recover time [7, 12], and decrease intraoperative/postoperative complications [12, 13]. In 2010s, Oshima et al. first described 27-G MIVS for the treatment of vitreoretinal diseases [14]. In the beginning, the 27-G vitrectomy was conducted mainly for simple cases such as epiretinal membrane (ERM), idiopathic macular holes, and vitreous hemorrhage [15–17]; recently, indications for 27-G vitrectomy have since been expanded to more complicated conditions, including proliferative

diabetic retinopathy, rhegmatogenous retinal detachment (RRD), and proliferative vitreoretinopathy [18–20]. Many studies have shown the advantages of 27-G MIVS in terms of patients' comfort, convalescence, inflammatory response, and visual recovery in the ERM surgery compared with traditional 25-G vitrectomy [15, 17, 21–23]. However, some studies concluded that 27-G vitrectomy requires longer operation time for the treatment of RRD cases because of the lower flow rate. Moreover, 27-G vitrectomy induced more postoperative inflammation because of sutureless wounds [20, 24–26].

We performed this meta-analysis to evaluate the feasibility, safety, and effectiveness of 27-G instrument for uncomplicated macular diseases such as ERM and complicated peripheral vitreoretinal disorders such as RRD. This study would expand our current knowledge of the safety and effectiveness of the 27-G MIVS.

2. Methods

2.1. Search Strategy and Inclusion Criteria. This meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement. Two researchers independently performed the literature search in the PubMed, the Cochrane Library, and EMBASE database until March 2020. The search used the following keyword strings: "27-gauge," "25-gauge," and "vitrectomy" in various combinations with the language limited to English. The reference lists of case reports, studies, and review articles were also reviewed for any additional citations. To increase sample size, we included both control trials and observational studies. Studies that appeared twice, or focused on other outcomes based on the same study group, were removed as the duplicated publications. All relevant articles identified through the search were scanned based on the title, keywords, and abstract by at least two investigators and were rejected in the initial screening if the article clearly did not meet the inclusion criteria. When a title/abstract could not be rejected with certainty, full texts of retrieved publications were reviewed and evaluated.

2.2. Inclusion Criteria. Studies were included if they (i) compared 27-G with 25-G vitrectomy for vitreoretinal disease, (ii) randomized controlled trials (RCTs), cohort, case-control or cross-sectional studies with at least four weeks' followup, and (iii) contained sufficient information of treatment outcome.

2.3. Data Extraction. The following information were extracted by the investigators independently from the published reports, using a standardized protocol and reporting form: first author's last name, year of publication, country of origin, number of enrolled eyes, mean age of patients, vitreoretinal disease, followup information, and related complications.

2.4. Outcome Measures. The main outcomes for this meta-analysis included operation time; best corrected visual acuity (BCVA) in logMAR at six months post-vitrectomy (POM6); intraocular pressure (IOP) at postoperative day 1 (POD1); primary anatomical success rate for RRD cases; postoperative central macular thickness (CMT) for ERM cases and intraoperative/postoperative complications. Complications were defined as adverse events result from surgery such as hypotony, intraocular hypertension, wound suture because of leakage, recurrent RD, vitreous hemorrhage (VH), iatrogenic retinal breaks (IRBs), and other surgery-related complications.

2.5. Assessment of Methodology Quality. Reviewers independently assessed the qualities of the included trials using a system which was previously reported by Downs and Blacks [27]. This system was appropriate for both randomized and nonrandomized studies. The system comprises 27 items distributed among five subscales regarding reporting (10 items), external validity (3 items), bias (7 items), confounding (6 items), and power (1 item). The total maximum score was 31. The studies with a quality score of more than 16 were considered to have adequate quality. Any discrepancy in the quality assessment between the two observers was discussed and a consensus was reached.

2.6. Statistical Analysis. Data were processed by REVMAN (Version 5.3; The Cochrane Collaboration, Copenhagen, Denmark). We calculated the mean difference (MD) for the continuous outcome along with 95% confidence intervals (CIs) by inverse variance method. For discontinuous outcomes, the summary odds ratios (ORs) were calculated by Mantel–Haenszel method. $P < 0.05$ was considered statistically significant, and 95% confidence intervals (CIs) were reported.

The between-study heterogeneity was tested by the chi-square-based (χ^2) Cochran's statistics and the inconsistency index (I^2) [28], which indicated the proportion of variability across studies due to heterogeneity rather than sample error. In the presence of substantial heterogeneity ($I^2 > 45\%$), the random effect model (REM) was adopted as the pooling method; otherwise, when $I^2 < 45\%$, the fixed effect model (FEM) was adopted as the pooling method.

The leave-one-out sensitivity analysis was performed using $I^2 > 50\%$ as the criteria for evaluating the key studies with a substantial impact on between-study heterogeneity. Subgroup analyses were conducted for RRD cases and ERM cases in order to reduce heterogeneity. A funnel plot was performed to look for evidence of publication bias. The funnel plot should be asymmetric when there is publication bias or symmetric in the case of no publication bias.

3. Results

3.1. Literature Search. A total of 190 studies were initially identified. The abstracts were reviewed, and 21 studies with potentially relevant trials were reviewed in their entirety. Subsequently, eight studies were excluded because they did

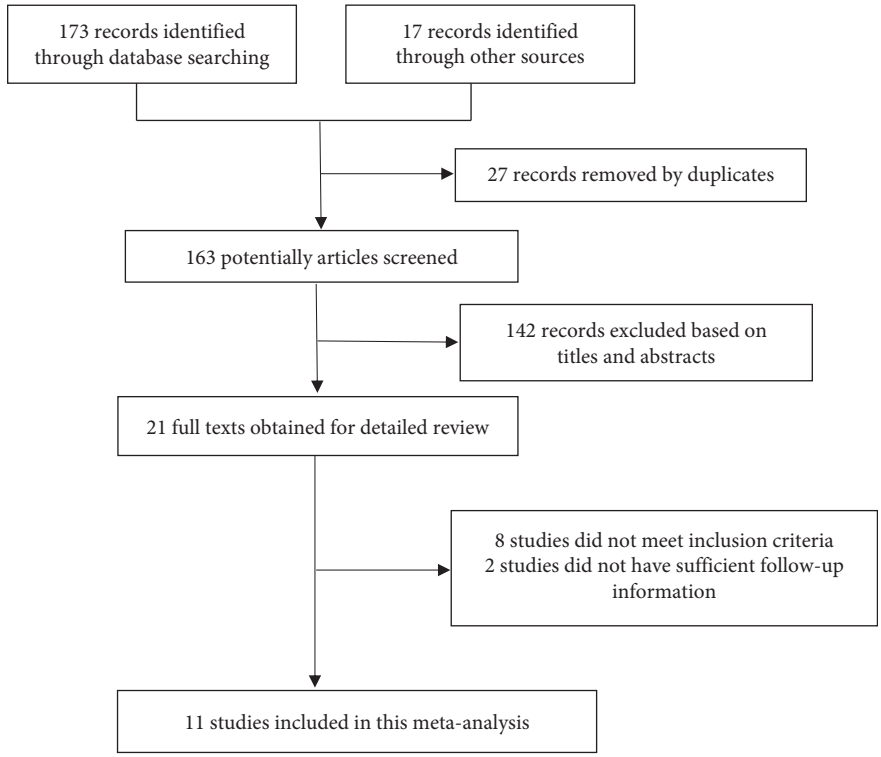

Figure 1: Flow diagram of literature search and study selection.

not have sufficient followup information and two studies were excluded because of design heterogeneity (Figure 1). Finally, a total of 11 studies were included in this meta-analysis.

