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Structural and functional outcomes of pars plana vitrectomy in patients with lamellar macular hole

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Abstract:

PURPOSE: To investigate the short-term functional and microstructural outcomes of pars plana vitrectomy (PPV) without gas tamponade in lamellar macular holes (LH).

MATERIALS AND METHODS: In this prospective case series, LH cases diagnosed by optical coherence tomography (OCT) underwent PPV with epiretinal membrane (ERM) removal and internal limiting membrane peeling without gas tamponade. All patients underwent a complete ophthalmologic examination, including best-corrected visual acuity (BCVA) and OCT imaging preoperatively and 3 months after the surgery.

RESULTS: Among 22 eyes, 10 degenerative (Deg) LH, 8 tractional (Trac) LH, and 4 mixed-type LH were assessed. After the surgery, anatomical closure occurred in 20 eyes (91%) without any significant difference between LH subgroups. Comparing preoperative and postoperative values, no significant changes were detected regarding BCVA neither totally ($P = 0.5$) nor in subgroups (P for Deg = 1.0, Trac = 0.71, Mix = 0.18). The overall central foveal thickness was increased significantly after surgery ($P < 0.01$), but in subgroup analysis, the increase was significant only for Trac LH ($P = 0.02$). The tractional LH eyes had less ellipsoid zone (EZ) disruptions compared to Deg or mixed subgroups before surgery. There were no changes in EZ integrity before and after the surgery. In regression analysis, no correlation was found between demographic or clinical characteristics and anatomical closure or BCVA improvement postoperatively.

CONCLUSION: PPV resulted in 91% anatomical closure of all cases of LH but without functional improvement in short-term. Further prospective clinical trials with larger sample size and longer follow-up would be required to confirm the clinical significance of these findings.

Keywords:

Epiretinal membrane, macular hole, vitrectomy

Introduction

Lamellar macular hole (LH) is a partial-thickness foveal defect which occurs by interruption of the typical macular hole formation process or by unroofing of the central fovea in chronic cystoid macular edema (CME).^[1] The LH entity was not completely understood until recently with the widespread use of optical coherence tomography (OCT).^[2] Witkin

et al. defined diagnostic criteria for LH with ultrahigh-resolution OCT, which is described as a defect with an irregular foveal contour with dehiscence of the inner from the outer layers in the fovea, with intact photoreceptor layer.^[1] In most cases, intraretinal cystoid spaces and epiretinal membranes (ERMs) are present.^[1] Clinical conditions which might lead to the formation of LH can be tangential traction by contraction of ERM, anterior-posterior or oblique traction during the processes of vitreomacular separation, and unroofing of chronic CME.^[3,4] Although

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the natural prognosis of idiopathic LH is usually good, some patients exhibit a visual acuity decrease which might need surgical treatment.^[5] The treatment choice for a full-thickness macular hole (FTMH) is pars plana vitrectomy (PPV), usually accompanied by the internal limiting membrane (ILM) peeling with gas tamponade.^[6] However, surgical treatment for LH is still controversial.^[7]

Recently, LH is categorized by underlying pathophysiology into degenerative, tractional, and mixed subgroups and each subgroup may have its specific course and management.^[7,8] As limited studies on the surgical outcomes based on LH subgroup have been reported in the literature, the purpose of this study is to investigate the anatomical and visual outcomes in patients with degenerative, tractional, and mixed LH who underwent PPV with ILM peeling.

Methods

Subjects

In this prospective case series, patients with LH diagnosed by OCT in Farabi Eye Hospital, Tehran, Iran from January 2018 to April 2020 were enrolled. Patients with visual acuity ≤ 0.4 were included and the exclusion criteria were: patients with eye disease other than cataracts and ERM, including macular disease, pathologic myopia (>8 diopters), optic atrophy, glaucoma, history of any prior intraocular surgery, except for cataract extraction. Patients with advanced cataracts, which do not allow for proper visualization of the posterior pole or proper OCT acquisition, were also excluded.

Twenty-five eyes from 25 patients were enrolled. All 25 eyes underwent preoperative standard clinical examination, including best-corrected visual acuity (BCVA) and complete ophthalmic examination. Visual acuity was measured on the Snellen chart and converted into a logarithm of the minimum angle of resolution (logMAR) value.

