Does vitrectomy of Lamellar Macular Hole benefit the patient's visual acuity?

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A retrospective multicentre cross-sectional study on Lamellar Macular Holes

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Abstract

Purpose: The aim of this study is to investigate the functional and anatomical parameters of Lamellar Macular Holes (LMH), both preoperative and after pars plana vitrectomy (PPV). The surgical approach, which limit the traction of the residual foveal tissue, is intended to improve the patients' deteriorating visual acuity. The investigation of which anatomical parameters that predict LMH, and which surgical technique that may improve the Best Corrected Visual Acuity (BCVA), will be useful in a future establishment of a standardized interventional protocol for Lamellar Macular Holes.

Method: A retrospective multicentre cross-sectional study including patients who underwent vitrectomy for LMH, with or without combined phacoemulsification and intraocular lens (IOL) implantation surgery, as well as injection of a gas-, air or balanced salt solution (BSS)-tamponade. The patients included were treated at the Department of Ophthalmology, Oslo university Hospital (Norway), Department of Ophthalmology, University Medical Centre Ljubljana (Slovenia), Department of Ophthalmology, University of Split (Croatia), Ophthalmic Clinic Jasne Blonia (Poland), and the Department of Ophthalmology, Justus-Liebig-University, University Hospital Giessen and Marburg GmbH (UKGM), Giessen (Germany). Pre- and postoperative Best Corrected Visual Acuity (BCVA) measurements, and Optical Coherence Tomography (OCT) scans were used to determine functional outcomes and anatomical parameters.

Results: 66 consecutive patients were included (age: 71.79 ± 8.52 years), of which 47 (71.2%) were diagnosed as tractional type LMH, and 19 patients (28.8%) as degenerative type. 31 patients (47.0%) underwent a combined phaco-vitrectomy procedure for their concomitant cataract, while the rest underwent 23G or 25G PPV. 17 of the total 66 received gas-tamponade (25.7%) - either SF_6 or C_3H_8, 26 received air-tamponade (39.4%), while the remaining 23 patients received balanced salt solution (BSS)-tamponade (34.9%) during vitrectomy. The total BCVA showed significant improvement postoperatively ($p<0.001$), and accordingly in the following groups: tractional LMH type ($p<0.001$), degenerative type ($p<0.001$), simple PPV ($p<0.001$), phaco-vitrectomy ($p<0.001$), BSS-injection (<0.01), gas-tamponade ($p<0.05$). An epiretinal membrane (ERM) was present in 63 of the patients (95.5%). In the group of tractional LMH the mean Central foveal thickness (CFT) was 81.1%

thicker ($P<0.05$) than in the degenerative group. None of our patients developed a Full Thickness Macular Hole (FTMH) postoperatively.

Conclusion: Pars plana vitrectomy (PPV) provided a high success rate and functional improvement for treating LMH for both tractional and degenerative types. Combined phaco-vitrectomy surgical treatment provided improvement in BCVA when cataract was present, and should be preferred in term of both socio-economic and individual interests.

Keywords: lamellar macular hole; surgical outcomes; tractional; degenerative; BCVA; OCT

Proem

This project thesis has been prepared during the fourth and fifth year of the Faculty of Medicine at the University of Oslo.

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1 Introduction

1.1 Retina and macula

Retina is made up of multiple neuron cell layers that convert absorbed photons to action potentials, which are transmitted through the brain's many complex structures, before they eventually end up in the visual cortex. The signals are further processed to our pictorial perception. Macula, that is localized at the center of the posterior part of retina, has the main responsibility for both visual acuity and colour vision, due to its high density of cones. Macula forms a depression in the otherwise surrounding retina, called fovea, and here the inner retinal neuron layers are pushed aside. Thus, the photoreceptors in the outermost layer are directly stimulated by the photons, which provide the eye's sharp visual discrimination ability. Any defect in macula will certainly cause decreased visual acuity and/or metamorphopsias, which may reduce the quality and capacity of life. Lamellar macular hole (LMH) is one such defect, and the impairment of visual acuity depends on the extent of the defect and the involvement of different retinal layers (1-5).

1.2 Lamellar Macular Hole

The pathogenesis of Lamellar Macular Holes, LMH, is not fully understood (6, 7), but degenerative changes, vitreomacular traction, posterior vitreous detachment (PVD), epiretinal membranes (ERM) and internal limiting membranes (ILM) appear to be involved in the majority of the patients (2, 3, 8-14). One hypothesis is that it could occur after a posterior vitreous detachment as an abortive process of a Full Thickness Macular Hole (FTMH) formation (15, 16).

LMH as a clinical entity was first described by Gass JD in 1975 (17), with the use of a slip-lamp biomicroscope. He described an oval reddish macular lesion in a pseudophakic patient, together with a histological evidence of foveal tissue loss. Through the exceptional technological emergence since that time, Optical Coherence Tomography (OCT) has become a major contributor to provide greater knowledge of the pathological mechanisms, and to detect anatomical parameters that contribute the LMH development. Today OCT is the gold standard for diagnosing and distinguishing Lamellar Macular Holes from other macular disorders (18-20).

Lamellar macular holes are defined by Witkin et al. (21), Hubschman et al. (22) and The International Vitreomacular Traction Study (IVTS) group (15) as a partial defect in the inner layers of fovea, with presence of irregular foveal contour, intraretinal splitting between the inner and outer retinal layers, loss of foveal tissue, but with intact photoreceptors in the outer layer and absence of a Full-Thickness Macular Hole (FTMH). The OCT-scans appear undermined. The persistence of the outermost neuroretinal layer ensures a partially preserved visual acuity, often with mild metamorphopsias, compared with the less favourable vision that usually is seen in patients with FTMH (5).

1.3 Tractional vs degenerative LMH

A more recent study by Govetto et al. published in 2016 (23) did a retrospective study to investigated whether LMH could be divided into different subgroups. The study resulted in a classification that currently is used internationally – the tractional and degenerative types of Lamellar Macula Holes.

The tractional type (23) is characterized by an associated Epiretinal Membrane (ERM) and/or vitreomacular traction (VMT), which cause a mechanical intraretinal separation, often between the outer plexiforme- and outer nuclear- layers (OPL and ONL). This leads to a schizis appearance; multiple narrow hyperreflective tissue bridges crossing wider hyporeflective spaces. Tractional LMH has a “moustache”-like morphology, with sharp intraretinal edges. The Ellipsoid Zone (EZ) is often intact.

The degenerative LMH (23) is characterized by a “top hat” shape, with its appearance of a round-edged cavitation that could affect all the retinal layers. A EZ disruption is more common in the degenerative type (7, 14, 23), due to the central foveal bump. Generally, the ratio between inner and outer horizontal diameter of the hole is more than 1:2. The degenerative type shows similar to the tractional type an epiretinal thickening, but in the degenerative ones this homogeneous intermediate reflective material seems to have less tractional property than the conventional ERM (22). This epiretinal material was named LMH-associated epiretinal proliferation (LHEP) by Pang et al. (11, 24). They theorized that LHEP is a result of migrating Müller glia cells, which hypothetically promote the closure of the LMH. Govetto (23) also agreed in the Müller theory, and that the recruitment may also be responsible for the disruption of the Ellipsoid Zone (EZ). The EZ disruption cause alternations in the photoreceptor layer, with a following impairment of visual acuity.

