IMPACT OF INNER LIMITING MEMBRANE PEELING ON VISUAL RECOVERY AFTER VITRECTOMY FOR PRIMARY RHEGMATOGENOUS RETINAL DETACHMENT INVOLVING THE FOVEA

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Purpose: To assess the impact of inner limiting membrane peeling during vitrectomy for macula-involving retinal detachment on best-corrected visual acuity (VA).

Methods: Retrospective analysis of 89 eyes with primary macula-involving retinal detachment, which was undergoing vitrectomy, endolaser, retinotomy, endodrainage, and SF_6 tamponade. Membrane-blue-assisted membrane peeling had been performed in 61 of the eyes (Group 1) but not in the other 28 (Group 2), which served as controls.

Results: Age, lens status, and incidence of proliferative vitreoretinopathy 26.2% versus 39.3%; $P = 0.23$ in the 2 groups were comparable. The preoperative visual acuity (Early Treatment Diabetic Retinopathy Study letters) was 25.7 ± 27.9 in Group 1 and 28.8 ± 29.9 in Group 2 ($P = 0.47$). After surgery, these rose from 62.3 ± 30.5 (Group 1) and 34.2 ± 35.8 (Group 2) after 1 week ($P = 0.090$), through 83.1 ± 8.0 and 57.2 ± 32.4 at 1 month ($P = 0.0005$), to 92.1 ± 4.5 and 74.4 ± 23.1 Early Treatment Diabetic Retinopathy Study letters after 6 months ($P = 0.0005$). More than 6-month incidences of proliferative vitreoretinopathy (13.1% vs. 28.6%; $P = 0.13$) were similar, whereas the redetachment rate (9.8% vs. 32.1%; $P = 0.014$), the incidence of secondary epiretinal membranes (1.6% vs. 35.7%; $P = 0.0005$), and the revitrectomy rate were lower in group 1 (9.8% vs. 53.6%; $P = 0.0005$).

Conclusion: Inner limiting membrane peeling during vitrectomy for macula-involving retinal detachment may substantially contribute to the visual recovery, reducing the incidence of secondary epiretinal membrane formation.

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In eyes with rhegmatogenous retinal detachment (RD), vitrectomy combined with either scleral buckling in younger individuals[1,2] or cataract surgery in aging ones is an increasingly popular intervention. Primary reattachment rates exceeding 80% are now achieved in the absence of preoperative proliferative vitreoretinopathy (PVR), even in cases in which no clear breaks are manifested.[3–6] If the macula is implicated, then the RD is more extensive, and in these cases, the long-term anatomical and functional outcomes are poorer. The functional prognosis depends, however, on the duration of the macular detachment: If this is treated within 3 to 7 days of the visual loss, the final Snellen best-corrected visual acuity may exceed 0.3.[7,8] If the vision is lost for 10 or more days, a satisfactory outcome is less likely.[8] The duration of the RD-associated visual loss is relevant not only for the functional recovery but also for the associated risk of redetachment requiring secondary surgery.[9] In up to 25% of the not or only moderately myopic eyes in which the loss of vision endures for

more than 1 week, secondary macular pathologies will develop macular puckering requiring additional surgery in 6%, cystoid macular edema in 17%, and full-thickness macular holes in up to 2%.[10]

The physiological role of the inner limiting membrane (ILM) is still not completely understood.[11–13] Although ILM peeling may theoretically have a negative impact on the physiology of the inner retina, its functional consequences have not yet been demonstrated.[14] During the past 2 decades, namely, since the introduction of vital dyes, ILM peeling has become a routine undertaking in the context of vitrectomy for macular diseases,[15] curtailing the duration of the surgical intervention, enhancing its safety, and rendering it a cost-effective therapy.[16] However, the trauma of the peeling itself or the toxic effects of the chosen dyes may give rise to the formation of microscotomata, which, nevertheless, do not interfere with the overall visual function.[17,18] The beneficial influence of ILM peeling on the closure rates of macular holes and on the need for further surgery is no longer an issue of debate.[19,20] Nor is it doubted that the procedure almost completely prevents the formation of secondary epiretinal membranes (ERMs) and of ERM recurrences after vitrectomy, which is the case also in the context of RD surgery[21] for highly myopic eyes with macular hole-associated detachment.[22] However, an impact of the ILM peeling on visual recovery has not been demonstrated in these highly myopic cases,[23,24] which are at risk of developing secondary macular holes.[25] Inner limiting membrane peeling has been shown to be advantageous in cases of recurrent, PVR, as well as in instances of complicated RD-requiring retinectomy and possibly also a silicone oil tamponade.[26–28] An explanation for this finding may be that 20% of the ILM material that is removed during ERM surgery carries glia and hyalocytes, which, if they remained, would contribute to the proliferative response that results in recurrent ERM formation and retinal traction.[29]