Optical coherence tomography imaging

OCT imaging was obtained by SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) and diagnosis of LH was made based on the criteria defined by Witkin *et al.*^[1], which includes (1) breaks in the inner layer of the fovea, (2) irregular foveal contour and thinning and (3) intraretinal splitting. However, in contrast to Witkin *et al.* criteria, in this study, we supposed that foveal photoreceptors might be intact or disrupted. LH cases were then categorized by OCT into degenerative (Deg), tractional (Trac), and mixed subgroups in accordance with the classification by Govetto *et al.*^[8] and Obata *et al.*^[9] Cases with round-edged intraretinal cavitation, presence of lamellar hole epiretinal proliferation (LHEP) as a

homogeneous material with intermediate reflectivity that conforms to the epiretinal surface at the margins of the lamellar hole, or a central retinal bump were classified as “Deg” subgroup [Figure 1a] while LHs with schitic sharp-edged intraretinal split, presence of tractional ERMs, and intraretinal cystoid spaces were classified as “Trac” subgroup [Figure 1c]. Intact or disrupted ellipsoid zone (EZ) was not considered as a discriminative marker between Deg and Trac subgroups in this study. If LH was not matched with either subgroup, it was labeled as “mixed” subgroup.

Maximum lamellar defect diameter, central foveal thickness (CFT), outer nuclear layer (ONL) thickness at 500 μm nasal and temporal to the foveal center, and integrity of EZ were evaluated. Foveal thickness was measured manually at the largest hole diameter of the lamellar defect. Thickness was measured in the central fovea from the surface of the hole to the sensory retinal pigment epithelium interface using a caliper feature on SD-OCT horizontal raster scans and vertical foveal scans. An intact EZ was defined as a continuous hyper-reflective line, whereas a loss or irregularity of the hyper-reflective line constituted a disrupted EZ.

Surgical technique

Patients underwent PPV without tamponade by an expert vitreoretinal surgeon (A.K.). The surgical

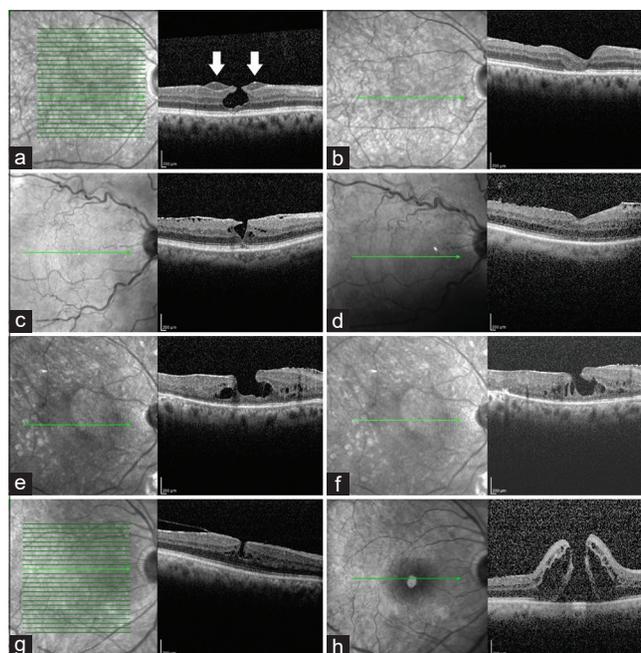


Figure 1: Preoperative and postoperative (3 months) optical coherence tomographic images of lamellar holes after pars plana vitrectomy without tamponade. (a and b) Closed degenerative LH; lamellar hole epiretinal proliferation was present as a homogeneous material with intermediate reflectivity pointed by arrow. (c and d) Closed tractional LH. (e and f) A degenerative LH that was not closed 3 months after the surgery. (g and h) A tractional macular hole that was converted into the full-thickness macular hole 3 months after the surgery

protocol was the same for all 25 patients. Six eyes underwent PPV plus phacoemulsification (due to significant cataract) and the rest of the eyes underwent PPV alone.