3.2. Characteristics and Quality of Included Studies. Table 1 lists the characteristics of the included studies. These studies were published between 2015 and 2019. Seven studies [15, 21–24, 26, 31] were designed as prospective randomized/nonrandomized comparative study and four studies [17, 25, 29, 30] were retrospective randomized/nonrandomized comparative study. Five trials [15, 17, 21, 24, 29] enrolled 554 eyes which were conducted on ERM and six studies [22, 23, 25, 26, 30, 31] enrolled 386 eyes which were conducted on RRD. In total, 940 eyes were included in this meta-analysis; 439 eyes were assigned to the 27-G vitrectomy group and 501 eyes to the 25-G group. The duration of followup ranged from one to twelve months. The mean age in each study was not significant difference between the 27-G and 25-G group. All the patients underwent vitrectomy with Constellation vision system.

For the Downs and Blacks score, all studies were over 16 which means the quality of these studies were adequate.

3.3. Operation Time. Ten studies compared operation time between 27-G and 25-G group, the total pooled result showed that 27-G vitrectomy needs approximately three minutes longer than 25-G, and the difference was statistically significant (MD = 2.89; 95% CI: 1.07, 4.72; $P = 0.002$) (Figure 2). There was moderate heterogeneity among studies ($I^2 = 56\%$, $P = 0.02$), and so, REM meta-analysis was used. In order to explore the potential sources of heterogeneity, sensitivity analysis (via excluding the studies one by one) was proceeded. After the Takashina et al. study [17] was excluded, the heterogeneity almost disappeared ($I^2 = 19\%$, $P = 0.27$; MD = 3.64; 95% CI: 2.29, 4.99; $P < 0.001$), which indicated this study can be identified as the main contributor of heterogeneity. We reevaluated the study of Takashina et al. in terms of design, statistics, and selection bias and did not find anything wrong. In fact, this study did not influence the final pooled result.

Subgroup analyses were conducted on RRD and ERM. For the treatment of ERM, the operation time was approximately 2.5 min longer in 27-G group, and the difference was significant (MD = 2.49; 95% CI: 0.26, 4.73; $P = 0.01$). However, the difference was not significant for the treatment of RRD (MD = 3.12; 95% CI: −0.95, 7.19; $P = 0.13$).

3.4. Visual Outcome. Data on BCVA were provided in eight studies. The pooled result indicated that the 27-G group had a favorable response in visual recovery at six months after vitrectomy, and the difference was significant (MD = −0.03; 95% CI: −0.06, −0.01; $P = 0.004$) (Figure 3). Random effect model was adopted as the pooling method because of obvious heterogeneity in the ERM subgroup ($I^2 = 45\%$). In ERM subgroup, BCVA at six months after vitrectomy was comparable between 27-G group and 25-G group (MD = −0.04; 95% CI: −0.08, 0.00; $P = 0.06$). The sensitivity analysis showed the study of Mitsui K was the main source of heterogeneity. However, there was no statistics and selection bias in this study. In the RRD subgroup, there was no

Table 1: Characteristics of involved studies.

Included studies	Design	Disease	Location	No. of eyes 27G/25G	Age (year) mean ± SD 27G/25G	Followup (months)	Complications (eyes) 27G/25G
Reibaldi et al. [21]	Prospective randomized comparative study	ERM	Italy	40/39	66 ± 6/64 ± 6 $P = 0.14$	12	IRB: 0/3 VH: 2/3 Hypotony: 1/2 ERM recurrence: 3/2
Mitsuiet al. [15]	Prospective nonrandomized comparative study	ERM	Japan	32/36	68.9 ± 5.3/65.4 ± 11.4 $P = 0.33$	6	Hypotony: 3/4
Takashina et al. [17]	Retrospective randomized comparative study	ERM	Japan	59/88	72.9 ± 6.3/71.3 ± 7.9 P: NA	1	NA
Rizzo et al. [9]	Prospective nonrandomized comparative study	RRD	Italy	20/20	64.7 ± 9.7/62.4 ± 9.8 P: NA	6	IRB: 2/1 Choroidal detachment: 1/0 RD: 2/3 Intraocular hypertension: 1/2
Naruse et al. [29]	Retrospective nonrandomized clinical trial	ERM	Japan	100/100	67.6 ± 9.6/69.4 ± 8.9 $P = 0.25$	6	RD: 0/1 VH: 1/1 Hypotony: 2/6 Intraocular hypertension: 4/10
Romanoet al. [23]	Prospective randomized comparative study	RRD	Italy	15/15	58 ± 8/59 ± 11 $P = 0.82$	6	RD: 1/1 VH: 1/0 Intraocular hypertension: 0/2
Liet al. [30]	Retrospective nonrandomized clinical trial.	RRD	China	34/58	58.5 ± 13.3/54.1 ± 12.5 $P = 0.1$	6	RD: 3/3 IRB: 1/2 Hypotony: 0/1 Intraocular hypertession: 0/1
Lubinski et al [24]	Prospective randomized comparative study	ERM	Poland	30/30	65.40 ± 4.29/67.50 ± 4.18 $P = 0.052$	6	RD: 1/1 Macular hole: 1/0 Hypotony: 3/7
Otsuka et al. [25]	Retrospective nonrandomized clinical trial	RRD	Japan	30/32	59 ± 13/55 ± 9 $P = 0.15$	6	RD: 1/2
Sborgia et al. [31]	Prospective randomized comparative study	RRD	Italy	42/46	59.9 ± 9.2/61.7 ± 8.7 $P = 0.35$	12	RD: 4/2 Choroidal detachment: 1/0 ERM: 5/2 CME: 2/1
Veritti et al. [26]	Prospective randomized comparative study	RRD	Italy	37/37	63.9 ± 13.5/63.1 ± 12.5 $P = 0.8$	6	RD: 4/3 Hypotony: 0/2 Intraocular hypertension: 4/5 Wound suture: 3/11

CME: cystoid macular edema; ERM: epiretinal membrane; IRBs: iatrogenic retinal breaks; RRD: rhegmatogenous retinal detachment; VH: vitreous hemorrhage; hypotony was defined as IOP < 6 mmHg and intraocular hypertension was defined as IOP > 21 mmHg.

obvious difference between 27-G group and 25-G group (MD = −0.08; 95% CI: −0.15, 0.00; $P \geq 0.05$, $I^2 = 0\%$).

3.5. IOP. Eight studies recorded IOP on the first day postoperative (POD1). 27-G group and 25-G group had the same effect in controlling postoperative IOP and there were no significant differences (MD = 0.53; 95% CI: −1.49, 2.54; $P = 0.61$). In the subgroup analysis, IOP on POD1 were comparable between 27-G and 25-G group for the RRD cases (MD = −0.36; 95% CI: −1.36, 0.63; $P = 0.47$) and ERM cases (MD = 0.83; 95% CI: −2.05, 3.7; $P = 0.57$). Significant heterogeneity was found ($I^2 = 92\%$), so random effects were used. The study of Lubinski et al. [24] was the main contributor of heterogeneity, and after reevaluating this study, we found nothing wrong (Figure 4).