In summary, the anatomical outcome of vitrectomy for RD involving the macula is good, whereas the functional recovery is limited.[19,23] Inner limiting membrane peeling is a safe procedure if the macula is attached,[16,20] which improves the primary reattachment rate of the retina[26,27] and reduces the risk of secondary ERM formation.[21,28] It also improves the functional outcome of macular surgery.[30] Consequently, nothing argues against the instigation of this procedure as an adjunct to standard vitrectomy if the benefits may outweigh the risks associated with its technically demanding removal in the case of a detached macula. This may affect namely the cases of RD with a poor visual acuity at the time of presentation. In this study, we retrospectively addressed this point, comparing the functional and the anatomical outcomes of eyes with primary RD, which underwent vitrectomy with or without ILM peeling.

Patients and Methods

Patients were eligible for this retrospective analysis if they had presented with an uncomplicated primary rhegmatogenous RD involving the entire macula between 2008 and 2016 (at the Berner Augenklinik am Lindenhofspital, University of Bern, Bern, Switzerland). The exclusion criteria are detailed below under a separate heading. All patients underwent 23-gauge vitrectomy, as well as endolaser photocoagulation and cryoretinopexy as needed, which was effected within 24 hours of presentation in more than 90% of the eyes in each group. In the remaining eyes (6 in Group 1 and 2 in Group 2), reattachment surgery was performed within 2 to 4 days of presentation. In most cases, the procedure was combined with retinotomy to effect complete drainage of the subretinal fluid. All eyes received an injection of approximately 4 mg of triamcinolone and an SF_6 tamponade.

Inner Limiting Membrane Peeling Technique

The first 10 eyes that underwent ILM peeling had presented with a hyperreflective line on the inner retinal surface, but with no wrinkling or clinically visible epiretinal membrane. The former manifestation evidenced the presence of a prominent ILM. In these 10 eyes, the visual acuity was poor (≤20/100 = a score of 65 Early Treatment Diabetic Retinopathy Study (ETDRS) letters on a scale in which 100 letters corresponds to a best-corrected visual acuity [BCVA] of 20/20). All other eyes in which surgery was performed at this time underwent no ILM peeling; they served as control group (Group 2). After a higher-than-expected visual gain in the first 10 eyes that underwent ILM peeling, a decision was made to perform the procedure in all consecutive eyes presenting with uncomplicated macula-involving primary RD. All eyes that had undergone membrane-blue-assisted ILM peeling (n = 61) were allocated to Group 1 and those in which no ILM peeling had been performed (n = 28) to Group 2. After the fluid/air exchange and endodrainage of subretinal fluid through accessible breaks or, as in most instances, creation of a retinotomy outside the temporal vessel arcades, trypan blue (Membrane Blue, Dorc International, Zuidland, the Netherlands) was applied for 30 seconds strictly to the macular area. This was performed to minimize the risk of its

Table 1. Descriptive Statistics for BCVA (ETDRS Letter Scores)

	Before Surgery			1 Week After Surgery			1 Month After Surgery			6 Months After Surgery		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
ILM peeling	61	25.7 (20/630)	27.9	24	62.3 (20/125)	30.5	61	83.1 (20/40)	8.0	53	92.1 (20/32)	4.5
No ILM peeling	28	28.8 (20/500)	29.9	9	34.2 (20/400)	35.8	23	57.2 (20/160)	30.1	17	74.4 (20/63)	23.1
P		0.47			0.09			0.0005			0.0005	

Snellen visual acuity is reported in brackets.

diffusion to the subretinal space and potential toxicity to the retinal pigmented epithelium. The dye was removed before air/fluid exchange, followed by total ILM removal within the vascular arcades from the optic nerve head toward the periphery using a Tano end-gripping forceps (DORC International, Zuidland, the Netherlands). No heavy fluids were applied.

In phakic eyes, phakoemulsification with implantation of an intraocular lens was performed simultaneously in all but four eyes. In these four cases, cataract surgery was effected before the final (6 months) visit; the earlier postoperative visual acuity values were excluded from the analysis. At the time of RD surgery, 31 of the eyes in Group 1 and 18 in Group 2 were pseudophakic.

Outcome Measures

The assessment before surgery and at the 1- and 6-month postoperative junctures included a full clinical examination with OCT and wide-field photodocumentation to assess the retinal situation where possible.

The primary outcome measure was an improvement in BCVA after 6 months. The secondary outcome parameters were central retinal thickness, single-surgery anatomical success, and complication rates.