A 23G, three-port PPV was performed with the following steps. We induced posterior vitreous detachment (PVD) and removed the core and peripheral vitreous. Then, we removed the ERM as extensively as possible, and the ILM was removed from 1 disc diameter around the fovea. Intravitreal staining with Brilliant Blue G (BBG) (DORC, Zuidland, Netherlands) was performed for 1 min to visualize the ERM, after which the epiretinal proliferation was removed. Then, additional staining with the same dye was performed for a further minute and then ILM was peeled. No air-fluid exchange was done and the eye was filled with fluid at the end of the surgery. All sclerotomies were sutureless and the conjunctiva was repositioned to cover the sclerotomy site completely. Patients were treated with chloramphenicol 0.5% eyedrops every 6 hours and betamethasone 1.0% every 4 hours for 1 week, after which the dose was tapered gradually during the first month.

Postoperation

The postoperative follow-up visits were performed on postoperative days 1, 7, 30, 60, and 90. BCVA measurement and OCT were repeated 3 months after the surgery and relevant data were extracted. Compared to preoperative OCT, one more parameter was measured in 3 months OCT, which was anatomical closure, defined as at least partial restoration of a physiologic appearance of the macula with a central dimple.

Ethical considerations

The study was conducted in Farabi Eye Hospital, Tehran, Iran based on the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (registration code of IR.TUMS.FARBIH.REC.1396.2765, Date: 2017/07/02). The written informed consent was provided for all the participants in this study and for publication of resulted data.

Data analysis

All data analyses were performed with SPSS version 20 (SPSS, Inc., Chicago, IL, USA). Qualitative variables were expressed as number and percentage and quantitative variables were expressed as mean and standard deviation (SD). To compare paired values, after assessing normality with Q-Q plot and Kolmogorov-Smirnov test, Wilcoxon nonparametric analysis was done. To compare subgroups, one-way analysis of variance was conducted; to compare categorical outcomes, Chi-square test was performed. Finally, to find probable associations between demographics or clinical characteristics and VA improvement or anatomical closure,

regression analysis with the best fit model was performed. $P < 0.05$ was considered to be statically significant.

Results

Among the enrolled participants, three patients were lost to follow up before 3 months and 22 eyes of 22 patients who completed the follow-up visit were included in analysis: 9 women (41%) and 13 men (59%) with the mean age of 67.9 ± 11.9 years (range: 33–85 years) [Table 1]. Twenty-one eyes were accompanied by ERM. Twenty eyes were phakic preoperatively. Six eyes underwent PPV plus phacoemulsification and 16 eyes underwent PPV alone. The mean maximum LH diameter was $991 \pm 595 \mu\text{m}$ (range: 427–2530 μm). Based on OCT, 10 cases were in the Deg subgroup (45.5%), 8 cases were in Trac (36.4%), and the remaining 4 were in mixed subgroup (18.2%).

Among our cases, 20 eyes (91%) achieved anatomical closure 3 months after the surgery [Figure 1a-d] and 2 eyes did not: one in Deg subgroup [Figure 1e and f] and the other one in Trac subgroup which was converted into the FTMH [Figure 1g and h].

Preoperative EZ integrity was found in only 3 cases all belonged to the Trac subgroup. The maximum lamellar defect was significantly higher in the EZ disruption group than the intact EZ group. (1153 vs. $691 \mu\text{m}$, $P = 0.02$). Three months after the surgery, there was no change in the EZ integrity rate and the integrity was seen only in the previously intact EZ band cases. Table 2

Table 1: Demographics and preoperative data of patients with lamellar macular hole

Variables	Value
Age in mean \pm SD years (range)	67.9 \pm 11.9 (33-85)
Gender, <i>n</i> (%)	
Male	13 (59.1)
Female	9 (40.9)
Eye, <i>n</i> (%)	
Right eye	15 (68.2)
Left eye	7 (31.8)
Phakic/pseudophakic, <i>n</i> (%)	
Phakic	20 (90.9)
Phacoemulsification was done in 6 patients	
Pseudophakic	2 (9.1)
Lamellar hole subgroup, <i>n</i> (%)	
Degenerative	10 (45.5)
Tractional	8 (36.4)
Mixed	4 (18.2)
Maximum lamellar defect, mean \pm SD μm (range)	
Degenerative	1385 \pm 693 (560-2530)
Tractional	661 \pm 168 (427-865)
Mixed	668 \pm 167 (464-873)

SD: Standard deviation

demonstrates the measured BCVA and thickness values preoperatively and postoperatively and also the results of statistical analysis comparing paired values.