3.6. Primary Anatomical Success Rate. The primary anatomical success rate after a single operation was 91.6% and

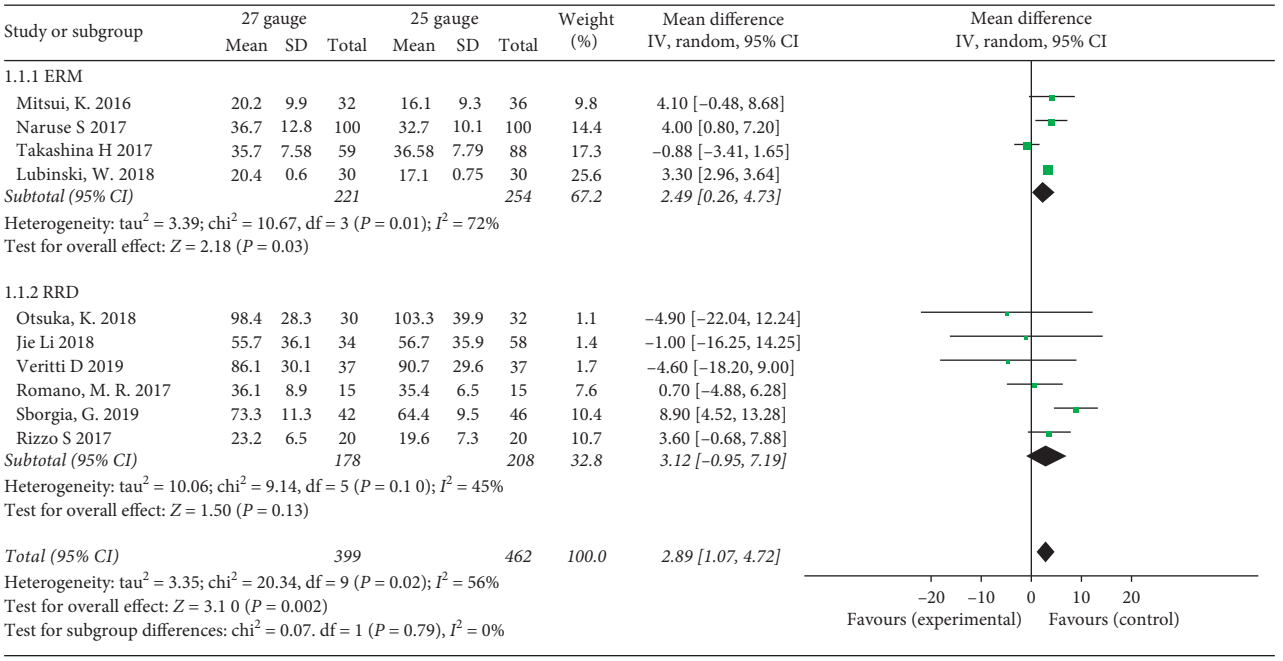

Figure 2: Forest plots of operation time compared between 27-G and 25-G vitrectomy in overall and subgroup analysis. RRD: rhegmatogenous retinal detachment; ERM: epiretinal membrane.

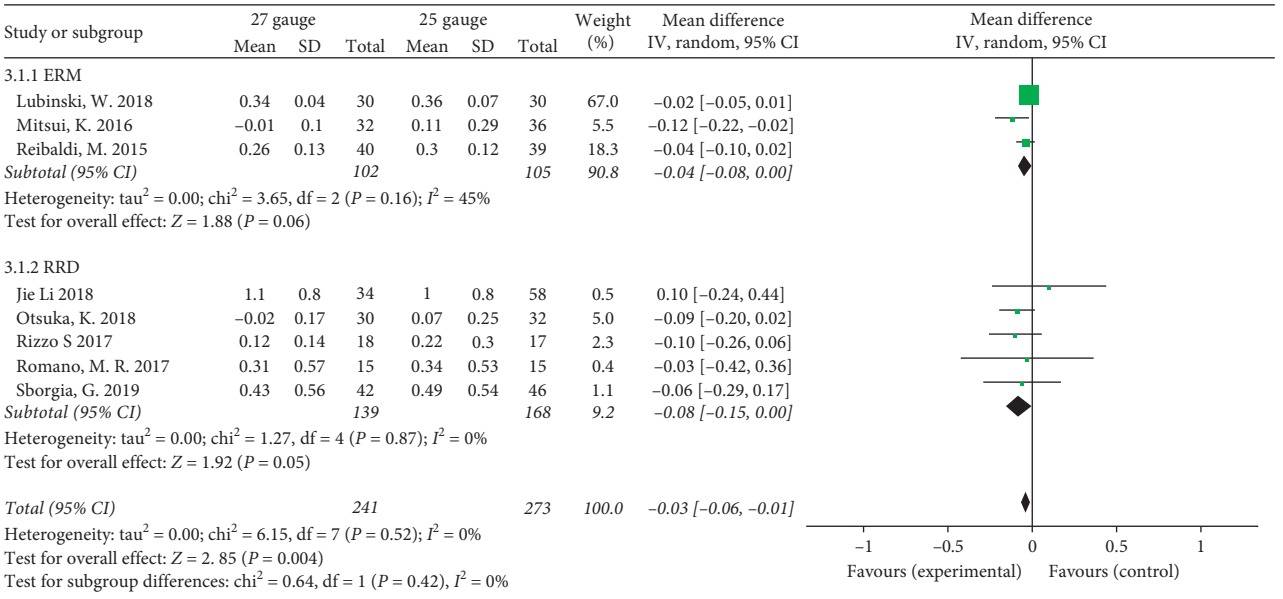

Figure 3: Forest plots of best corrected visual acuity (BCVA) compared between 27-G and 25-G vitrectomy at 6 months postoperative in overall and subgroup analysis.

93.3% in the 25-G and 27-G groups, respectively (Figure 5). The pooled result indicated that there was no significant difference in primary anatomical success rate between 27-G and 25-G group for the treatment of RRD without obvious heterogeneity (OR = 0.8, 95% CI: 0.38, 1.71; $P = 0.57$; $I^2 = 0\%$).

3.7. CMT. Three studies provided information on CMT with at least six months' follow-up. This meta-analysis collected data on CMT at one month (POM1) and six months postoperatively (POM6). The pooled result showed there were no significant differences in CMT for the treatment of ERM between the 25-G and 27-G groups during followup (1 month: $P = 0.36$; 6 months: $P = 0.18$, resp.) (Figure 6). No heterogeneity was found ($I^2 = 0\%$).

3.8. Intraoperative and Postoperative Complications. Complications in each involved study were summarized in Table 1. Ten studies (6 on RRD and 4 on ERM) reported

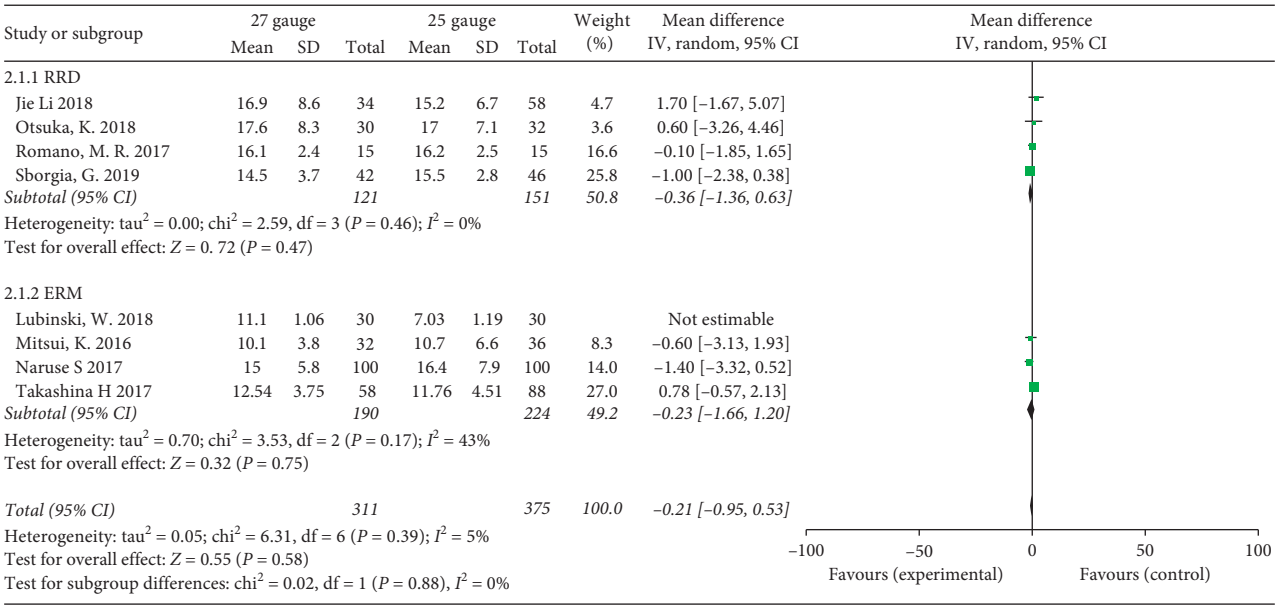

Figure 4: Forest plots of intraocular pressure (IOP) at POD1 compared between 27-G and 25-G vitrectomy in overall and subgroup analysis. POD1: postoperative day one.

