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Prognostic Factors in Patients with Persistent Full-Thickness Idiopathic Macular Holes Treated with Re-Vitrectomy with Autologous Platelet Concentrate

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Keywords

Persistent macular hole · Re-vitrectomy · Autologous platelet concentrate

Abstract

Purpose: To identify the predictors for anatomical and functional outcome after re-vitrectomy with application of autologous platelet concentrate (APC) in eyes with persistent idiopathic macular hole (MH). ***Methods:*** Retrospective study of 103 eyes with persistent MHs after vitrectomy with peeling of internal limiting membrane (ILM) and expansive gas. All patients underwent re-vitrectomy with APC and endotamponade. The anatomical MH closure rate and postoperative best-corrected visual acuity (BCVA) were evaluated. Further, predictive factors influencing the success of the surgery were analyzed. ***Results:*** Median BCVA (logMAR) before the surgery was 1.00 (interquartile range [IQR] 0.80–1.30) and the median of minimum diameter between hole edges was 508 µm (IQR 387–631). The final closure rate after re-vitrectomy with APC was 60.2% (62 of 103 eyes). The following predictors were identified to significantly influence the closure rate: tractional hole index (THI), axial length, time between first and second surgery, and the experience of the surgeon ($p < 0.05$). ***Conclusions:*** Re-vitrectomy with APC led to the closure of 60.2% of the persistent MHs. The closure rate negatively correlates with increasing axial length, time between the first and second surgery, and the decreased THI. Further, experienced surgeons (with a history of >100 pars plana vitrectomies with ILM peeling) had significantly higher closure rates.

Introduction

Since the pioneering work by Kelly and Wendel [1], the treatment of macular holes (MH) has been considerably refined. Gold standard treatment now includes pars plana vitrectomy (PPV), induction of posterior vitreous detachment, internal limiting membrane (ILM) peeling, and gas endotamponade. The reported closure rate after initial MH surgery is 85–90% [2–5].

Despite the vast improvement, persistent MHs still occur with a rate ranging from 8 to 44% [6–8]. Several treatment options have been described for persistent MHs including: repeated PPV with ILM re-peeling with or without adjuvants [9–13], membranectomy and autologous

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serum [14], autologous transplantation of ILM [15–17], autologous retinal transplant (ART) [18, 19], radial retinal incisions [20], lens capsular flap transplantation [21], and induction of macular detachment [22]. Furthermore, various adjuvants have been proposed: pneumatic retinopexy plus repeated fluid-gas exchange [23], endotamponade with long-lasting gas [9], laser photocoagulation to hole edges [24–27], silicone oil tamponade [28–30], autologous platelet concentrate (APC) [12, 31], and amnion membrane plug [32].

The sheer variety of different surgical strategies, however, shows that there is no consensus about the best treatment for persistent MHs so far [33]. This is mainly due to the lack of clinical studies with sufficiently large cohorts. There are multiple studies about new surgical strategies but hardly any with cohorts of a sufficient size to allow for confident judgement.

Therefore, we performed a retrospective, single-center chart review analyzing anatomical and functional results of patients with persistent MHs treated with re-vitrectomy and APC application to explore the underlying factors that decide between surgical success and failure.

To the best of our knowledge, this is the largest reported cohort of patients with persistent MHs treated with re-vitrectomy with APC application.

Materials and Methods

Study Participants

We retrospectively reviewed charts of all patients who underwent re-operation due to persistent idiopathic MH at the Department of Ophthalmology of the University Hospital Leipzig, Leipzig, Germany, between January 1, 2008 and June 30, 2018. The following were set as inclusion criteria, with all the criteria being met: (1) idiopathic MH, (2) persistent MH after first PPV seen on optical coherence tomography (SD)-OCT, (3) data available prior and after first and second surgery, and (4) age >18 years. Exclusion criteria were (1) traumatic MHs, (2) any concomitant ocular or neurological condition that could affect the visual acuity (VA) except cataract, and (3) degenerative myopia, defined as axial length >26 mm with presence of pathological myopic maculopathy.