There was no significant difference between preoperative and postoperative BCVA considering totally ($P = 0.5$), or in subgroup analysis (P : Deg = 0.1; Trac = 0.71, and Mixed = 0.18). Furthermore, there was no difference between either preoperative values of the three subgroups ($P = 0.38$) or postoperative values ($P = 0.51$).

Regarding CFT, there was no difference between preoperative values of the three subgroups ($P = 0.96$). One-hundred percent of the cases showed improvement in CFT 3 months after the surgery [Figure 1]; however, the CFT increased significantly only in the Trac subgroup ($P = 0.02$). The CFT also increased in the two other subgroups, but not significantly (P : Deg = 0.09, and Mixed = 0.18).

Considering ONL thickness at 500 μm nasal or temporal to the fovea, there was no significant difference between preoperative and postoperative values [for P values refer to Table 2]. However, the increased ONL

thickness was significantly higher in the Trac subgroup compared to the other two subgroups (P : nasal = 0.01 and temporal <0.01). Figure 2 shows a box and plot chart of thickness measurements of Deg and Trac subgroups and their significant differences calculated by least significant difference (LSD) *post hoc* test.

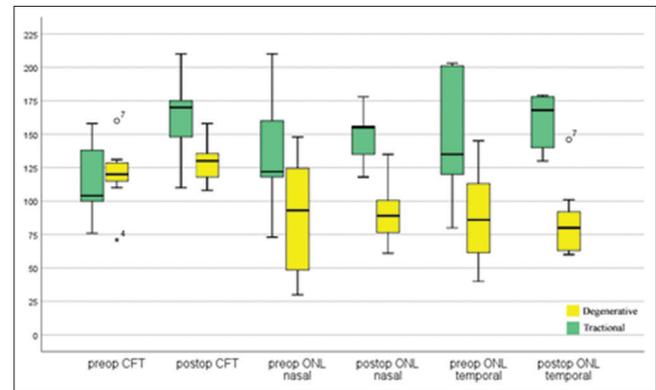


Figure 2: The box plot graph of measured retinal thicknesses, including central foveal thickness, outer nuclear layer thickness at 500 μm nasal and temporal to the retina in degenerative and tractional subgroups of lamellar macular hole. CFT = Central foveal thickness, ONL = Outer nuclear layer

Table 2: Visual and anatomical outcomes before and after the surgery in lamellar hole patients

	Degenerative (n=10)	Tractional (n=8)	Mixed (n=4)	Total (n=22)	$P^{\#}$ (between subgroups)	Post hoc test (pairwise comparison) (P)
Best-corrected visual acuity (LogMAR)						
Preoperative	1.02±0.53	0.71±0.44	1.02±0.47	0.90±0.49	0.38	
Postoperative	0.91±0.34	0.68±0.50	0.80±0.24	0.80±0.39	0.51	
Difference	0.11±0.51	0.02±0.15	0.22±0.33	0.10±0.37		
$P^{\$}$	1.0	0.71	0.18	0.50		
Central foveal thickness						
Preoperative	117±22	114±31	114±19	116±24	0.96	
Postoperative	132±20	157±31	135±7	141±26	0.04	Tractional and degenerative (0.03) Tractional and mixed (0.02)
Difference	14±23	42±33	21±26	25±29		
$P^{\$}$	0.09	0.02	0.18	<0.01		
Thickness of ONL; nasal						
Preoperative	88±47	136±51	114±9	108±50	0.14	
Postoperative	91±24	148±22	121±43	114±35	0.01	Tractional and degenerative (<0.01)
Difference	3±61	11±48	7±23	6±52		
$P^{\$}$	1.0	0.50	0.15	0.88		
Thickness of ONL; temporal						
Preoperative	88±37	147±53	128±26	113±50	0.12	
Postoperative	85±30	159±22	121±21	116±44	<0.01	Tractional and degenerative (<0.01)
Difference	3±40	11±52	7±13	3±42		
$P^{\$}$	0.61	0.89	0.20	0.91		
EZ integrity						
Preoperative	0	3	0	3	0.04 ^{\\$}	
Postoperative	0	3	0	3	0.04 ^{\\$}	
Anatomical closure (%)	9 (90)	7 (87)	4 (100)	20 (91)	0.77 ^{\\$}	