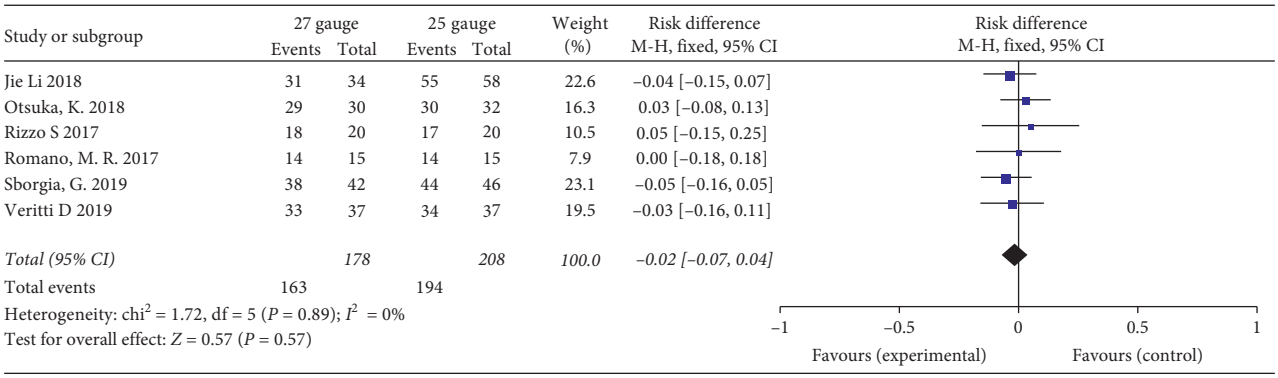

Figure 5: Forest plot of primary anatomical success rate compared between 27-G and 25-G vitrectomy for rhegmatogenous retinal detachment (RRD) cases.

intraoperative and postoperative complications during followup. In the total analysis, 27-G group was associated with less complication compared with the 25-G group with a pooled OR of 0.66 (95% CI: 0.45 to 0.93, $P = 0.03$). However, the difference was not significant in the RRD cases in the subgroup analysis with a pooled OR of 0.86 (95% CI: 0.52, 1.44; $P = 0.58$). No significant heterogeneity was found ($I^2 = 29\%$) (Figure 7).

4. Discussion

To the best of our knowledge, this is the first meta-analysis to assess the effectiveness and safety of 27-G MIVS compared with 25-G MIVS for vitreoretinal disease, although only data on the treatment of ERM and RRD were available.

The pooled result illustrated that the time for performing 27-G vitrectomy was longer than that for 25-G vitrectomy. The difference between the two groups was attributed to the different internal diameters of the vitrectomy probe of the two surgery systems used. Some studies concluded that when comparing 27-G, 25-G, 23-G, and 20-G vitrectomy, more time is required for vitreous excision as the instrument gauge decreases [9, 12]. However, other studies reported the difference in operation time primarily due to the substantially lower infusion and aspiration rate of the 27-G vitrectomy system used in the present studies but not distinct instrument gauges [14, 15]. The difference of operation time was significant in the ERM subgroup, but not in the RRD subgroup, which can be explained by three reasons. First, in the RRD surgery, peripheral vitrectomy was more strenuous and complicated than in ERM surgery, and as a result, the operation time mostly depends on the proficiency of surgeon rather than the instrument gauges. Second, Veritti et al. [26] reported that the 27-G probe has excellent fluidics procedures and high cut rate (7500 cpm) and it is very effective in shaving peripheral vitreous for RRD cases, so the operation time was not prolonged by smaller gauge in 27-G group. Third, although the qualities of included studies were

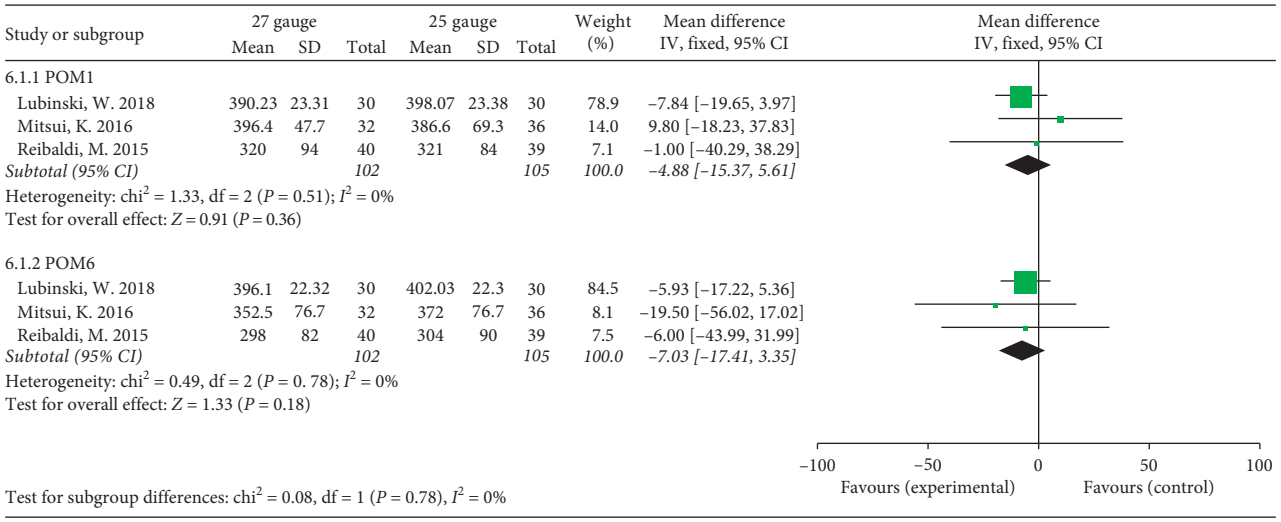

Figure 6: Forest plots of central macular thickness (CMT) at one month and six months postoperatively compared between 27-G and 25-G vitrectomy for epiretinal membrane (ERM) cases.