Data Collection

For eligible patients, the following data were collected from their medical charts: demographic data (i.e., age, sex), lens status at baseline, axial length, VA pre- and postoperatively as well as in follow-up visits.

Outcome Measures

The main outcome measure was the MH closure rate after second surgery. Secondary outcome measures were VA, maximum hole diameter, diameter at ILM level, minimum diameter between edges, hole height, and tractional hole index (THI) after second surgery. VA was determined by a decimal VA chart at 5 m or at 1 m and then converted to logarithm of the minimum angle of resolution (logMAR).

OCT Analysis

In all eyes, macular OCT scans were captured using SD-OCT (Heidelberg Spectralis, Heidelberg, Germany). At each visit, 6 radial scans through the fovea were obtained. Morphological parameters as, for example, diameter and height of the MH as well as the length of defect zones in the ellipsoid zone (EZ) were manually measured using the "measure distance" function of the Spectralis OCT device. All manual measurements were performed independently by 2 graders (V.D. and M.R.). The THI was calculated as the ratio of the maximum height to minimum diameter of the MH as described by Ruiz-Moreno et al. [34].

Surgical Procedure

The re-vitrectomy was performed under general anesthesia and consisted of a standard 3 ports PPV using the 20-, 23-, or 25-gauge technique. ILM was stained with Brilliant Blue G: 0.125 mg (0.25 g/L; ILM-BLUE® D.O.R.C, The Netherlands). The additional peeling was performed if residual ILM was detected in the foveal region. After fluid-air exchange, with the vitreous cavity and the MH completely dry, 2 drops of APC were applied over the MH with a vitrectomy back-flush needle mounted on a 2-mL syringe, followed by endotamponade with either sulfur hexafluoride (SF6) or octafluoropropane (C3F8). A combined PPV with cataract surgery was performed when necessary. After the surgery, the patient was required to maintain a supine position for 12 h and a prone position thereafter for 3–5 days.

APC Preparation

APC was prepared at the Institute for Transfusion Medicine of the University Hospital Leipzig. Around 250 mL of venous blood was taken from the patient and stored overnight on cooling elements, 1 day before surgery. The next day, a 2-step centrifugation was performed (500 g, 2 × 10 min) to obtain platelet-rich plasma (PRP) which was stored for at least 2.5 h in a thrombocyte agitator at 22 °C. The final product had a volume of 5–10 mL, and the average concentration of thrombocytes was $1–5 \times 10^{10}$/mL.

Statistical Evaluation

The demographic and clinical characteristics of our study cohort were evaluated using traditional descriptive methods. A logistic regression model for the outcome measure (MH closure after second surgery) was run for the entire study population and for the cohort with SF6 tamponade separately by testing the following predicting variables: (1) age, (2) gender (male vs. female), (3) axial length, (4) maximum diameter at the ILM level after first surgery, (5) change in the maximum diameter at the ILM level, (6) the minimum diameter between hole edges after first surgery, (7) change in the minimum diameter between hole edges, (8) the maximum base diameter after first surgery, (9) change in the maximum base diameter, (10) MH height after first surgery, (11) change in MH height, (12) THI after first surgery, (13) change in THI, and (14) experienced surgeon (yes vs. no). The surgeon was classified as "experienced" if he/she had performed PPVs with ILM peeling >100 times. To control for the correlated nature of our data, we used a generalized estimating equations (GEE) procedure. Confounders with $p \leq 0.15$ in the univariable analysis were included in the final GEE model. A backward selection procedure was applied that retained only those variables with $p < 0.05$. With all significant confounders of the final GEE model, a predicted value of the mean of macular closure was computed. Values are presented as median and interquartile range (IQR). Statistical analysis was performed with SPSS Statistics 25 (IBM, Armonk, NY, USA).

Results

The study cohort comprised 103 eyes of 100 patients with a median age of 71.1 years. Baseline characteristics and morphological data of the MHs before first and second vitrectomy are displayed in Table 1. The main characteristics of the first and second surgery are shown in Table 2. APC was rarely used in first surgery.

Outcomes after Second Surgery

The outcomes of the re-vitrectomy are summarized in Table 3. The overall closure rate was 60.2% (62 of 103 eyes).