^{\\$}Wilcoxon, ^{\#}One-way ANOVA, ^{\\$}Chi-square: Comparing the relation of EZ integrity and anatomical closure with three subgroups of lamellar hole. EZ=Ellipsoid zone, logMAR=Logarithm of the minimum angle of resolution, ONL=Outer nuclear layer

In comparison between subgroups of PPV plus phacoemulsification ($n = 6$) and PPV alone ($n = 16$), no statistical difference was found regarding anatomical closure ($P = 0.8$), BCVA improvement ($P = 0.45$) or change in CFT ($P = 0.20$) after the surgery.

In this study, Deg subgroup was defined as the presence of round-edged intraretinal cavitation, LHEP, or central retinal bump; from the total of 10 eyes in this subgroup, LHEP was detected in 8 eyes. Hence, the results of comparison between LHEP negative and LHEP-positive groups regarding functional and anatomical outcomes were quite similar to the comparison between the Deg subgroup and other subgroups.

To find a possible correlation between demographics or clinical characteristics and study outcomes, regression models were used. Logistic regression and linear regression were performed for the outcomes of anatomical closure and BCVA improvement 3 months after the surgery. Table 3 lists different factors evaluated for association with study outcomes. But as it is reported, none of these factors had a meaningful relationship with anatomical closure or BCVA improvement.

Discussion

LH is an acquired macular defect, which can be detected as irregular fovea contour and dehiscence of the inner from the outer retinal layer by OCT.^[2] Although in most of the patients with LH visual acuity remains in an acceptable range, surgical treatment is an option that offers some improvement in theory which remains controversial in practice.^[7] Incomplete ERM or ILM removal might result in residual ERM or failure for MH closure. Kanzaki *et al.* noted that in the case of large ILM removal, ERM formation does not affect visual function significantly^[10] which was consistent with our study. Although in Figure 1d and f, we had the residual or recurrent ERM, it

was not presented in central foveal and parafoveal regions where we completely removed ERM and ILM. In a study by Purtskhvanidze *et al.* in which PPV and ERM removal was performed in 36 patients with LH with 5 years follow-up period, it was reported that final visual and functional improvement after surgery was not significant and surgical treatment should be considered in cases with significant visual loss or functional progression.^[11] In contrast, Guber *et al.* evaluated functional and anatomical outcomes after PPV with ERM surgical treatment in 36 eyes with LH associated with ERM.^[12] This study showed that surgical treatment resulted in both foveal contour and visual acuity improvement in most patients after short time follow-up (3 months) and recommended PPV with ILM peeling as a safe treatment with favorable functional and anatomical outcomes.^[12]

Witkin *et al.* reported that visual acuity improved in 19 eyes (63%) after vitrectomy.^[1] Subgroup analysis showed that significant visual benefit was only observed in patients with an intact photoreceptor EZ.^[1] In our study, preoperative intact EZ was found in only 3 cases; all of which belonged to the Trac subgroup. Furthermore, the increase in CFT and ONL was higher in Trac compared to Deg and mixed eyes. Hence, intact EZ may affect the surgical outcomes, but we did not find any correlation in regression models. In a study by Coassin *et al.*, PPV and ILM peeling was performed in 106 patients with LH.^[13] This management resulted in BCVA improvement in 70% of cases after 36 months follow-up period. They also reported that preoperative phakic/pseudophakic status influenced the functional outcomes.^[13] However, we did not find any correlation between lens status and surgical outcomes. We also did not find any difference between surgical outcomes of PPV and PPV plus phacoemulsification.