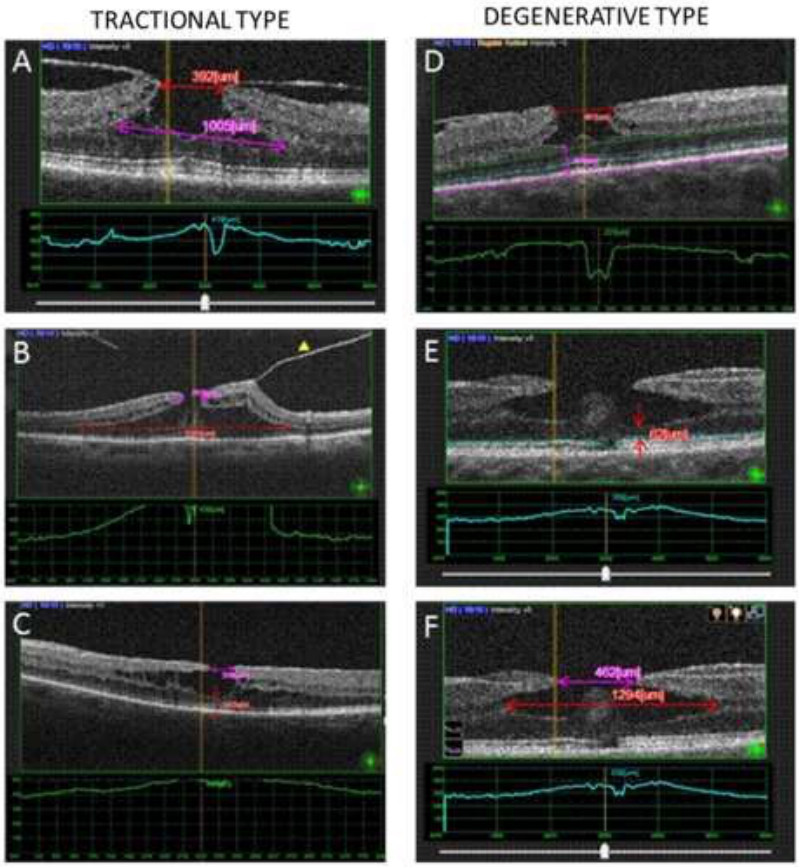


Figure 1. Structural features of the lamellar macular hole types (tractional vs. degenerative) studied by optical coherence tomography. Representative images of the tractional type are shown: (A) the callipers show the following measurements - Purple: base size of the hole; Red: top size of the hole. The schitic appearance is visible from the multiple narrow hyperreflective tissue bridges crossing the intraretinal splitting; (B) A tractional LMH with posterior vitreous detachment (yellow triangle), intraretinal cavities, sharp splitting edges, and EZ continuity are shown in the "moustache"-like morphology; (C) The traction of the ERM on the top of retina pulls the edges antero-lateral, thus splitting the retinal layers into a lamellar macular hole. The purple calliper measures the top size of the hole, while the red calliper measures the MFT. Representative images of the degenerative type are shown: (D) A round-edged cavitation, with a foveal bump and epiretinal proliferation is detected in the "top hat" morphology. The MFT was measured manually using a calliper (Purple), as the thinnest vertical distance from the base of the LMH down to the Brunch's membrane. Horizontal lines - purple: Brunch's membrane, blue: Ellipsoid Zone (EZ); green: Outer Nuclear Layer (ONL); (E) Round-edged cavitation, with a foveal bump, and EZ disruption (blue horizontal line); MFT (red); (F) the callipers show the following measurements - Purple: top size of the hole; Red: base size of the hole.

1.4 LMH – today's procedure

Currently the majority of patients diagnosed with LMH are considered not to be candidates for vitrectomy during their first evaluation, and rather a follow-up examination approximately in half-a-year is being practiced (25). If the visual acuity is deteriorating during this period, vitrectomy is recommended according to an individual assessment. Patients with LMH do very often have some degree of visual impairment, despite that the condition has been considered as stable in several follow-up studies (2, 5, 23, 26). Regardless of this stability, however, other studies have significantly proved that pars plana vitrectomy (PPV) improves the visual acuity in this patient group, which certainly should be validated further (1, 3, 6-8, 27-30).

1.5 Purpose

The aim of the study is to determine the efficacy of pars plana vitrectomy (PPV) in closing Lamellar Macular Holes. This retrospective multicentre study compared pre- and postoperative Best Corrected Visual Acuity (BCVA) in the context of anatomical OCT parameters, to consider whether surgical intervention should be indicated to improve the patients' vision and the quality of life. If the outcomes of vitrectomy, based on a sample of patients from different countries, give rise to statistically significant improvement of the visual acuity, one should be liberal to evaluate currently procedure and in drafting a new protocol. This certainly leads to a clinical upheaval, where surgical intervention may should be indicated at an earlier stage. This will simply not only improve the individual visual acuity, but goes hand in hand with the quality of life.

LMH is a condition that correlates with aging, and with the anticipated increase in the aging population worldwide, it is appropriate to establish protocols for diseases management, such as that for LMH. We hereby compare the different surgical approaches including type of tamponades and vitreoretinal surgical steps, in order to optimize the procedure and lay the foundation to a future protocol.

2 Methods

2.1 Design

The retrospective multicentre cross-sectional study is based on clinical records of 66 patients with LMH treated in the Department of Ophthalmology, Oslo university Hospital (Norway), University Medical Centre Ljubljana (Slovenia), Department of Ophthalmology, University of Split (Croatia), Ophthalmic Clinic Jasne Blonia (Lodz, Poland), and the Department of Ophthalmology, Justus-Liebig-University Giessen, UKGM (Germany), in the periode between April, 2016 and April, 2021. LMH was defined according to the following OCT parameters (15, 21, 22): presence of irregular foveal contour, separation of the neuroretinal layers, and absence of Full-Thickness Macular Hole (FTMH). All the LMH patients have underwent a pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling, with or without combined phacoemulsification and intraocular lens (IOL) implantation. During the surgeries different trochar sets were used (20G/23G/25G) as well as various endotamponades (gas-air mixture (SF_6-/C_3F_8), air or balanced salt solution (BSS)) that were applied for each individual. Patients with concomitant eye diseases or previous surgical interventions were also included in the study. Macular Pseudoholes and foveoschisis are distinct other macular entities, and consequently excluded from the study.

2.2 Measurements

BCVA assessment and OCT scans were retrieved for statistical analysis, as well as data on age and gender. BCVA was measured with Snellen chart. The following parameters were analyzed on OCT: tractional versus degenerative type of LMH, central foveal thickness (CFT), minimal foveal thickness (MFT), Base and Top size of the holes, Ellipsoid zone (EZ) disruption, Epiretinal membrane (ERM). The CFT was automatically measured by the OCT software, while the MFT was measured manually as the thinnest vertical distance from the base of the LMH down to Brunch's membrane, with the use of a software-based caliper. The Base- and Top- size of the hole were defined as the horizontal diameter (μm), respectively, at the outer and inner edges of the hole, and were also measured manually.

2.3 Surgical procedure

Pars plana vitrectomy (PPV) is in general a standardized procedure, but has some variations due to both the international and the individual surgeons' preferences. Differences of importance regarding the surgical procedure are noted to enable statistical comparison.

PPV were performed under retrobulbar anaesthesia (Xylocaine 20mg/ml or Lidocaine 20mg/ml: 2.5ml + Marcaine 5mg/ml: 2,5ml), combined with phacoemulsification, if cataract was present. In the latter cases, the procedure with implantation of an acrylic foldable Intraocular Lens (IOL) in the capsular bag was performed at first. Then a standard 3-port PPV with either 23- or 25-Gauge was performed in each patient, where the sclerotomies were placed 3.5 to 4 mm peripherally to the limbus. Central core vitrectomy was performed followed by detachment of the posterior hyaloid using vacuum with the vitrectomy probe. The peripheral vitreous was then removed with careful inspection of the retinal periphery.