Functional Results

VA improved when the MH was closed and worsened when the MH remained open after re-vitrectomy (–0.2 resp. +0.18 logMAR).

Anatomical Results

In closed MHs, EZ damage was present in 81.4% with a median diameter of 459 µm. The central subfield thickness was 170 µm (IQR 110–208). In unclosed MHs, all morphological characteristics worsened by the second surgery (Table 3).

Predictors for MH Closure after Second Surgery

Multivariate analysis of the entire study cohort revealed that odds of MH closure after second surgery increased with shorter axial length ($p = 0.044$), decreased time interval between the first and second surgery ($p = 0.025$), increased THI ($p < 0.001$), and if an experienced surgeon operated ($p = 0.003$; see Table 4).

Because the majority of patients received a tamponade with SF6 gas, an additional analysis of the cofounders was performed separately for this subgroup. For these patients, no correlation with the time interval between the first and second surgery could be confirmed ($p = 0.119$). Further, due to the smaller number of patients with SF6 tamponade, the correlation between axial length and the closure rate just missed the significance level ($p = 0.06$).

Based on data from the entire study population, Figure 1 displays the predicted probability of MH closure at different THI and different axial length values stratified for surgeon experience.

Table 1. Baseline characteristics of 100 patients ($n = 103$ eyes)

Median age, years (IQR)	71.1 (66.6–75.5)
Male gender, *n* (%)	22 (22.3)
Pseudophakia, *n* (%)	15 (14.6)
Median axial length, mm (IQR), $n = 87$	23.1 (22.7–23.7)
Before first surgery, median (IQR)	
VA, logMAR	0.80 (0.70–1.00)
Maximum diameter at ILM, µm	834 (648–1,001)
Minimum diameter between edges, µm	434 (292–529)
Maximum base diameter, µm	886 (673–1,090)
Height, µm	458 (424–509)
THI	1.15 (0.83–1.58)
Before second surgery, median (IQR)	
VA, logMAR	1.0 (0.80–1.30)
Maximum diameter at ILM, µm	1,039 (904–1,197)
Minimum diameter between edges, µm	508 (387–631)
Maximum base diameter, µm	1,138 (836–1,399)
Height, µm	555 (457–649)
THI	1.14 (0.90–1.50)
Days between first and second surgery	102 (68–144)

Table 2. Characteristics of first and second surgery

First surgery	
Vitrectomy gauge, *n* (%)	
20 gauge	2 (1.9)
23 gauge	99 (96.1)
25 gauge	2 (1.9)
Used tamponade, *n* (%)	
SF6 gas	98 (95.1)
C3F8 gas	4 (3.9)
Air	1 (1.0)
Vitrectomy combined with cataract surgery	6 (5.8)
Second surgery	
Vitrectomy gauge, *n* (%)	
20 gauge	4 (3.9)
23 gauge	97 (94.1)
25 gauge	2 (1.9)
Experienced surgeon, *n* (%)	68 (66.0)
Used tamponade, *n* (%)	
SF6 gas	88 (85.4)
C3F8 gas	14 (13.6)
Air	1 (1.0)
Vitrectomy combined with cataract surgery, *n* (%)	9 (8.7)

Discussion

In the last decades, retinal surgeons, globally, have refined the technique for MH surgery with hole closure rates of up to 90% being reported in several publications [3–5]. However, persistent MHs still occur with a rate ranging from 8 to 44% [33]. The treatment for such holes

Table 3. Outcomes after second surgery (*n* = 103)