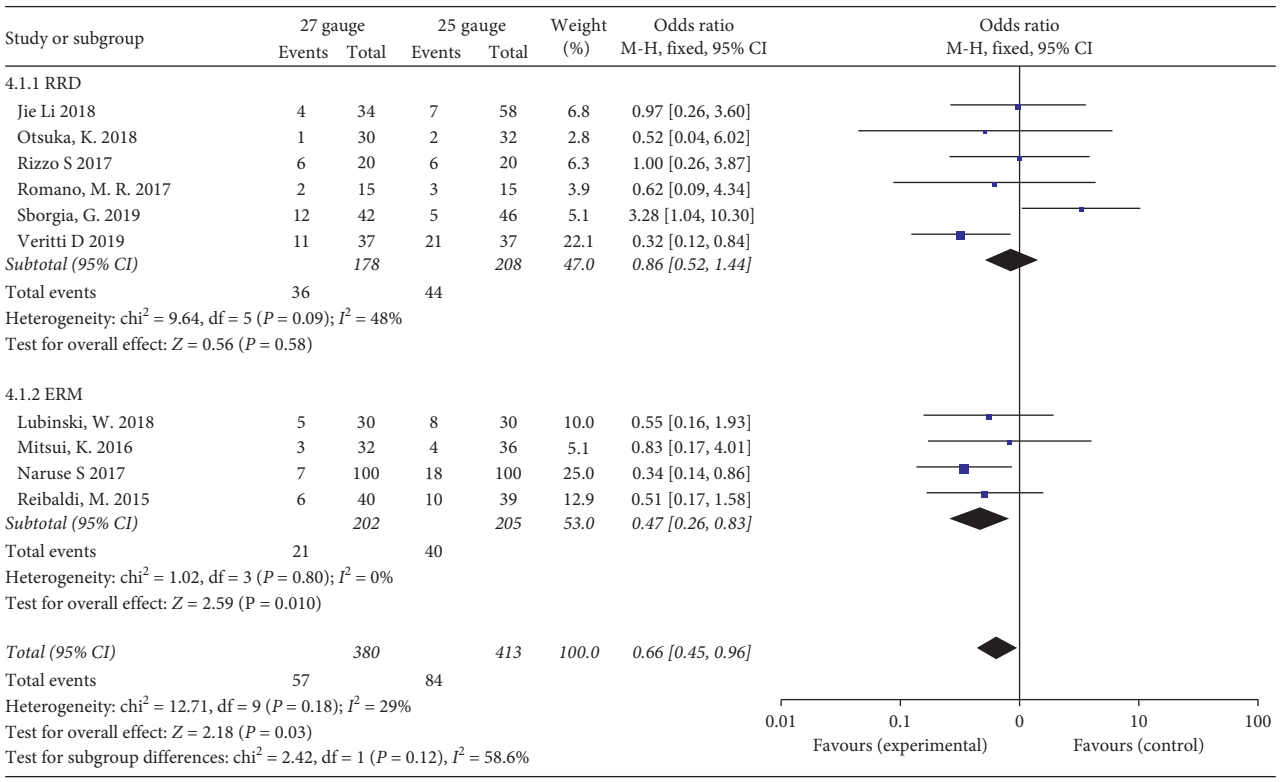

Figure 7: Forest plots of intraoperative and postoperative complication between 27-G and 25-G vitrectomy in overall and subgroup analysis. RRD: rhegmatogenous retinal detachment; ERM: epiretinal membrane.

adequate and the sensitive analysis minimized the heterogeneity as much as possible, the heterogeneity in the ERM subgroup may influence the final result.

Regarding the relationship between gauge of instrument and postoperative BCVA, our study showed that BCVA was significantly better in the 27-G group at six months after vitrectomy compared with the 25-G groups. It is hard to explain the reason for this difference. With small gauge vitrectomy, significant inflammation and astigmatism is rarely seen at six months after the operation. For the treatment of RRD, early visual recovery is limited by the using of gas or silicone oil. However, most of the silicone oil was removed before six months after surgery. Also, there were no difference in CMT during followup, so postoperative macular edema should not play a role in visual recovery.

Postoperative IOP at POD1 in 27-G group were as stable as 25-G group. Postoperative hypotony induced by leakage

of sutureless wound still remains a major complication that can lead to underfilling of tamponade, choroidal detachment, and endophthalmitis. However, Takashina et al. [17] reported that hypotony is usually transient and, in most cases, resolved spontaneously due to small gauge in 27-G vitrectomy. Furthermore, it was suggested that surgeons use oblique incisions and displacement of the conjunctiva to reduce wound leakage and stabilize postoperative IOP.

Operation effectiveness is one of the major theoretical concerns regarding 27-G instrument. Romano et al. [23] reported that the lower flow rate of 27-G system may influence the operation effectiveness. However, Veritti et al. [26] reported that dual pneumatically operated vitrectomy probes of 27G system with ultrahigh cut rates (7500 cpm) can maintain an efficient vitreous flow rate. For RRD cases, the primary anatomical success rate of included studies ranged from 89% to 97% using 27-G and 85% to 96% using 25-G MIVS and did not differ significantly between two groups. For ERM cases, there were no differences in postoperative CMT between 27-G and 25-G groups during the six-month follow-up period. This relationship suggests that 1 mm diameter reduction of sclerotomy in 27-G MIVS, as compared with 25-G MIVS, has no influence on the recovery of normal retinal structure in the vitreoretinal surgery and the 27-G was as effective as the 25-G system.

Speaking of the safety of the 27-G vitrectomy system, besides being less invasive when compared with 25-G system, 27-G carries additional potential advantages; the shorter but flexible vitrectomy probe generates the shortest attraction distance and a smaller "sphere of influence." This allows a more accurate fluid control and a greater dissection precision, theoretically allowing for safer procedures with less intro- and postoperative complications compared with 25-G system [26].

The first point of strength in this meta-analysis was that the measurement of outcomes was fairly consistent and pooled results should not be biased due to misclassification. The second point of strength was that the likelihood of bias was minimized by performing a meticulous search for published studies and using explicit methods for study selection, data extraction, quality assessment, and statistical analysis. Third, subgroup and sensitivity analyses were used to confirm the reliability of the pooled results.

This meta-analysis has several potential limitations that should be taken into account. First, the main limitation of this review is the small number of RCTs. Second, we cannot fully exclude publication bias. Third, our analysis was based on only 11 trials, and most of them have a small sample size, which can affect the interpretation of the results. Fourth, some results were limited by heterogeneity between the involved trials.

5. Conclusions

In conclusion, our data demonstrated that although 27-G vitrectomy need longer operation time, it had obvious advantages in reducing complications compared with 25-G system for the treatment of ERM. However, these features were not obvious for the treatment of RRD cases. Multicenter controlled trials should be conducted to determine the overall long-time benefits of 27-G vitrectomy for the treatment of all kinds of vitreoretinal disease.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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Research Article

Outcomes of Idiopathic Full-Thickness Macular Hole Surgery: Comparing Two Different ILM Peeling Sizes

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Purpose. This study aimed to show the impact of different extents of internal limiting membrane (ILM) peeling on visual and anatomical outcomes following idiopathic full-thickness macular hole (FTMH) surgery. *Methods*. In this single-center prospective study, patients with idiopathic FTMH underwent standard pars plana vitrectomy with two different extents of ILM peeling: 2-disc diameters (DD) or 4 DD. The main outcome measures were the closure rate of the holes based on optical coherence tomography (OCT) findings at three months after surgery. *Results*. Forty eyes from 39 patients were enrolled in the study. After three months, anatomical closure was achieved in 78% and 76% eyes in 2 DD peel and 4 DD peel groups, respectively. From 29 eyes with macular hole index (MHI) ≤ 0.5, type 1 closure was achieved in 42% eyes receiving a 2 DD ILM peel, compared to 66% eyes receiving a 4 DD peel ($p = 0.041$). In comparison, this significant difference was not seen in the subgroup of MHI > 0.5 ($p = 061$). In the subgroup of subjects with baseline MHI ≤ 0.5, visual improvement was significantly more in eyes with 4 DD ILM peeling ($p = 0.034$), which was not seen in the MHI > 0.5 subgroup ($p = 0.61$). *Conclusion*. In patients with idiopathic full-thickness macular hole (MHI ≤ 0.5), a larger ILM peel of 4 DD appears to yield better anatomical outcomes than a more limited 2 DD peel.

1. Background

An idiopathic FTMH is a foveal defect, which is responsible for central vision loss [1]. When left untreated, it often leads to severe central vision loss to the levels of 20/200 or worse [2]. By the introduction of the modern vitrectomy, FTMH has now become a surgically treatable disease [3]. Over the past decade, several surgical technique modifications have been introduced [4].

A surgical approach for the management of idiopathic macular hole (MH) is pars plana vitrectomy (PPV) and a combination of adjuvant techniques, including internal limiting membrane (ILM) peeling, gas tamponade, and postoperative prone posturing [5].

Although there has been controversy over the role of the ILM peeling in surgical success in the past, ILM peeling has been proven to ameliorate anatomical and functional success rates, especially in holes with a diameter larger than 300 microns [5–8]. ILM peeling has been simplified by using different dyes such as brilliant blue-green (BBG) [9]. It has been shown that BBG assisted ILM peeling could contribute to better visual acuity outcomes than other dyes in patients with FTMH [8, 10].

Although ILM itself has no contractile characteristics, the myofibroblastic cells use this membrane as a scaffold to differentiate into contractile tissues [11]. ILM peeling reduces the tangential forces by these tissues on the fovea. Also, it decreases the chance of macular hole reopening by removing this scaffold for postoperative retinal surface glial cell proliferation [2, 5, 10]. Some surgeons reserve this maneuver to treat large FTMH while others use it routinely in all cases [12].