The macula was further stained using internal limiting membrane (ILM) blue dye (TissueBlue, 0.025%) to facilitate the peeling. If an ERM was present, it was removed in advance of or together with the ILM-peeling. Eventually, a complete fluid-air exchanged (BSS) was performed, with or without a gas-tamponade at the surgeon's discretion. The gas-air mixtures were either sulphur hexafluoride (SF_6) or octafluoropropane (C_3H_8), and the respective concentrations of the gases were noted for each patient. The gas is intended to push and hold retina back against the underlying choroidea, to ensure an approximation of the LMH and prevent postoperative complications, such as retinal detachment or FTMH. Alternatively, the eyes were filled with air or only BSS. The cannulas were then removed, and the conjunctiva was repositioned to cover the sites of the sclerotomies. The procedure is primary closed without sutures, but if leakage was apparent, the sclerotomies and conjunctiva were sutured accordingly. Subconjunctival gentamycin is administrated (40mg/ml: 20mg), covered with Chloramphenicol bandage.

Following surgery, the patients with gas endotamponades were introduced to maintain face prone position for 3 days postoperatively, to optimize the pressure of the gas against the macula. Topical Maxitrol, combination of steroids and antibiotics, (3 times daily for 3 weeks) and cycloplegics (Cyclopentolate 1%, 2 times daily for 10 days) were prescribed. Patients were examined on the first day postoperatively at the hospital, and where then either summoned back, or told to schedule a follow-up appointment at their referring

ophthalmologist, 3-4 weeks postoperatively. By that time, the gas would have resorbed for the applicable patients. In retrospect, we inquired these ophthalmologists to obtain the data of the follow-up, BCVA, OCT-scans and asked for any postoperative complications or remarks. Postoperative OCT was used to confirm the status of the LMH compared to the preoperative scans.

2.4 Ethical clearance

The present study adhered to the tenets of the Declaration of Helsinki, and was approved by the Regional Committees for Medical and Health Research Ethics (REK No.: 2017/691)

2.5 Statistics

The data analysis was performed using descriptive statistical analysis; percentage distribution, mean and standard deviation (SD). In case of non-normality of continuous variables, median and interquartile range (IQR) and maximum/minimum ranges were calculated. Normality of continuous variables were tested on histogram and by the Shapiro-Wilk and Kolmogorov-Smirnov test. When the normality assumption was satisfied, the independent sample t-test was used to compare means of continuous- and numerical variables. Otherwise, the Wilcoxon signed rank test was used to compare repeated measurements (pre- and postoperative measurements) between two groups. Chi-square test (χ^2) was used to test the differences of the distribution of categorical variables, while the column proportion were compared using a z-test. The significance level was set as $p<0.05$ and in case of the χ^2test it was adjusted with Bonferroni correction to $p < 0.05/n$ (where n is the number of analyses). Statistical Package for STATA (Stata version 14.0; College Station, TX, USA) and SPSS (SPSS version 24, IBM, Armonk, NY, USA) were used for the statistical analyses.

The Best Corrected Visual Acuity (BCVA), measured with Snellen chart, was converted into logarithm of the minimal angle of resolution (logMAR) values for the statistical analysis purposes. The different gas tamponades, SF_6 and C_3H_8, were collected into a common group in the statistical analysis, as each of them had a small number of patients and different injected concentrations within. Since the use of the gas tamponades has the same intention, to push and hold retina back against the underlying choroidea, it was appropriate to merge these patients' groups for a more representative comparison.

2.6 Literature search strategy

A systematic search in PubMed and MEDLINE were initially done to achieve a comprehensive knowledge of Lamellar Macular Hole, and to get an overview of previous conducted studies and their outcomes. This was useful for an overall perspective, since each study has different strengths and limitations that affect the presented outcomes. The search was based on the PICO-model, and the MeSH terms and text words are shown below.

Search History (11. January 2021):

1. (Lamellar macular hole* OR Lamellar hole*).mp.
2. exp Vitrecotmy/
3. (Vitrectomy OR Pars plana vitrectomy OR phaco vitrectomy OR internal limiting membrane peeling OR ILM peeling).mp.
4. 2 OR 3
5. exp Visual Acuity/
6. Visual acuity.mp.
7. 5 OR 6
8. exp Tomography, Optical Coherence/
9. (OCT OR Optical Coherence Tomography).mp.
10. 8 OR 9
11. 1 AND 4 AND 7 AND 10
12. Limit 11 to English
13. Limit 12 to yr =”2010 -Current”

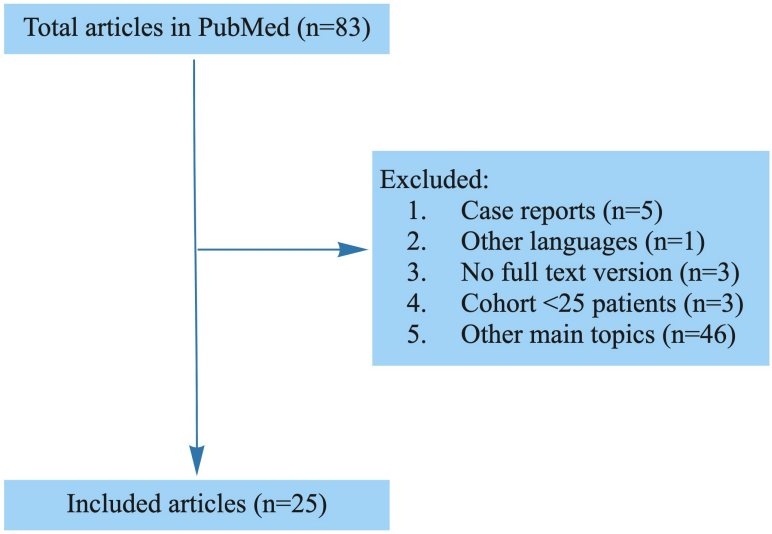
The search retrieved 83 articles, and these were further screened based on the title and abstract in terms of the following criteria;

Inclusion:

- Original Clinical Trials, both retrospective and prospective studies
- Cohort > 25 patients
- Lamellar Macular Hole (LMH) as main topic
- Available full text version

In total 25 articles were included and reviewed in full text.

Figure 2: *Flowchart for inclusion*



3 Results

3.1 Characteristics of the studied population

The retrospective study included 66 consecutive patients having LMH that had underwent PPV: 23 males (34.9 %) and 43 females (65.1 %). Mean age at surgery was 71.79 ± 8.52 years (range: 59-87 years).

Forty-seven (71.2%) of the total 66 eyes were diagnosed as tractional LMH, while remaining 19 (28.8%) as degenerative type, without any significant differences in gender and age between the two LMH types. 31 patients (47.0%) underwent a combined phaco-vitrectomy: 4 patients of the degenerative type, and 27 of the tractional type. Seventeen of the total 66 patients got gas-tamponade (25.7%), either SF_6 or C_3H_8; 26 got injection of air (39.4%), while the remaining 23 patients received BSS-tamponade (34.9%). The characteristics of the studied group are summarized in **Table 1.**

Table 1.: Characteristics of the studied population

	LMH type		
	Degenerative N=19 (%)	**Tractional N=47 (%)**	**Total N=66 (%)**
Gender			
Male	5 (26.32)	18 (38.30)	23 (34.85)
Female	14 (73.68)	29 (61.70)	43 (65.15)
Age (mean±SD)	70.47±8.70	72.32±8.48	71.79±8.52
Type of tamponade			
BSS	***15 (78.95)*** [a]	***8 (17.02)*** [b]	23 (34.85)
AIR	***2 (10.53)*** [a]	***24 (51.06)*** [b]	26 (39.39)
GAS	***2 (10.53)*** [a]	***15 (31.91)*** [a]	17 (25.76)

N=Number; SD: Standard Deviation; LMH: Lamellar macular hole; BSS: balanced salt solution; Each subscript letter (a, b) denotes a subset of LMH type categories whose column proportions do not differ significantly from each other at the 0,05 level. P<0,05; After Bonferroni correction: ***P<0,017*** (3 pairwise comparison).