Hole closure overall cohort, *n* (%)	62 (60.2)
Days between second surgery and final follow-up, median (IQR)	60.0 (47.0 to 87.0)
Closed MH, n = 62	
Morphologic parameters before 2nd surgery, median (IQR)	
Maximum diameter at ILM, μm	1,004 (863 to 1,165)
Minimum diameter between edges, μm	457 (370 to 563)
Maximum base diameter, μm	1,122 (826 to 1,441)
Height, μm	582 (478 to 671)
THI	1.27 (1.03 to 1.71)
Morphologic parameter after 2nd surgery	
Median VA change from first surgery, logMAR (IQR)	–0.20 (–0.40 to 0.00)
Median central subfield thickness, μm (IQR)	170 (110 to 208)
Presence of EZ damage, *n* (%)	48 (81.4)
Median diameter of EZ damage, μm (IQR)	459 (291 to 784)
Unclosed MH, n = 41	
Morphologic parameters before 2nd surgery, median (IQR)	
Maximum diameter at ILM, μm	1,086 (964 to 1,226)
Minimum diameter between edges, μm	563 (490 to 713)
Maximum base diameter, μm	1,172 (996 to 1,363)
Height, μm	547 (451 to 637)
THI	0.93 (0.77 to 1.19)
Morphologic parameter after 2nd surgery, median (IQR)	
VA change from first surgery, logMAR	0.18 (0.04 to 0.31)
Maximum diameter at ILM, μm	1,111 (1,001 to 1,310)
Change in maximum diameter at ILM, μm[a]	382 (146 to 470)
Minimum diameter between edges, μm	609 (498 to 766)
Change in minimum diameter between edges, μm[a]	216 (–36 to 418)
Maximum base diameter, μm	1,142 (779 to 1,549)
Change in maximum base diameter, μm[a]	433 (–187 to 740)
Height, μm	544 (448 to 636)
Change in height, μm[a]	90 (–11 to 184)
THI	0.92 (0.71 to 1.12)
Change in THI[a]	–0.02 (–0.24 to 0.12)

[a] Change from first surgery.

is still challenging, which is evident by the sheer number of different surgical techniques having been introduced in the previous years. Especially, when study cohorts are small, very high closure rates are published. Furthermore, heterogeneous study populations with persistent and recurrent MHs make it difficult to draw any valid conclusion.

We present the results of a large cohort of patients with persistent MHs treated with re-vitrectomy and APC application. We achieved an overall closure rate of 60.2% (62 of 103 eyes) which is comparable to the study published by Hillenkamp et al. [12] who reported a closure rate of 68% (17 of 22 eyes). Nevertheless, some studies show a higher closure rate: Valldeperas and Wong [13] with 76% (38/51), Dimopoulos et al. [35] with 78% (21/27), and Purtskhvanidze et al. [36] with 85% (52 of 61 eyes). The multicenter study published by Grewal et al. [19] showed a closure rate of 88% (36 of 41 eyes) in large MH after re-vitrectomy with ART.

According to the International Vitreomacular Traction Study (IVTS) group [37], large MHs are defined by a diameter >400 μm at the narrowest point of the hole and reportedly have a limited prognosis. Our study cohort showed a median diameter of 434 μm (IQR 292–529) before first surgery and 508 μm (IQR 387–631) before second surgery. Moreover, 33% of re-vitrectomies were performed by surgeons with limited experience. These circumstances may partly explain our rather low closure rate. Furthermore, in some cases, the surgeons decided to

Table 4. Confounders of closure rate after second surgery

	All tamponades (n = 103)			SF6 gas tamponade (n = 88)		
	univariable analysis, *p* value	multivariable analysis, *p* value	OR (95% CI)[a]	univariable analysis, *p* value	multivariable analysis, *p* value	OR (95% CI)[a]
Age, years	0.746	–	–	0.885	–	–
Gender, male vs. female	0.630	–	–	0.399	–	–
Axial length, mm	0.048	**0.044**	0.568 (0.335–0.962)	0.070	0.060	0.474 (0.380–1.020)
Time between first and second surgery, days	0.003	**0.025**	0.992 (0.984–0.999)	0.009	0.119	
Longest diameter at ILM level after first surgery, μm	0.027	0.698	–	0.011	0.659	–
Change in longest diameter at ILM level, μm	0.174	–	–	0.088	0.610	–
Minimum diameter between edges after first surgery, μm	0.001	0.210	–	0.001	0.996	–
Change in minimum diameter between edges, μm	0.027	0.903	–	0.037	0.340	–
Longest base diameter after first surgery, μm	0.347	–	–	0.311	–	–
Change in longest base diameter, μm	0.130	0.168	–	0.176	–	–
Height, μm	0.160	–	–	0.321	–	–
Change in height, μm	0.570	–	–	0.720	–	–
Height/minimum-diameter-between-edges ratio	0.002	**<0.001**	8.699 (2.166–34.939)	0.002	**<0.001**	10.734 (3.095–37.230)
Change in height/minimum-diameter-between-edges ratio	0.062	0.634	–	0.088	0.421	–
Experienced surgeon (yes vs. no)	0.019	**0.003**	4.047 (1.347–12.162)[b]	0.012	**0.002**	5.436 (1.836–16.098)[b]