Although ILM peeling as a part of surgical treatment for FTMH has become widely accepted, there is no consensus about the optimal size of ILM peeling [13]. The impact of different extents of ILM peeling on anatomic and functional

outcomes of FTMH surgery is not clear [12]. Different investigators have described different extents of the peels, from measuring only a disk diameter centered on the fovea to extended peels about four-disc diameter (about 6.5 mm) to the vascular arcades [14, 15].

Significant improvement of postmacular hole surgery metamorphopsia has been reported with a larger extent of ILM peelings. Nevertheless, some complications such as macular thinning and retinal nerve fiber layer (RNFL) injury may be more prevalent [13, 16, 17].

This study aimed to show the impact of different peeling sizes on closure rate, visual outcomes, and anatomical restoration of outer retina layers following FTMH surgery.

2. Methods

This is a single-center prospective study of patients who were diagnosed with idiopathic FTMH at Farabi eye hospital and were enrolled between July 2017 and October 2019. All the patients underwent standard pars plana vitrectomy (PPV) with ILM peeling to have their macular holes treated. All the patients provided written informed consent, and the study was performed with the approval of the Institutional Review Board and ethics committee of Tehran University of Medical Science and complied with the guidelines of the Declaration of Helsinki.

We excluded eyes with a traumatic FTMH, or high myopia-associated MH (defined as eyes with a myopic refractive error of greater than 6.00 diopters), a retinal detachment-associated FTMH, and long-standing macular holes (defined as a duration of 6 months or more based on previous OCT or patient's symptoms). Patients with other causes of decreased vision (e.g., uveitis, glaucoma, corneal opacity, age-related macular degeneration, and diabetic retinopathy), history of any intraocular surgery other than uncomplicated cataract surgery, and eyes with poor image quality were also excluded.

Before standard pars plana vitrectomy, eligible patients were randomly allocated 1 : 1 ratio to either group 2 DD or 4 DD:

(1) 2 DD peel group included the eyes undergoing ILM peeling with a radius of one-optic-disc diameter (approx. 3.6 mm)

(2) 4 DD peel group included the eyes undergoing ILM peeling with a radius of two-optic-disc diameter (approx. 7.2 mm)

Baseline demographic data including gender, age, and lens status were recorded for each subject.

All the enrolled patients underwent a complete preoperative baseline evaluation, followed up 3 months after surgery, including examination for best-corrected visual acuity (BCVA), slit-lamp examination, Goldmann applanation tonometry, dilated fundus examination, and horizontal OCT scans through the fovea with spectral-domain OCT (SD_OCT) (Spectralis HRA-OCT, Heidelberg Engineering, Heidelberg, Germany).

All clinical personnel were masked as to which patients were in the 2DD or 4DD groups.

2.1. FTMH Measurements. An experienced technician performed all OCT scans. The minimum diameters of FTMH (minimum linear dimension of FTMH) and MHI were measured (defined as the ratio of the hole height to the basal hole diameter: length of the retinal pigment epithelium (RPE) not in contact with the photoreceptors) (Figure 1).

According to previous studies, the holes were divided into more or less than 400 microns based on the minimum diameter of FTMH, and all the holes were divided into smaller or larger than 0.5 based on MHI [18, 19].

All the measurements were done by using the built-in caliper of Spectralis mapping software, Heidelberg Eye Explorer (version 6.0c). After the surgery, the anatomical status of the macular holes was classified into 3 categories based on SD-OCT appearance [20]:

(1) Macular hole closure type 1: FTMH is closed without bare RPE.

(2) Macular hole closure type 2: foveal defect persists after operation, although the hole rim is attached to the RPE.

(3) Open: the foveal defect persists after operation, and the edges of the hole also remain detached from the beneath RPE.

Ellipsoid zone (EZ) status was also categorized into three groups: complete resolution, interrupted (incomplete resolution), and not improved.

Two masked vitreoretinal specialists did all the measurements, and a third masked specialist made a final decision if disagreement existed.

2.2. Surgical Procedure. A standard 3-port 23-gauge, sutureless, pars plana vitrectomy, and gas tamponade were performed for all patients by a single surgeon (A.K). After core vitrectomy, triamcinolone assisted posterior vitreous detachment was done. Then, patients had the BBG assisted ILM peeling with a peeling diameter of 2 DD (radios of 1 DD) or 4 DD (radios of 2DD) with ILM forceps, according to the surgeon's perception, respectively. Following the complete air-fluid exchange, tamponade was done by sulfur hexafluoride (SF6 20%) in all patients, who were instructed to face-down position for at least 3-4 days following surgery.

The patients with significant cataract enough to preclude the ILM peeling would receive combined phacoemulsification with intraocular lens implantation and PPV. For patients with persisting macular hole after PPV, they were advised to undergo a second surgery with a more extended ILM peeling. Nd : YAG laser treatment was done for the eyes developing visually significant posterior capsular opacification.

The primary outcome was the proportion of eyes with complete closure of the holes based on OCT findings within each group at three months after operation. The secondary outcome measure consisted of the BCVA and anatomical outcomes difference between two groups, along with the difference between the BCVA and anatomical outcomes in

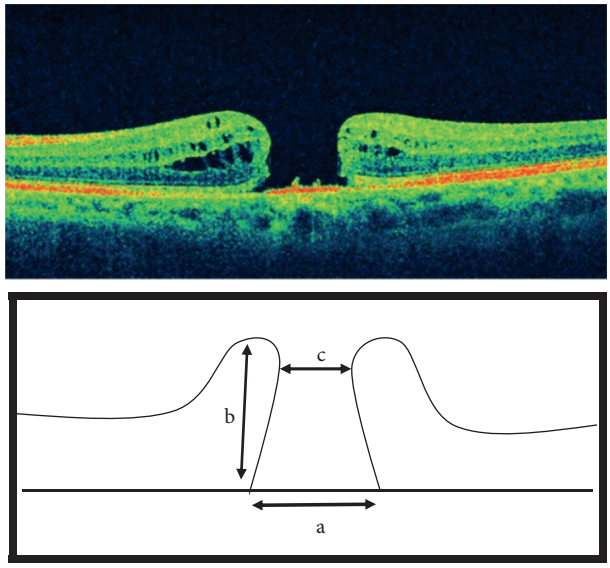

Figure 1: The macular hole index (MHI) [18]. Top: optical coherence tomography (OCT) cross-sectional image of a macular hole. Bottom: diagram showing the base diameter of the hole (a), hole height (b), and minimum diameter of the hole (c), as measured by OCT. The MHI is defined as b/a.

subgroups when subjects were stratified by baseline macular hole minimum diameter and MHI.

2.3. Statistical Analysis. Continuous variables were expressed as mean (±standard deviation), and categorical variables were expressed as percentages.

Chi-square test/Fisher's exact test was used to assess the association between categorical variables. Independent *t*-test/Mann–Whitney *U* test was used to discover the significant difference of continuous variables between the two study groups.

A Chi-square test was applied to compare the structural outcomes between the groups based on OCT findings. The independent sampled *t*-test was used to analyze the postoperative visual outcomes between the groups. Fisher's exact tests were also utilized in subgroup analysis divided by the cut-off value of MHI or macular hole diameter to compare the anatomical outcomes between the two groups. Logistic regression was used for multivariable analysis.

All analyses were conducted using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered statistically significant.

3. Results

Forty-four eyes from 43 patients were enrolled in this study. From the 44 eyes, four eyes from 4 patients were excluded due to low image quality or failure to follow-up before finishing the three months after surgery. Forty eyes of 39 patients were randomized into either the 2 DD ($n = 19$, 47%) or 4 DD ($n = 21$, 52%) ILM peeling group.

The mean preoperative minimum macular hole diameters in 2 DD peel group and 4 DD peel group were $466.97 \pm 161.88\,\mu$m and $522.90 \pm 126.61\,\mu$m, respectively ($p = 0.23$). The mean base diameters in 2 DD peel group and 4 DD peel group were $1048.11 \pm 220.58\,\mu$m and $975.33 \pm 254.56\,\mu$m, respectively ($p = 0.28$). The macular hole index (MHI) was not significantly different between the groups ($p = 0.43$). The mean BCVA in groups 2 DD and 4 DD were 0.97 ± 0.37 and 0.99 ± 0.20, respectively, based on log MAR ($p = 0.12$) (Table 1).