3.2 Anatomical pre- and postoperative characteristics

An ERM was present in 63 of the 66 patients (95.5%), of which all of the patients with tractional type had an ERM, and the remaining 3 patients belonged to the degenerative group. The presence of an ERM showed significant statistical difference between the tractional and degenerative type (P<0.05). Ellipsoid zone (EZ) disruption was present in 8 (12.1%) of the patients at the preoperative OCT scans, which all belonged to the tractional group.

In the tractional LMH group the mean Central foveal thickness (CFT) was 81.1% thicker (P<0.05) than the degenerative type of LMH (379.89 ± 117.69 μm, range 100-595 μm; vs. 209.79 ± 60.40 μm, range 94-351μm, respectively).

The other OCT parameters: Minimal Foveal Thickness (MFT), Base- and Top size, showed no significant difference between the tractional and degenerative group. The values of these OCT parameters, as well as CFT, EZ and ERM, are presented in **Table 2.**

Table 2.: OCT characteristics

	LMH type	
	Degenerative N (%)	**Tractional N (%)**
CFT (mean±SD)	***209.79±60.40***	***397.89±117.69***
MFT (mean±SD)	215.53±66.27	211.25±79.21
EZ continuity		
No	0 (0.00)	8 (17.02)
Yes	19 (100.00)	39 (82.98)
ERM presence		
No	***3 (15.79)***	***0 (0.00)***
Yes	***16 (84.21)***	***47 (100.00)***
Base size (median, IQR),¨ Range	703 (530-910) 155-1452	483 (230-1019) 75-2541
Top size (median, IQR),¨ Range	472 (339-611) 172-899	374 (283-517) 137-1581

N=Number; SD: Standard Deviation; CFT: Central Foveal Thickness; MFT: Minimal Foveal Thickness; EZ: Ellipsoid zone; ERM: Epiretinal Membrane; IQR: Interquartile Range;
P<.0.05

In the degenerative group, the mean top size of the hole was 472 μm (range 339-661 μm), and the mean base size was 703 μm (range 530-910 μm). This was closer to the 1:2 ratio that generally is case for the degenerative type of LMH, compared to the tractional group that had a mean Top size of 374 μm (range 137-1581μm) and a mean base size of 483 μm (range 230-1019 μm). The ratios are thus 0.67 and 0.77, respectively, for the degenerative and tractional group.

3.3 Functional outcomes

The mean preoperative BCVA in total was median: 0.30, IQR 0.22-0.52, Range 0.00-1.70 on the LogMAR scale. The median preoperative BCVA in the tractional group was 0.30; IQR: 0.20-0.49; range: 0.00-1.70, while in the degenerative group it was median: 0.49; IQR: 0.3-0.60; range: 0.10-1.22.

In total BCVA showed significant improvement postoperatively ($p<0.001$). In the tractional group, the BCVA improved postoperatively to a median 0.20; IQR: 0.10-0.30; range: 0.00-1.00, while in the degenerative group it improved to a median 0.22; IQR: 0.15-0.49; range: 0.00-0.60.

Significant postoperative improvement was recorded in following groups: total sample size, tractional type, degenerative type, BSS, gas-tamponade, simple PPV, phaco-vitrectomy. The BCVA also improved in the subgroup with air tamponade, but not significantly. None of the groups showed any decrease of BCVA postoperatively. The functional values, BCVA (logMAR), are presented in **Table 3** for each group.

Table 3.: Relationship between pre- and postoperativ BCVA (logMAR) and groups.

	Pre-op (Median, IQR, Range)	**Post-op** (Median, IQR, Range)
	BCVA (logMAR)	
Tamponade		
BSS	***0.4 (0.3-0.6) 0.05-1.22***	***0.15 (0.05-0.40) 0.00-0.60***
Air	0.30 (0.20-0.52) 0.00-1.70	0.26 (0.20-0.30) 0.05-0.10
Gas	***0.30 (0.20-0.40) 0.10-1.70***	***0.20 (0.10-0.30) 0.10-0.49***
Phaco-vitrectomy		
No	***0.30 (0.22-0.60) 0.00-1.22***	***0.20 (0.10-0.30) 0.10-0.49***
Yes	***0.40 (0.20-0.52) 0.05-1.70***	***0.20 (0.15-0.30) 0.00-1.00***
LMH type		
Degenerative	***0.49 (0.30-0.60) 0.10-1.22***	***0.22 (0.15-0.49) 0.10-1.22***
Tractional	***0.30 (0.20-0.49) 0.00-1.70***	***0.20 (0.10-0.30) 0.00-1.00***

BCVA: Best Corrected Visual Acuity; MAR: Minimum Angle of Resolution; IQR: Interquartile Range; ***P<.0.05***. ***Difference between pre- and post-op measurements.***

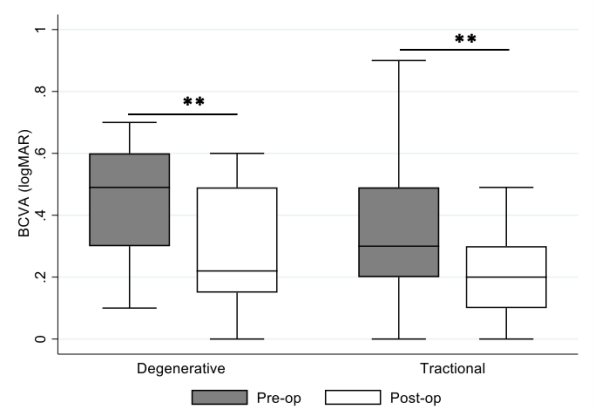
Since CFT differenced significantly between the tractional and degenerative type ($p<0.05$), we further investigate whether the preoperative CFT had any correlation with the preoperative and postoperative BCVA.

Preoperative BCVA in the group with CFT <300μm was median: 0.40, IQR: 0.28-0.60, Range: 0.10-1.22 LogMAR, while the postoperative BCVA significantly improved to median: 0.22, IQR: 0.15-0.42, range: 0.00-0.60 LogMAR ($p=0.008$).

The preoperative BCVA in the group with CFT>300μm was median: 0.30, IQR: 0.20-0.52, Range: 0.00-1.70 LogMAR, and the postoperative BCVA significantly improved to median: 0.20, IQR: 0.10-0.30, Range: 0.00-1.00 LogMAR ($p=0.003$). The functional improvement was significant in both subgroups, and additionally, the outcome of this study suggests that the visual improvement is best in patients with a higher preserved preoperative CFT.

Figure 3.: Relationship between pre- and postoperativ BCVA (logMAR) in the studied groups. a, LMH types; b, Vitrectomy; c, Tamponade.

a,



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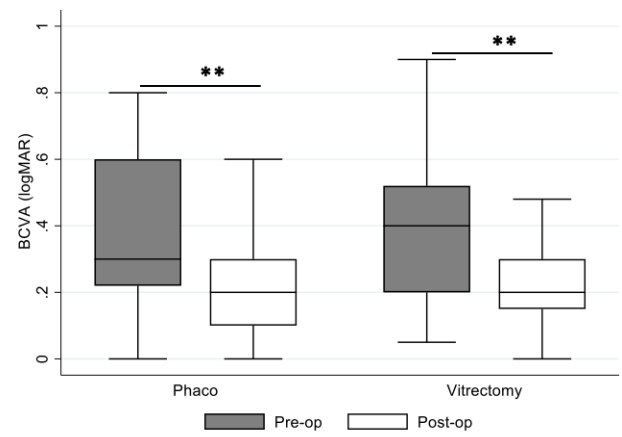
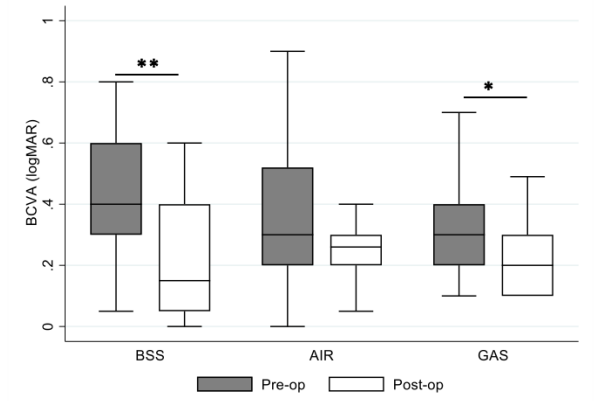


c,



*P<0.05; **P<0.01; BSS: Balanced Salt Solution; BCVA: Best Corrected Visual Acuity; MAR: Minimum Angle of Resolution.