Tested by generalized estimating equations model, logistic regression. [a] Odds of MH closure for one unit increase in the independent variable (first column). [b] Odds of MH closure for experienced surgeon.

enlarge the area of ILM peeling during re-vitrectomy. It could be speculated that an insufficient ILM peeling might have prevented the closure of the MH. Therefore, the additional benefit of APC is questionable in these cases.

The median time interval between the first and second surgery of 102 days (IQR 68–144) may contribute to the low closure rate in our series, as we found a shorter time interval to be predictive of higher surgical success.

Our anatomical results in terms of an observed EZ damage in 81% of patients with 459 μm in diameter (IQR 291–784) compares well to Purtskhvanidze et al. [36] who reported EZ damage in 76% of patients with 550 μm in diameter (±340 μm). Regarding the central subfield thickness, our findings (170 μm, IQR 110–208) are in tune with the aforementioned study group (179 ± 72 μm). This seems to indicate that after re-vitrectomy with APC, slight atrophy of the retina is to be expected. Therefore, one might consider EZ damage and retinal atrophy as a complication of APC use. However, due to limited data, it remains unclear whether the EZ damage is related to the APC or the surgical procedure only.

Hillenkamp et al. [12] proposed a classification depending on the MH configuration ("with cuff" or "without cuff") and reported a "with cuff" configuration to be a positive prognostic factor for anatomical closure after re-vitrectomy. Purtskhvanidze et al. [36] recently published contradicting results regarding this classification, finding no correlation between the hole configuration and the closure rate. Therefore, it seems that a more mathematical approach to describe the MH configuration with OCT based indices, as firstly proposed by Kusuhara et al. [38] and later by Ruiz-Moreno et al. [34], offers a more refined method for prognostication. We adopted this approach to identify patients with favorable prognosis and found a strong confounder in the THI.

The multivariate analysis of confounders for anatomical success of the surgery with APC identified the correlation between closure rate and the axial length (p = 0.044). However, the analysis of the role of this factor in the subgroup with SF6 tamponade only just missed the level of significance (p = 0.06), which could be explained by the smaller sample size in this subgroup.

It is common knowledge that experienced surgeons reach a higher level of surgical safety, efficacy, and effectivity than their less experienced colleagues. Nevertheless, expertise is rarely considered as a determining aspect of a surgical procedure. Our data underlines what is intuitively expected by surgeons and patients: a well-trained and experienced surgeon provides for a better surgical outcome.

Unlike Purtskhvanidze et al. [36], we found a correlation between the MH closure rate and time between primary and secondary surgery. However, this correlation was observed only in the multivariate analysis of the en-