Among the eyes undergoing surgery, 30 eyes were phakic (75%) and 10 were pseudophakic (25%). There was no significant difference in the number of pseudophakic or phakic eyes in each group. Cataract surgery with intraocular lens implantation was done just before vitrectomy in one session in all phakic eyes. Combination surgery did not reveal a significant influence on macular hole closure ($p = 0.47$). Posterior vitreous detachment (PVD) was present in 10 eyes (25%) before surgery, while PVD was induced during surgery in the remaining eyes.

Anatomical closure was achieved in 78% ($n = 15/19$) and 76% ($n = 16/21$) eyes in 2 DD peel group and 4 DD peel group, respectively (−2.3% difference, 95% confidence interval (CI) : −9.2%–4.6%; $p = 0.83$). The closure type 1 was 52% ($n = 10/19$) in 2 DD peel group versus 76% ($n = 16/21$) in 4 DD peel group. Type 1 closure was achieved significantly more in 4 DD peel group (23.6% difference; 95% CI : 13.9%–33.3%; $p = 0.041$). Overall, MH in 9 cases were not closed (anatomic failure) after the first surgery, and a second surgery was recommended for them.

Logistic regression analysis revealed that the ILM peeling size independently from other covariate had a significant effect (odds ratio (OR) = 2.74; 95% CI : 1.07–6.99; $p = 0.035$) on the type 1 MH closure rate.

In macular holes with minimum linear dimension equal to or greater than 400 microns, closure type 1 occurred in 6/13 (46%) of the eyes with 2 DD peeling size, in contrast to 13/17 (76%) eyes with 4 DD peeling size. This difference was statistically significant (30.3% difference; 95% CI : 21.9%–38.7%; $p = 0.031$). In macular holes with a minimum linear dimension less than 400 microns, all holes were closed successfully after surgery in both groups, and the rate of closure type 1 was not different significantly between these two groups 4/6 in 2 DD peel group versus 3/4 in 4 DD peel group (8.4% difference; 95% CI : 4.2%–12.6%; $p = 0.42$) (Table 2).

Based on the previous studies, an MHI cut-off value of 0.5 was chosen to evaluate the closure rate for clinical application in each peeling group. The comparison analysis between the two groups was done on the subgroups of subjects with MHI values below and above the 0.5 cut point.

After three months, based on Fisher's exact test, from 29 eyes with MHI ≤ 0.5, type 1 closure was achieved in 6/14 eyes (42%) receiving a 2 DD ILM peel, compared to 10/15 eyes (66%) receiving a 4 DD peel (23.8% difference; 95% CI : 17.3%–30.3%; $p = 0.041$). In contrast, in the subgroup of patients with MHI more than 0.5, type 1 closure was achieved in 4/5 eyes (80%) in the 2 DD group versus 6/6 (100%) in the 4 DD group ($p = 0.61$) (Table 3).

Table 1: The baseline characteristics of the two groups.

	Group A (2 DD peel group)	Group B (4 DD peel group)
Number	19	21
Male: female	10 : 09	12 : 09
Mean age	64.6 ± 6.7	67 ± 8.4
Mean minimum diameter	466.97 ± 161.88 μm	522.90 ± 126.61 μm
Mean base diameter	1048.11 ± 220.58 μm	975.33 ± 254.56 μm
Mean macular hole index (MHI)	0.36	0.4
Mean basal visual acuity	0.97 ± 0.37	0.99 ± 0.20

Table 2: Anatomical outcome different between groups after 3 months following stratification by macular hole diameter.

	MH ≥ 400			MH < 400		
	2 DD ($n = 13$)	4 DD ($n = 17$)	p value*	2 DD ($n = 6$)	4 DD ($n = 4$)	p value*
Type 1 closure	6 (46%)	13 (76%)	0.031	4	3	0.42
Type 2 closure	3 (23%)	0	N/A	2	0	N/A
Open	4 (30%)	4 (23%)	0.89	0	1 (25%)	N/A

*Fisher exact test.

Table 3: Anatomical outcome different between groups after 3 months following stratification by macular hole index.

	MHI ≤ 0.5			MHI > 0.5		
	2 DD ($n = 14$)	4 DD ($n = 15$)	p value*	2 DD ($n = 5$)	4 DD ($n = 6$)	p value*
Type 1 closure	6 (42%)	10 (66%)	0.041	4	6	0.61
Type 2 closure	6 (42%)	0	N/A	1	0	N/A
Open	4 (28%)	5 (33%)	0.82	0	0	N/A

*Fisher exact test.

The status of twenty-one eyes showed an interrupted EZ 3 months after the surgery while 13 eyes revealed no EZ after 3 months in the central fovea. From 6 eyes with complete postoperative EZ, 5/19 (26%) eyes were in 2 DD peel group, and 1/21 (4%) eye was in 4 DD peel group ($p = 0.028$). Nevertheless, the eyes with no central EZ were significantly more in 2 DD peel group [8/19 (42%) eyes in 2 DD peel group vs. 5/21 (23%) eyes in 4 DD peel group ($p = 0.032$)].

Preoperative mean logMAR BCVA was 0.98 ± 0.35, which was significantly improved to 0.61 ± 0.46 logMAR 3 months after surgery ($p = 0.0012$). The mean BCVA improvement showed no difference in month 3 between the two groups (0.361 logMAR vs. 0.381 logMAR, 0.02 difference; 95% CI : 0.007–0.033; $p = 0.904$). BCVA improvement was significantly higher in FTMH with a minimum diameter of fewer than 400 microns than larger holes (0.54 logMAR vs. 0.30 log MAR, 0.24 difference; 95% CI : 0.13–0.35; $p = 0.02$) (Table 4).

Although BCVA improvement was higher across the 4 DD peel group (0.36 logMAR) than in 2 DD peel group (0.25 logMAR) among eyes with a minimum diameter equal to or greater than 400 microns, this difference was not significant (0.11 difference; 95% CI, 0.03–0.19; $p = 0.59$).

BCVA improvement was significantly correlated with macular hole postoperative anatomical status as with closure type 1 ($p = 0.0091$) and EZ status ($p = 0.021$). Eyes with no improvement in EZ status had significantly worse BCVA than eyes with complete or interrupted EZ ($p = 0.023$ and 0.012).

Three months after surgery, in the subgroup of subjects with baseline MHI ≤ 0.5, there was a significant difference between the two ILM peeling groups based on the BCVA : 2 DD group (0.82 ± 0.21), 4 DD group (0.53 ± 0.27) (−0.29 difference; 95% CI : −0.41–−0.17; $p = 0.034$) ($p = 0.034$) although, in the MHI > 0.5 subgroup, BCVA revealed no significant difference between the two ILM peeling groups (−0.11 difference; 95% CI : −0.21–0.01; ($p = 0.61$) (Table 5).

4. Discussion

Based on this interventional case series on patients with FTMH, although macular hole closure (type 1 + type 2) was not significantly different between 2 DD and 4 DD peeling groups, type 1 closure was found significantly more in 4 DD peel group. In macular holes with a minimum linear dimension equal to or greater than 400 microns or with MHI ≤ 0.5, type 1 macular hole closure occurred significantly more in the 4 DD peeling group. This difference was not observed in the eyes with macular holes with a minimum linear dimension smaller than 400 or MHI greater than 0.5.

Glial and myofibroblastic cells use ILM as a scaffold for proliferation and differentiation into contractile tissues, which is thought to be essential in the pathogenesis of MH formation [21]. Therefore, ILM peeling is responsible for neutralizing these tangential traction forces and for increasing retinal compliance, allowing the retina to move more freely to assist MH closure [6]. Lois et al [14]. found that extended and more complete ILM peeling could

Table 4: Functional outcome in the two groups after 3 months following stratification by macular hole diameter.