4 Discussion

4.1 What are the results in the light of the purpose?

To date, there is no international consensus on the type of tamponade used during vitrectomy for LMH, nor about the optimal duration time of postoperative prone position. Sun et al. (30), used 15% C_3F_8 and encouraged 3-5 days of prone positioning, and this provided a greater chance for restoration of the foveal configuration, compared with non-gas tamponade ($p=0.0016$). Nevertheless, both Sun (30) and Michalewska (31) found that foveal improvement was not essential for the improvement of the visual acuity, but rather depended on the release of the tractional ERM and to the continuity of the Ellipsoid Zone (EZ). Our study shows that BCVA significantly improves both with gas tamponade ($p<0.05$) and BSS ($p<0.01$). For the patients with air tamponade, the BCVA also improved, but not significantly.

Since the visual improvement was best in the BSS group in our study, as well as the gases increase the probability of postoperative cataract formation; furthermore, none of our patients developed Full-Thickness Macular Hole postoperatively, one can suggest BSS to be a better initial tamponade in LMH surgery. However, if FTMH secondary complication does appear, then a gas tamponade could be the tamponade of choice.

Full-Thickness Macular Hole is a possible complication of a progressive LMH, according to the pathological hypothesis that LMH occur as an abortive process of a FTMH (15, 16). Any further changes in macula will certainly reoccupy the development and the establishment of a FTMH. One of our LMH patients at Ullevål University Hospital, that was indicated for a follow-up observation, unfortunately developed a FTMH. It should be in consideration whether vitrectomy at an earlier stage could have prevent this complication. Surgery cannot guarantee an improvement of the visual acuity postoperatively, but by peeling and repairing the pathological damages, we may prevent progression and complications such as FTMH. Of that reason, it is just as important to analyse postoperative OCT-scans, not only the postoperative BCVA, since an improvement of the foveal architecture and absence of ERMs are more reliable predictors for the stabilization of the visual acuity, than the measurement of the visual acuity itself.

In our study, all patients diagnosed with tractional LMH had an ERM present as well. Only 3 patients had no presence of ERM and they belonged to the degenerative LMH group. The degenerative type often has a LHEP instead of, or together with an ERM. Since we did not distinguish these two different types (ERM vs. LHEP) in the preoperative anatomical analysis, it is likely that the remaining 3 patients had a degree of a LHEP. It could also be case that the degenerative patients with presence of an ERM, rather bordered to a LHEP. This is likely since the degenerative type usually is considered with more permanent anatomical and functional changes, while the tractional Lamellar Macular Holes, forced by an ERM, often improve anatomically and functionally once the traction has been removed surgically. Nevertheless, both the tractional and degenerative types showed a significant functional improvement postoperatively ($p<0.001$) in our study, which are in favour of surgical intervention in both groups.

None of our patients with degenerative LMH had an EZ disruption. It is difficult to determine whether this is due to a small sample size, inaccurate anatomical analysis, or if it is conditioned by a poor clarification of its definition. The Ellipsoid Zone (EZ) is proximal to the Outer Nuclear Layer (ONL), and such ONL alternations often are present and difficult to differentiate from the EZ disruption, with the possibility of both conditions being actually present as well.

Thirty-one (47.0%) of our 66 patients had combined phaco-vitrectomy, which suggests that many had concomitant cataract, thus difficult to determine in what extent cataract contributes to their impaired visual acuity. However, it is in the patients' advantageous to perform a combined phaco-vitrectomy to improve their visual outcome. Principally, the improvement in the two groups should be similar regarding the LMH, but it is convincible that cataract impairs the visual acuity the most, and that phaco-emulsification is a more effective intervention to date. Thus, the combined phaco-emulsification group would appear with a greater functional improvement postoperatively. In our study the visual acuity significantly improved in both the group of simple PPV and phaco-vitrectomy ($p<0.001$). The patients with combined surgery showed a tendency to better improvement postoperatively, however, this difference was not significant.

If one could affirm that the cataract impairs the visual acuity the most, it would indirectly imply that these patients would have a better preoperative BCVA regard to LMH alone. However, if better preoperative BCVA provides a better improvement postoperatively, these patients would achieve a great improvement when a combined phaco-vitrectomy additionally is performed. This may imply it would be advantageous to intervene at an early stage, and not observe the patients a half year ahead in anticipation of a visual deterioration due to an eminent cataract.

Phaco-vitrectomy is cost-saving for the patients, and cost-beneficial for the healthcare system (32), compared to two separate surgeries. Combined phaco-vitrectomy will prevent the individual patient in use of unnecessary time, resources, rehabilitation and any sick leave. Furthermore, a surgical intervention will be favourable in a sosio-economic perspective, as it prevents a possible and dreaded FTMH development. Full-thickness macular hole is an acute condition, that precedence over the elective surgeries, and thus delaying the schedule. Prophylactic LMH intervention prevents such an unfortunate occurrence, as well as ensuring a more predictability in the already burdened health care system.

4.2 Strengths and limitations

The study's retrospective nature, combined with multicenter information gathering, made it difficult to ascertain the exact time for postoperative examinations for each patient. The length of the follow-up postoperatively is an important factor, as well as the time until a possible improvement, which can be used to inform the patients at what time in postoperative period they might expect a noticeable effect. The patients' feedbacks and the examinations postoperatively would have contributed to increase the knowledge whether the surgical improvement occur immediately, or if the healing process needs a giver number of months to be adequate enough for a functional improvement. Therefore, one should have standardized, regular follow-ups over a certain period of time. Additionally, several numbers of follow-ups postoperatively provide more reliable values to analyse, since individual conditions and the extent of the hole not only affect the degree of an improvement, but also when it takes place.

Another limitation with this retrospective study was that the patients at Oslo university Hospital did not have their postoperative examinations at the hospital, but instead at their referring ophthalmologist – the latter had not the opportunity to send the postoperative OCT-scans for each case, but a journal description. Therefore, pre- and postoperatively OCT parameters could not be compared, and rather used the data about presence or absence of postoperative FTMH. Similarly, the other centres involved could not forward OCTs, thus the analysis of the anatomical outcomes was prevented. A comparison of pre- and postoperative anatomical parameters is useful in obtaining information about the CFT, MFT, Base size, Top size, EZ-continuity, Posterior Vitreous Detachment, Macular Edema, since the anatomical improvement is just as important as the functional one. An anatomical improvement may indeed prevent a deteriorating visual acuity that can occur without a surgical intervention, although the functional outcome would not improve significantly.

Furthermore, the study did not exclude patients with other eye diseases, since the retrospective nature made it difficult to collect a sufficiently cohort of patients without current or previous eye diseases. Different clinical entities mutually influence each other, and aging is a factor of risk for the majority. Posterior Vitreous Detachment (PVD) is one example of an eye condition that contribute to pathological mechanisms causing LMH. Myopia is a risk factor for PVD, and possible indirectly for LMH as well. Dividing the patients in av myopic and hypermetropic subgroup would have contribute to ascertain whether myopia increase the probability of Lamellar Macular Hole development.