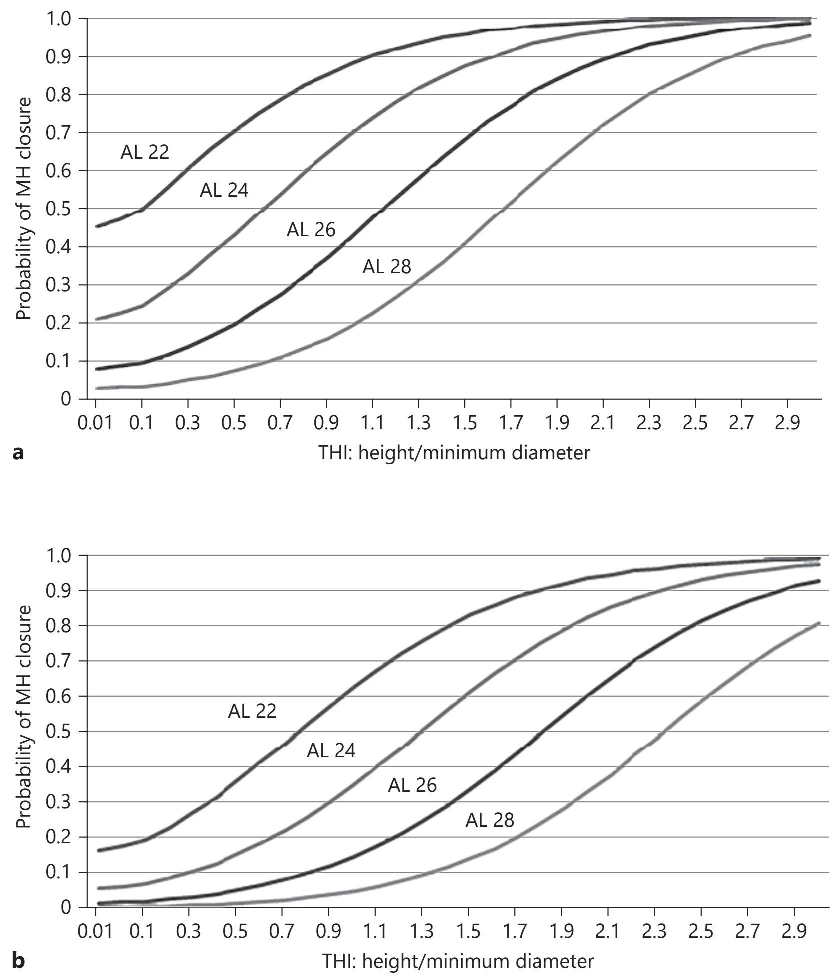

Fig. 1. Predicted probability of MH at different THI and AL values stratified for experienced (**a**) and unexperienced surgeon (**b**). AL is given in millimeters. AL, axial length; MH, macular hole; THI, tractional hole index.

tire study population and could not be observed in eyes with SF6 tamponade. Therefore, the role of the time point of the re-vitrectomy needs to be clarified in further studies.

To evaluate the visual outcome of our surgery, we chose to compare relative gains or losses. This seemed more reliable, since much depends on whether cataract surgery is performed. For closed MHs, the median visual gain was –0.20 logMAR (IQR –0.40 to 0). These findings are in line with results published by Valldeperas et al. [13] and Dimopoulos et al. [35] who reported a visual gain of –0.16 logMAR. More recently, Purtskhvanidze et al. [36] reported a gain in VA of –0.4 logMAR in eyes with successful re-vitrectomy and APC. The much better visual gain in this study might be explained by the higher proportion of pseudophakic eyes. Grewal et al. [19] observed a mean VA improvement of –0.08 logMAR after re-vitrectomy with ART; the improvement of ≥0.3 logMAR was observed in 15 of 41 eyes (36.6%).

In eyes, in which MHs remained unclosed, we observed a visual loss of +0.18 logMAR (IQR 0.04–0.31), which might be also caused by cataract development due to re-vitrectomy. Dimopoulos et al. [35] reported no change in VA in unclosed MHs. Therefore, based on our results as well as previous reports, it can be concluded that patients with persistent MH may expect a moderate gain in VA in case of a MH closure while expecting a moderate decrease of vision in case of an unsuccessful re-vitrectomy.

Limitations of our study include its retrospective nature and shortcomings of the real-world setting. Some parameters such as the reasons for the choice of endotamponade at the end of the surgery cannot be traced in a retrospective analysis. The lack of a control group without APC hinders comparability with results from other study groups who treated persistent MHs without APC.

Furthermore, we conducted multiple testing, which could have led to false-positive results.

In conclusion, we showed that re-vitrectomy with APC is an effective treatment for persistent MHs. We identified several parameters which influence the closure rate and functional recovery after re-vitrectomy. The THI was found to be the strongest cofounder, followed by the experience of the surgeon and the time between first and second surgery. Increased axial length correlated negatively with the closure rate.

Statement of Ethics

Institutional review board approval was obtained from the Ethical Committee of the Medical Faculty of the University of Leipzig, Leipzig, Germany. This research adhered to the tenets of the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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