	Total	MH ≥ 400			MH < 400		
		2DD ($N = 13$)	4DD ($n = 17$)	p value*	2DD ($n = 6$)	4DD ($n = 4$)	p value*
Baseline	0.98 ± 0.35	1.01 ± 0.26	1.02 ± 0.31		0.93 ± 0.17	0.97 ± 0.21	
3 Months after surgery	0.61 ± 0.46	0.76 ± 0.31	0.65 ± 0.21	0.59	0.39 ± 0.28	0.42 ± 0.17	0.89

*independent sampled t-test: visual acuity improvement after 3 months.

Table 5: Functional outcome in the two groups after 3 months following stratification by macular hole index.

	Total	MHI ≤ 0.5			MHI > 0.5		
		2 DD ($N = 14$)	4 DD ($N = 15$)	p value*	2 DD ($n = 5$)	4 DD ($N = 6$)	p value*
Baseline	0.98 ± 0.35	1.07 ± 0.32	1.04 ± 0.31		0.901 ± 0.2 7	0.96 ± 0.30	
3 months after surgery	0.61 ± 0.46	0.82 ± 0.21	0.53 ± 0.27	0.034	0.351 ± 0.41	0.43 ± 0.21	0.61

*Independent sampled t-test: visual acuity improvement after 3 months.

enhance the chance of MH closure. It has been shown that extended ILM peeling in a second surgery for patients with unsuccessful previous macular hole surgery leads to success in FTMH closure and visual acuity improvement [22, 23]. Yek et al. concluded that visual acuity gain after two years was significantly higher in eyes undergoing secondary surgery with extended ILM peeling after the first surgery failure than the eyes that were followed without any secondary intervention [23].

Anatomical closure was achieved in 78.5% and 76.2% eyes in 2 DD peel group and 4 DD peel group, respectively. Our success rate was lower than the previous studies; it maybe due to our mean macular hole diameter that was very large or smaller sample size compared to other studies. Indeed, we have studied on large macular holes. The mean preoperative minimum macular hole diameters in 2 DD peel group and 4 DD peel group were 466.97 ± 161.88 μm and 522.90 ± 126.61 μm, respectively. The mean preoperative minimum macular hole diameter in both groups was 494.93 ± 143.28.

We observed that type 1 closure as a closing without foveal defect of the neurosensory retina was achieved significantly more in the extended peel group. It is presumed that the residual ILM with a membrane on its surface may act as a traction force that pulls the retina toward itself. Therefore, in cases with 4 DD ILM peeling, the ridge of the remnant ILM is more distant from the margins of the macular hole, and these tractional forces have less effect on the macular hole status, thereby improving reconstruction. This phenomenon may be more prominent in larger macular holes with lower MHI [16, 24, 25].

However, regarding the role of ILM in retinal function as a footplate of Müller cells and the mechanical damage to retina layers during the procedure of ILM peeling itself, some concerns have been raised about potential adverse effects, particularly in case of extended peeling due to degenerative thinning of the bare retina over time [26]. Some studies found that the retina became thinner after vitrectomy with extended ILM peeling for large MH, which might be associated with the migration of paramacular tissue [16, 27].

Inner retinal defects frequently occurred once the ILM was peeled, and it was composed of dark spots in the same orientation as the optic nerve fibers [28]. Nerve fiber layer disruption was also reported after ILM peeling based on OCT findings [29]. Furthermore, the dysfunction of Müller cells has been documented by delay in the recovery of the focal macular electroretinograms b-wave after removing the ILM in the macular area [30]. The retinal sensitivity may be reduced after extended ILM peeling, notably increasing the incidence of microscotomas [31]. Larger ILM peeling may be accompanied by more interventions to pinch and grasp the ILM; it could be confirmed with more pit like inner retinal defects coursing along the nerve fiber layer using SD-OCT. Furthermore, these dimples may be enlarged in the postoperative period [32].

In this study, the postoperative BCVA improved significantly at each visit, 3 months after surgery. BCVA improvement was significantly correlated with macular hole postoperative anatomical status, such as closure type 1 and EZ status.

Steel et al [33]. observed that the larger ILM peel size associated with the shortening of the distance between fovea and disc, shortening of the macular area, and the optic nerve fiber layer dissociation. This may lead to lower postoperative visual acuity than the surgeon's expectation. Considering these observations, the authors suggested limiting the ILM peeling size.

We also observed that the complete EZ line restoration was significantly higher in the 2 DD peel group than in the 4 DD group, which may be due to less anatomical changes and macular thinning. Although the visual improvement was not different significantly between the groups as the presence of EZ was higher in 4 DD peel group, the complete EZ line was significantly higher in the 2 DD peel group.

The present study observed that in the holes with MHI less than 0.5, visual improvement was significantly higher in the 4 DD peel group, which was accompanied by more type 1 closures. It seemed that the final visual acuity in the holes with MHI < 0.5 was correlated with the proper anatomical closure type, which might be achieved with extended peeling size.

This would appear to highlight that baseline MHI is a more accurate index for the decision on ILM peeling size than MH size itself. Kusuhara et al. [18] suggested the MHI

as a more powerful predictor for visual outcome following MH surgery than the macular hole diameter. In several studies, a positive association was found between MHI and postoperative visual acuity [19, 34–36].

Thus, achieving type 1 closure of MH should be a prerequisite when considering the extent of the ILM peeling. In this regard, the present study showed that the 4 DD group achieved more encouraging structural results in a subgroup of patients with MHI less than 0.5.

In a published article, multiple regression analyses showed a correlation between structural outcomes and the diameter of the MH as well as the extent of the peeling area [37]. However, this study was retrospective with a small sample. In another study, Modi et al. [38] demonstrated that there was no relationship between the ILM peeling size and type 1 closure of MHs, regardless of its size, staging, or duration. Although Modi's study was a prospective trial, some factors may be responsible for these differences between their project and the current study. First, the difference in the extent of the ILM peeling (3 mm diameter and 5 mm diameter ILM peels) may have been too small to yield a difference in closure rates. Secondly, the subgroup analysis was based on MH size and MH stage rather than MHI. As we showed earlier, MHI was a more powerful predictor for macular hole closure.

Bae et al. [16] indicated that enlarging the size of ILM peeling is beneficial to improve postoperative metamorphopsia. Based on a prospective study by Yao et al, in comparison with 2 DD ILM peeling, 4 DD ILM peeling could lead to better structural outcomes in eyes with macular hole closure index(MHCI) or hole form factor [13]. In contrast to our study, they used HFF instead of MHI. The HFF is calculated by the summation of the EZ lengths in each side of the macular hole divided by the basal hole diameter. The HFF is suggested to be positively correlated with the postoperative visual acuity. Still, this correlation is weaker than that for the basal hole diameter and minimum diameter of the macular hole [39, 40]. In this study, in contrast to our study, macular holes with a history of more than one year differed between the two groups, which might affect the study results. Another advantage of the current study in contrast to their study was that all the operations were done by a single surgeon.

There are several limitations to the current study. First, the analysis was based on three months of follow-up data, and thus our results may not reflect the long-term MH surgery results. Secondly, the present study was a single-center study with low sample size. Of the above limitations, the relatively small sample size is the most critical shortcoming of this study. Thus, a multicenter trial with a larger sample size should be considered to reevaluate our results and to reach a more exhaustive conclusion. Finally, MHI had to be manually calculated by one trained grader, and there was no automated software for calculation.

5. Conclusion

In conclusion, our results suggested that 4 DD ILM peeling for MHs with MHI ≤ 0.5 can reach better structural and visual outcomes in macular hole surgery. On the other hand, for the MHs with MHI > 0.5, limited ILM peeling may be adequate to achieve satisfactory anatomical and functional outcomes. Therefore, careful, individualized assessment of preoperative MH anatomy based on OCT is necessary to optimize surgical arrangements.

Data Availability

The derived data supporting the findings of this study are available from the corresponding author on request.

Ethical Approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

Informed consent was taken from all individual participants.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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