A strength with our study is the multicentre sample size, including patients from 5 different countries. The hospitals and clinics have some different preferences within the surgical procedure, which does it able to compare and determine which technique that promotes the best postoperative result. Whether gas or non-gas tamponade improve the visual acuity the most was an important investigation, since each of the options have pros and cons. The gas intends to push retina back against the underlying choroidea, preventing FTMH and retinal detachment. The gases will, in term of their chemical properties, expediate development of cataract, especially in predisposition eyes, and in a long-term perspective deteriorate the visual acuity. In our study the BCVA improved most in the group with injection of BSS ($p<0.01$), but gas-tamponade also showed a significant improvement as well ($p<0.05$). Thus, gas or non-gas tamponade should be an individual assessment, preferably with BSS, simultaneous as the patients' age, risk factors and LMH severity should be in consideration.

4.3 Comparison to equal studies

Theodossiadis et al. (33) did a long-term follow-up study of 41 LMH patients, with a mean follow-up period of 31.1 months. Visual Acuity (VA) remained stable in 30 of the patients (75%), the mean Central Foveal Thickness (CFT) decreased during the same period ($p < 0.001$), which correlated with the patients that experienced a deteriorated visual acuity ($p = 0.002$). Although the majority maintained a stable VA, as many as 39 patients complained of metamorphopsias at the final examination. That was 8 more than at the first examination. Based on this study the VA can be relatively stable, so to claim that vitrectomy is not indicated for LMH, it might inflict upon the remaining 25% who had unstable VA a restricted quality of life. It is difficult to predict which of the patients whom will experience a deteriorating in their visual acuity, and simultaneously it is a socio-economic issue whether prophylactic operation should be indicated to all the patients diagnosed with LMH.

ERMs were identified in 63 of our patients at baseline (95%). This is in agreement with previous reports where ERM was reported in 100% of the patients (3, 8, 13, 14, 31). Ergo, ERMs appear to have a role in the pathogenesis of LMH. Theodossiadis (5) found that ERM participates in the enlargement of LMH, and that deteriorating VA for these patients should be an indication for vitrectomy.

The high number of patients that underwent a combined phaco-vitrectomy (47.0%), due to age-related lens opacifications, clarifies that LMH is an age-related condition as well. Chois et al. (34) studied a sample of 34 patients, where 32 of them were pseudophakic at the final postoperative control. It is of that reason difficult to determine in what extent the obscuration of the lens is responsible for the visual impairment. Nevertheless, it can be favourable to both treat the cataract and the LMH in the same surgery, since the main purpose is it improve the VA and the quality of life. Coassin et al. (35) studied 106 symptomatic LMH patients that either underwent simple PPV or phacovitrectomy, in which the postoperative BCVA improved significantly ($p<0.001$). Additionally, they did a subgroup analysis where they excluded the phaco-vitrectomized patients, and still the postoperative BCVA improved significant ($p=0.0036$). In our study both the simple PPV and phacovitrectomized patients had a significantly improved BCVA postoperatively ($p<0.001$).

A correlation between a low minimum foveal thickness (MFT) and poor preoperative visual acuity has been detected in a study by Holland (1) on 89 eyes. These two parameters in context could probably give rise to a new guideline for vitrectomy. In that way, the observation of the patients with relatively well-preserved VA and MFT will be continued as the current procedure. On the contrary, Holland at al. (1) also found a significant correlation between the level of pre- and postoperative VA: the better preoperative VA, the better the postoperative VA gets. In such cases, it will be beneficial to perform PPV to the majority of these patients, to ensure that the VA improves as much as possible, preferably up to the normal.

It has been reported (9) that LMH-associated Epiretinal Proliferation (LHEP), described as yellowish pigmented and soft material over the retina, turn the ERM/ILM-peeling into a more difficult task to perform surgically than "conventional ERM". The robustness of the LHEP certainly explains its ability to induce permanent changes, which results in poorer preoperative BCVA and lack of improvement postoperatively (34). LHEP is commonly presented in the degenerative type of LMH, and confirms that this is a more permanent condition than the tractional type. The result by Coassin et al. (35) concluded that BCVA significantly improved postoperatively in the tractional group ($p<0.0001$), but not in the degenerative group ($p=0.27$).

This is in agreement with the recently published meta-analysis by Xu et al. (36), which included 8 studies that have been investigating whether LHEP may can be used to predict the VA postoperatively. The meta-analyse confirmed that patients without LHEP had better postoperative VA than patients with LHEP. Our multicenter study could not investigate the presence of LHEP; however, 3 patients of the degenerative type had no conventional ERM presented. Nevertheless, both LMH types gained advantage from the ILM/ERM-peeling, with a significant improvement of the BCVA ($p<0.001$).

Full Thickness Macular Hole, as already mentioned, is a feared but not unpreventable complication of LMH, both in the natural pathophysiological course and as a postoperatively complication. A recent study published in 2021 by Chehaibou et al. (37) performed a centripetally oriented ILM-peeling, where they left some proliferative material at the edges of the hole, in order to not impair its connection with the underlying retinal layers. The peri-hole peeling technique was used to reduce to risk of postoperative FTMH, and none of their 11

patients developed this complication. Additionally, the remaining material will, in terms of its contents of cells and tissue, contribute to migration and closure of the foveal defect. The study's limited sample size does it necessary to attempt this technique in several studies with a larger number of included patients. New and possible more preferred techniques, that may result in better postoperatively outcomes and simultaneous minimize the risk of complications, are important to determine for future treatment purposes.

Moreover, a recently published study by Hagenau et al. (38) injected highly concentrated autologous Platelet-Rich Plasma (PRP) to restore the foveal anatomy. The autologous PRP, where the thrombocytes serve as a natural reservoir of multiple growth factors, constitutes an important role in the healing process as it interacts and recruits Mueller cells and glial cells of neuroretina. The centrifugal exclusion of white blood cells from the plasma (e.g., neutrophil granulocytes) reduces the potential proinflammatory effects. The use of autologous plasma in macular surgery has been described since the 1990s in patients with FTMH (39), and it is therefore appropriate to attempt this procedure to Lamellar Macular Hole as well, as it presumably accelerates to restoration of the LMH compared to a natural healing process.

In the study by Hagenau (38) all of the 8 patients, whom got implantation of highly concentrated autologous Platelet-Rich Plasma, showed closure of the LMH with normal foveal configuration 3 months postoperatively at the OCT scans. The functional outcome, BCVA, also improved significant ($p=0.03$). The restricted number of included patients does it necessary to do several comparative trials, preferably prospective.

This study has been an eye opener for that LMH not can be considered as only one morphological condition, but that the combination and extent of the different anatomical parameters, such as; depth, width, EZ continuity, macular edema, ERM and vitreomacular detachment, cause a broad spectrum of conditions. Of that reason we agree with Choi et al. (34) in their conclusion that the different combinations of parameters may explain the wide variability of visual acuity that has been reported after vitrectomy of LMH. Consequently, one cannot apply the same yardstick to all the LMH patients, and the intervention should be individualized in same direction as any other precisions medicine, that is a current affair in the health care. The comparison with previous studies can be used as a tool to predict the prognosis based on given parameters in each patient, and be used to evaluate the best option for intervention.

OCT parameters may predict whether surgical intervention improve the visual acuity or not. However, this should not prevent an individual with poor potential for improvement, based on predicting parameters, to be offered vitrectomy when one's condition is progressing. We are in agreement with Choi et al. (34) in their recommendation of vitrectomy for patients who have progressive, disabling visual loss and an increase in EZ disruption. This should be included in a new, consolidated protocol for LMH intervention.