Exclusion Criteria

Excluded from the analysis were 200 eyes with the following conditions: secondary RD developing as a result of previous vitreal surgery (n = 32), trauma (n = 5), phakic eyes not receiving cataract surgery before the end of follow-up (n = 10), complications of cataract surgery that had arisen during the previous 6 months (n = 2), proliferative retinal vasculopathy (i.e., any stage of diabetic retinopathy [n = 4]), preexisting wet age-related macular degeneration (n = 6), RD in the context of a choroidal melanoma (n = 1), high myopia ($\geq$−7 dpt; n = 9), advanced ($\geq$Stage C2) PVR (n = 1), hereditary atrophy of the optic nerve (n = 2), and sarcoidosis (n = 2). Likewise excluded were all eyes presenting with primary RD involving the fovea in which a primary tamponade of silicone oil or longer-acting gases had been introduced (n = 107), those which had undergone cerclage without vitrectomy (n = 2), those which had been lost to the follow-up before 1 month (n = 4), and those in which redetachment of the retina with macular involvement had occurred within 28 days of surgery (Group 1: n = 10; Group 2: n = 3).

Statistical Analysis

Assuming that the data were not normally distributed, a series of nonparametric tests were conducted. Wilcoxon's signed-rank test was implemented to ascertain whether changes in the ETDRS letter scores within each of the two groups attained statistical significance. Mann–Whitney U test was performed to determine the significance of differences in the ETDRS letter scores over time between the groups.

Qualitative data appertaining to the number of eyes that required secondary surgery were analyzed at the 1- and 6-month junctures by applying Pearson chi-square test. The statistical analyses were performed using the SPSS software package V.23 (SPSS, Inc, Chicago, IL) and the ggplot2 packages (R Development Core Team, 2008). The level for statistical significance was set at a P value of less than 0.05. Unless otherwise indicated, the data are represented as mean values together with the SD.

Results

Eighty-nine eyes satisfied the criteria for inclusion in the analyses. Group 1 was composed of 61 and Group 2 of 28 eyes. The age of the patients, their lenticular status, and the incidence of PVR (26.2% [Group 1] vs. 39.3% [Group 2]; P = 0.23) were comparable in the two groups. After surgery, the presenting ETDRS letter scores (25.7 ± 27.9 in Group 1 and 28.8 ± 29.9 in Group 2 [P = 0.47]; ranging from counting fingers to 0.3 on Snellen scale) rose progressively from 62.3 ± 30.5 (Group 1)

Table 2. Change in BCVA (ETDRS Letter Scores)

	T0–T1		T0–T2		T0–T3		T2–T3	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
ILM peeling	+34.5, $P = 0.001$	35.8	+57.4, $P = 0.0005$	27.6	+64.9, $P = 0.0005$	27.8	+8.8, $P = 0.0005$	7.2
No ILM peeling	+17.2, $P = 0.33$	49.7	+26.5, $P = 0.003$	34.6	+44.6, $P = 0.001$	32.6	+8.2, $P = 0.07$	12.9
Mann–Whitney U test	$P = 0.33$		$P = 0.0005$		$P = 0.014$		$P = 0.38$	

Wilcoxon signed-rank test was implemented to ascertain whether the ETDRS letter scores within a group changed significantly between the time points (upper two-thirds of the Table). Mann–Whitney U test was applied to ascertain whether the ETDRS letter scores differed significantly between the two groups and between the time points (lower third of the Table).

T0, before surgery; T1, 1 week after surgery; T2, 1 month after surgery; T3, 6 months after surgery.

and 34.2 ± 35.8 (Group 2) after 1 week ($P = 0.09$), through 83.1 ± 8.0 (Group 1) and 57.2 ± 32.4 (Group 2) at 1 month ($P = 0.0005$), to 92.1 ± 4.5 (Group 1) and 74.4 ± 23.1 (Group 2) after 6 months ($P = 0.0005$, Table 1). Although the increase in visual acuity was statistically significant at the 1- and 6-month junctures in both groups ($P < 0.05$, Table 2), the greatest improvements were observed in the Group 1 eyes, namely, in those that had undergone ILM peeling ($P < 0.05$; Figure 1).

The redetachment and the PVR rates over 6 months in the 2 groups were as follows: redetachment rates (9.8% [Group 1] vs. 32.1% [Group 2]; $P = 0.014$) and PVR rates (13.1% [Group 1] vs. 28.6% [Group 2]; $P = 0.13$). The incidence of revitrectomy within 6 months was higher in Group 2 eyes (9.8% [Group 1] vs. 53.6% [Group 2]; $P = 0.0005$). This latter finding reflects the formation of secondary ERMs in Group 2 eyes (1/61 [Group 1] vs. 10/28 [Group 2]; $P = 0.0005$). Table 3 represents the incidences of redetachment, PVR, ERMs, and revitrectomy during the 6-month follow-up period. Our data revealed no evidence of a correlation between the duration of preoperative visual loss and the final visual outcome after ILM peeling ($r = 0.14$, $P = 0.24$; Figure 2).