In 2014, Pang *et al.* evaluated the prevalence and imaging characteristics of a distinct entity of epiretinal

Table 3: Evaluation of probable factors associated with anatomical closure and improvement of best corrected visual acuity 3 months after surgery

Variables	Anatomical closure after surgical treatment		Improvement of BCVA 3 months after surgical treatment	
	OR (95% CI)	P	Standardized coefficients (95% CI)	P
LH subgroup	1.000 (0.999-1.001)	1.000	-0.102 (-0.613-0.409)	0.630
Age	1.193 (0.312-21.123)	0.992	-0.006 (-0.029-0.018)	0.566
Maximum lamellar defect	1.000 (0.998-1.002)	0.998	0.000 (0.000-0.001)	0.273
Baseline VA (LogMAR)	1.192 (0.108-13.106)	0.996	0.583 (-0.303-1.468)	0.152
Phakic/pseudophakic	1.000 (0.999-1.002)	1.000	0.663 (-0.296-1.623)	0.136
Phacoemulsification	1.003 (0.995-1.005)	0.997	-0.557 (-1.288-0.175)	0.108
Baseline central foveal thickness	1.016 (0.955-1.081)	0.996	0.003 (-0.007-0.014)	0.441
ONL thickness	1.005 (0.997-1.034)	0.994	0.000 (-0.010-0.009)	0.922
Preoperative EZ integrity	0.999 (0.998-1.001)	1.000	-0.001 (-1.016-1.014)	0.997
Postoperative EZ integrity	-	-	-0.738 (-1.749-0.273)	0.119

BCVA=Best-corrected visual acuity, EZ=Ellipsoid zone, LH=Lamellar hole, logMAR=Logarithm of the minimum angle of resolution, ONL=Outer nuclear layer, OR=Odds ratio, CI=Confidence interval, VA=Visual acuity

proliferation associated with LH, identified two different subtypes based on the presence (about 60% of cases) or absence of LHEP, and reported poorer VA and more disrupted photoreceptor layer in LHEP-positive group.^[14] This finding was then confirmed by other case-series studies^[15,16] which concluded that there was no visual benefit after surgery in LH patients with LHEP. In 2016, Govetto *et al.* moved further and classified the LH based on morphological and functional characteristics into degenerative and tractional categories.^[8] Later studies oriented their design according to this classification. Coassin *et al.* studied 106 patients with LH for 3 years.^[13] They reported BCVA improvement at 6 months and last follow-up (36 months); however, in subgroup analysis, visual acuity significantly increased only in the tractional but not in the degenerative forms of LH.^[13] In another study, Obata *et al.* evaluated 32 eyes for 12 months and reported significant VA improvement in both subgroups of degenerative and tractional.^[9] However, CFT change was significant in the tractional subgroup only, decreasing from 419 μm at baseline to 364.2 μm at 12 months, while there was no change in CFT in degenerative LHs.^[9] In our study, the subgroups were defined due to the latest understanding of LH into the tractional, degenerative, and mixed types; with the evaluation of 22 LH cases after 3 months of follow-up, no significant improvement in VA either totally or comparing subgroups were detected in contrast to the Coassin *et al.*^[13] and Obata *et al.*^[9] studies, which may be due to shorter time of follow-up (3 months vs. 36 and 12 months, respectively). Regarding macular thickness in this study, CFT and ONL thickness was significantly increased in the tractional subgroup compared to the degenerative and mixed types that might be an antecedent to the functional improvement, which might occur later. Although Obata *et al.*^[9] reported a significant decrease in CFT of tractional LHs, this study demonstrated a significant increase in CFT of tractional LHs, which may be due to diverse and variable morphological aspects of LH. In a recent review study by Haritoglou *et al.*, it was commented that generally tractional subgroup of LH is associated with less disruptions of the outer retina, which is the reason (at least theoretical) for their better response to surgery.^[7]

The most important limitation of this case-series study is its small sample size and short-term follow-up that decreases the probability of finding differences in comparing subgroups, and it might be the reason for results of “no difference” in the comparison between preoperative and postoperative values. Although recent investigations recommended PPV with complete ILM peeling or fovea-sparing technique^[17] or even combined with LHEP- embedding technique to cause distinct visual and anatomical outcomes due to different disease entities,^[18] we performed this study from January 2018 to April 2020 and we did not use these surgical methods

for LH treatment. The strength of this study compared to the similar previous studies^[9,13] includes its prospective design, performing surgeries by only one surgeon with the same technique for all patients, and adjusting for the effect of simultaneous phacoemulsification in the analysis.

Conclusion

Based on morphological and functional characteristics, retinal thickness measurements were improved in tractional LH 3 months after PPV, while there was no change in degenerative or mixed subgroups. No visual benefit was found in all subgroups of LHs 3 months after the surgery, however, anatomical closure occurred in 91% of cases 3 months after the surgery.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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