4.4 Utility value – clinical implications

To date, vitrectomy of FTMH has given extensive successful evidence, as well as established surgical procedure worldwide. On the contrary, the surgical intervention for Lamellar Macular Holes has been disputed the last decade, with studies claiming LMH to be a stable condition (2), while other studies disagreeing, and additionally showing that vitrectomy has a beneficial effect (7, 35, 40). The lack of clinical unambiguity and studies with limited cohorts, led to the desire to retrospectively study our own patients, with the intention of a future new and more standardized protocol for LMH.

Despite the absence of a clear guideline for LMH at our hospital today, a serial OCT follow-up is usually a preferred approach for the asymptomatic patients, while deteriorating of visual acuity or metamorphopsias are indications for a surgical intervention.

Based on this retrospective multicenter study, in purpose of an improved approach of LMH as condition, the future procedure appear to treat the majority of Lamellar Macular Holes with PPV. The patient's pros and cons of the surgical intervention should be in consideration in advance, and individual trade-offs done if needed. If cataract simultaneous is presented, a combined phaco-vitrectomy should be performed, in regard to both socio-economic and individual interests.

4.5 Further research

In the recent years there has been an increased interest and a number of conducted clinical studies of Lamellar Macular Holes, due to the revolutionary Optical Coherence Tomography. With its detailed resolution, the knowledge of the condition and contributing mechanisms has reached a level where the surgical intervention truly is debated. Although the scientific questions of the development and undiscovered risk factors are many, the society influence the research in a treatment driven direction. This is of importance to preserve the patients' vision and quality of life. Nevertheless, the science has to continue mapping the underlying pathophysiological mechanisms, as this may contribute to halt the progression or initiation of the defects in macula. In that case, research will be about exploring preventive aspects, rather than the effects of the post-accidentally, repairing surgery for LMH.

Further research should also focus whether the pathological mechanisms reoccupy postoperatively, and if so, how fast these changes occur. It is conceivable that the pathological mechanisms slowly damage macula into a Lamellar Macular Hole, since the condition mainly affect the elderly population, although it sometimes suddenly progresses to a Full-Thickness Macular Hole. If any LMH re-development also is an equally slow progress, it may be unlikely in a perspective of time that this will be a problem for the majority of the elderly patients. This hypothetic reflection needs to be studied in long-term follow ups of postoperative LMH patients, and will be useful to achieve a greater holistic knowledge of Lamellar Macular Holes.

Furthermore, prospective studies are useful to determine preoperative factors, such as concomitant eye disorders, and either subgroup or exclude these patients from the study. Prospective studies will also ensure more standardized pre- and postoperative examinations. In our case, either do the postoperative controls ourselves, or make sure that other ophthalmologists routinely send copies of the journals with OCT-scans. In that way one would be able to compare pre- and postoperative OCT-scans, thus investigate the anatomical outcomes, and whether these changes correlate with the functional outcomes.

Standardized examinations should also include a longer follow-up period, with several postoperative controls. For example, first day postoperatively, and at 4 weeks, 6 months and 12 months. This according to the not well-known time of foveal healing, combined with the individual differences that affect this process.

Larger sample size would moreover be useful in addressing the question whether there is differential efficacy between the surgical techniques within the vitrectomy. This especially applies the recently peri-hole peeling technique attempted by Chehaibou et al. (37), the double inverted flap technique studied by Frisina et al. (41), the foveal sparing ILM-peeling by Morescalchi et al. (42), the embedding of LHEP into the foveal cleavage by Takahashi et al.(43), and the implantation of highly concentrated autologous Platelet-Rich Plasma (PRP) used by Hagenau et al. (38), to recruit and stimulate migration Mueller cells, and thereby the foveal restoration.

5 Conclusion

Until now visual and anatomical outcomes of PPV for LMH have shown inconsistent outcomes, where some have proven a beneficial improvement, while others do not find any statistical significance postoperatively. This discrepancy could be explained by the different surgical approaches. This study, which includes use of the different tamponades during PPV, has taken this into account, so that the pre- and postoperatively outcomes could be used for a representative comparison.

In conclusion, the procedure which tends to best improve the functional and anatomical outcomes in this study is injection of only BSS, preferably with combined phaco-vitrectomy, if cataract is presented. The surgical intervention improves both the BCVA in the tractional ($p<0.001$) and the degenerative group ($p<0.001$). The use of BSS could also be preferred, since it does not dispose for any postoperative cataract development, which is the case with the use of gas-tamponades. Additionally, none of our patients experienced a LMH reopening or FTMH development, which are complications one previously thought could be prevented by gas-tamponade.

Abbreviations

LMH – Lamellar macular hole

PPV – Pars plana vitrectomy

ILM – Internal limiting membrane

OCT – Optical coherence tomography

ERM – Epiretinal Membrane

VMT – Vitreomacular traction

BCVA – Best Corrected Visual Acuity

VA – Visual acuity

EZ – Ellipsoid zone

LHEP – LMH-associated epiretinal proliferation

CFT – Central foveal thickness

MFT – Minimal foveal thickness

ONL – Outer nuclear layer

OPL – Outer plexiform layer

BSS – Balanced salt solution

PRP – Platelet-Rich Plasma

References

1. Holland L, Chen JC, Lee LR. Anatomical and Functional Outcomes of Pars Plana Vitrectomy for Lamellar Macular Defects. Asia Pac J Ophthalmol (Phila). 2015;4(3):134-9.
2. Purtskhvanidze K, Balken L, Hamann T, Wöster L, von der Burchard C, Roider J, et al. Long-term follow-up of lamellar macular holes and pseudoholes over at least 5 years. Graefes Arch Clin Exp Ophthalmol. 2018;256(6):1067-78.
3. Lee CS, Koh HJ, Lim HT, Lee KS, Lee SC. Prognostic factors in vitrectomy for lamellar macular hole assessed by spectral-domain optical coherence tomography. Acta Ophthalmol. 2012;90(8):e597-602.
4. Yeo JH, Oh R, Lee JY, Kim JG, Yoon YH, Kim YJ. Optical coherence tomography angiographic findings of lamellar macular hole: comparisons between tractional and degenerative subtypes. Sci Rep. 2020;10(1):13331.
5. Theodossiadis PG, Grigoropoulos VG, Emfietzoglou I, Nikolaidis P, Vergados I, Apostolopoulos M, et al. Evolution of lamellar macular hole studied by optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2009;247(1):13-20.
6. Sanisoglu H, Elbay A, Sevim S, Celik U, Aktas FB, Durmus E. Surgical therapy versus observation for lamellar macular hole: a retrospective comparison study. Clin Ophthalmol. 2013;7:1843-8.
7. Figueroa MS, Govetto A, Steel DH, Sebag J, Virgili G, Hubschman JP. PARS PLANA VITRECTOMY FOR THE TREATMENT OF TRACTIONAL AND DEGENERATIVE LAMELLAR MACULAR HOLES: Functional and Anatomical Results. Retina. 2019;39(11):2090-8.
8. Figueroa MS, Noval S, Contreras I. Macular structure on optical coherence tomography after lamellar macular hole surgery and its correlation with visual outcome. Can J Ophthalmol. 2011;46(6):491-7.
9. Parolini B, Schumann RG, Cereda MG, Haritoglou C, Pertile G. Lamellar macular hole: a clinicopathologic correlation of surgically excised epiretinal membranes. Invest Ophthalmol Vis Sci. 2011;52(12):9074-83.
10. Romano MR, Vallejo-Garcia JL, Camesasca FI, Vinciguerra P, Costagliola C. Vitreo-papillary adhesion as a prognostic factor in pseudo- and lamellar macular holes. Eye (Lond). 2012;26(6):810-5.
11. Pang CE, Spaide RF, Freund KB. Comparing functional and morphologic characteristics of lamellar macular holes with and without lamellar hole-associated epiretinal proliferation. Retina. 2015;35(4):720-6.
12. Casparis H, Bovey EH. Surgical treatment of lamellar macular hole associated with epimacular membrane. Retina. 2011;31(9):1783-90.
13. Garretson BR, Pollack JS, Ruby AJ, Drenser KA, Williams GA, Sarrafizadeh R. Vitrectomy for a symptomatic lamellar macular hole. Ophthalmology. 2008;115(5):884-6.e1.
14. Michalewska Z, Michalewski J, Odrobina D, Nawrocki J. Non-full-thickness macular holes reassessed with spectral domain optical coherence tomography. Retina. 2012;32(5):922-9.
15. Duker JS, Kaiser PK, Binder S, de Smet MD, Gaudric A, Reichel E, et al. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. Ophthalmology. 2013;120(12):2611-9.

16. Nava U, Cereda MG, Bottoni F, Preziosa C, Pellegrini M, Giani A, et al. Long-term follow-up of fellow eye in patients with lamellar macular hole. Graefes Arch Clin Exp Ophthalmol. 2017;255(8):1485-92.
17. Gass JD. Lamellar macular hole: a complication of cystoid macular edema after cataract extraction: a clinicopathologic case report. Transactions of the American Ophthalmological Society.73:231-50.
18. Haouchine B, Massin P, Tadayoni R, Erginay A, Gaudric A. Diagnosis of macular pseudoholes and lamellar macular holes by optical coherence tomography. Am J Ophthalmol. 2004;138(5):732-9.
19. Hee MR, Puliafito CA, Wong C, Duker JS, Reichel E, Schuman JS, et al. Optical coherence tomography of macular holes. Ophthalmology. 1995;102(5):748-56.
20. Puliafito CA, Hee MR, Lin CP, Reichel E, Schuman JS, Duker JS, et al. Imaging of macular diseases with optical coherence tomography. Ophthalmology. 1995;102(2):217-29.
21. Witkin AJ, Ko TH, Fujimoto JG, Schuman JS, Baumal CR, Rogers AH, et al. Redefining lamellar holes and the vitreomacular interface: an ultrahigh-resolution optical coherence tomography study. Ophthalmology. 2006;113(3):388-97.
22. Hubschman JP, Govetto A, Spaide RF, Schumann R, Steel D, Figueroa MS, et al. Optical coherence tomography-based consensus definition for lamellar macular hole. Br J Ophthalmol. 2020;104(12):1741-7.
23. Govetto A, Dacquay Y, Farajzadeh M, Platner E, Hirabayashi K, Hosseini H, et al. Lamellar Macular Hole: Two Distinct Clinical Entities? American Journal of Ophthalmology.164:99-109.
24. Pang CE, Spaide RF, Freund KB. Epiretinal proliferation seen in association with lamellar macular holes: a distinct clinical entity. Retina. 2014;34(8):1513-23.
25. Norsk Oftalmologisk Forening IS-J. Maculakirurgi Helsebiblioteket 2016 [24.04.21]. Available from: https://www.helsebiblioteket.no/retningslinjer/oftalmologi/retina/maculakirurgi.
26. Bottoni F, Deiro AP, Giani A, Orini C, Cigada M, Staurenghi G. The natural history of lamellar macular holes: a spectral domain optical coherence tomography study. Graefes Arch Clin Exp Ophthalmol. 2013;251(2):467-75.
27. Androudi S, Stangos A, Brazitikos PD. Lamellar macular holes: tomographic features and surgical outcome. Am J Ophthalmol. 2009;148(3):420-6.
28. Lee SJ, Jang SY, Moon D, Choi KS, Jung GY. Long-term surgical outcomes after vitrectomy for symptomatic lamellar macular holes. Retina. 2012;32(9):1743-8.
29. Coassin M, Mastrofilippo V, Stewart JM, Fanti A, Belpoliti M, Cimino L, et al. Lamellar macular holes: surgical outcome of 106 patients with long-term follow-up. Graefes Arch Clin Exp Ophthalmol. 2018;256(7):1265-73.
30. Sun JP, Chen SN, Chuang CC, Lin CW, Lin CJ, Huang JY, et al. Surgical treatment of lamellar macular hole secondary to epiretinal membrane. Graefes Arch Clin Exp Ophthalmol. 2013;251(12):2681-8.
31. Michalewska Z, Michalewski J, Odrobina D, Pikulski Z, Cisiecki S, Dziegielewski K, et al. Surgical treatment of lamellar macular holes. Graefes Arch Clin Exp Ophthalmol. 2010;248(10):1395-400.
32. Hertzberg SNW, Veiby N, Bragadottir R, Eriksen K, Moe MC, Petrovski B, et al. Cost-effectiveness of the triple procedure - phacovitrectomy with posterior capsulotomy compared to phacovitrectomy and sequential procedures. Acta Ophthalmol. 2020;98(6):592-602.

33. Schumann RG, Vogt D, Haritoglou C, Hagenau F, Siedlecki J, Wolf A, et al. [Histopathological correlation of epiretinal tissue in lamellar macular holes and macular pseudoholes]. Ophthalmologe. 2017;114(12):1110-6.
34. Choi WS, Merlau DJ, Chang S. Vitrectomy for Macular Disorders Associated with Lamellar Macular Hole Epiretinal Proliferation. Retina. 2018;38(4):664-9.
35. Coassin M, Mastrofilippo V, Stewart JM, Fanti A, Belpoliti M, Cimino L, et al. Lamellar macular holes: surgical outcome of 106 patients with long-term follow-up. Graefes Archive for Clinical & Experimental Ophthalmology. 2018;256(7):1265-73.
36. Xu H, Qin L, Zhang Y, Xiao Y, Zhang M. Surgery outcomes of lamellar macular eyes with or without lamellar hole-associated epiretinal proliferation: a meta-analysis. BMC Ophthalmol. 2020;20(1):345.
37. Chehaibou I, Philippakis E, Mané V, Lavia C, Couturier A, Gaudric A, et al. Surgical outcomes in patients with lamellar macular holes selected based on the optical coherence tomography consensus definition. Int J Retina Vitreous. 2021;7(1):31.
38. Hagenau F, Nobl M, Vogt D, Schworm B, Siedlecki J, Kreutzer T, et al. Highly Concentrated Autologous Platelet-Rich Plasma Restores Foveal Anatomy in Lamellar Macular Hole Surgery. Klin Monbl Augenheilkd. 2021;238(8):885-92.
39. Liggett PE, Skolik DS, Horio B, Saito Y, Alfaro V, Mieler W. Human autologous serum for the treatment of full-thickness macular holes. A preliminary study. Ophthalmology. 1995;102(7):1071-6.
40. Sanisoglu H, Elbay A, Sevim S, Celik U, Aktas FB, Durmus E. Surgical therapy versus observation for lamellar macular hole: a retrospective comparison study. Clin. 2013;7:1843-8.
41. Frisina R, Parrozzani R, Pilotto E, Midena E. A Double Inverted Flap Surgical Technique for the Treatment of Idiopathic Lamellar Macular Hole Associated with Atypical Epiretinal Membrane. Ophthalmologica. 2019;242(1):49-58.
42. Morescalchi F, Russo A, Gambicorti E, Cancarini A, Scaroni N, Bahja H, et al. PEELING OF THE INTERNAL LIMITING MEMBRANE WITH FOVEAL SPARING FOR TREATMENT OF DEGENERATIVE LAMELLAR MACULAR HOLE. Retina. 2020;40(6):1087-93.
43. Takahashi K, Morizane Y, Kimura S, Shiode Y, Doi S, Okanouchi T, et al. Results of lamellar macular hole-associated epiretinal proliferation embedding technique for the treatment of degenerative lamellar macular hole. Graefes Arch Clin Exp Ophthalmol. 2019;257(10):2147-54.