Fig. 1. Functional outcome (BCVA [ETDRS letter scores]). *$P < 0.05$.

Discussion

Our retrospective analysis revealed ILM peeling during primary reattachment surgery to confer a great benefit on visual rehabilitation up to 6 months (the end of the follow-up period) in eyes which, because of severe visual loss after primary RD involving the fovea, is presumed to have a poor prognosis.[31,32] A reduction in the incidence of PVR was not observed. Albeit so, the number of revitrectomies that were performed was lower after ILM peeling, because of a relevant reduction in the risk for secondary ERM formation from 35.7% to 1.6%. This latter observation accords with the findings of several other groups.[21,23,28,33] That Akiyama et al[23] reported a relevant reduction in the development of secondary ERMs after ILM peeling, but no positive effect on visual outcome, which may reflect the circumstance that cases of RD without macular involvement were included. In our analysis, all of the eyes had RD involving the entire macula and in the vast majority of eyes a presenting vision of 10/200 or below. Aras et al likewise observed no positive effect of ILM peeling on the visual outcome. However, they focused on PVR-complicated cases of RD and used silicone oil as a tamponade.[28] In contrast to the aforementioned authors, Nam and Kim reported an improvement in visual outcome after vitrectomy, even in cases of macula on RD. This retrospective finding was attributed to the lower risk of secondary ERM formation.[21] In our Group 2 eyes, which underwent no ILM peeling, the 6-month visual outcomes were partially influenced by the development of ERMs. This explanation cannot be offered to account for the superior early visual recovery that was observed in peeled eyes (before the development of ERMs would be expected). The finding is in line with the data of a recently published analysis of a case series.[34] The authors used membrane blue and heavy liquids to reattach the central retina before peeling away the ILM. We performed the procedure after endodrainage of the subretinal fluid and staining with membrane blue under air. The dye was thereby
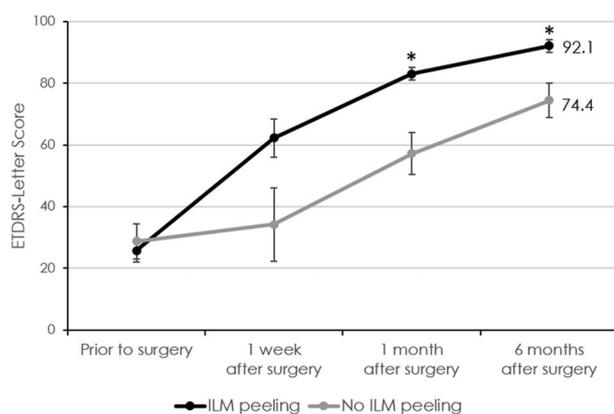
Table 3. Total Percentages of Redetachment, Proliferative Vitreoretinopathy, Epiretinal Membranes, and Revitrectomy Over 6 Months

	Redetachment, n (%)	PVR, n (%)	ERM, n (%)	Revitrectomy, n (%)
ILM Peeling	6 (9.8%)	8 (13.1%)	1 (1.6%)	6 (9.8%)
No ILM Peeling	9 (32.1%)	7 (25.0%)	10 (35.7%)	15 (53.6%)
P	0.014	0.13	0.0005	0.0005

prevented from entering the subretinal space[18] and exerting a potentially toxic effect on the retinal pigmented epithelium. However, this option may technically be more demanding. We are fully aware that this approach cannot be currently recommended for any case of macula-involving retinal detachment. Nevertheless, when the visual acuity is initially poor (as in most of our cases), the measure would be justified to regain a useful visual function. In eyes with a visual acuity of $\geq$20/100, the potential visual gain might outweigh the inherent surgical trauma and the risks that are associated with ILM peeling when the macula is detached. Inner limiting membrane peeling was associated with no postoperative complications other than perifoveal spot hemorrhages in several cases, which resolved spontaneously after 1 month and an extramacular retinal break in one instance, which was laser treated. Indeed, the course of function-limiting postoperative macular edema was also ameliorated.

In two prospective randomized clinical trials that assessed the effects of macular hole surgery, ILM peeling led to an improvement in the visual outcome[33] and a reduction in the number of revitrectomies.[16] Despite the difference in the primary pathology, the data may nevertheless support our retrospective impression that ILM peeling had a beneficial influence on the functional and the anatomical outcomes, which
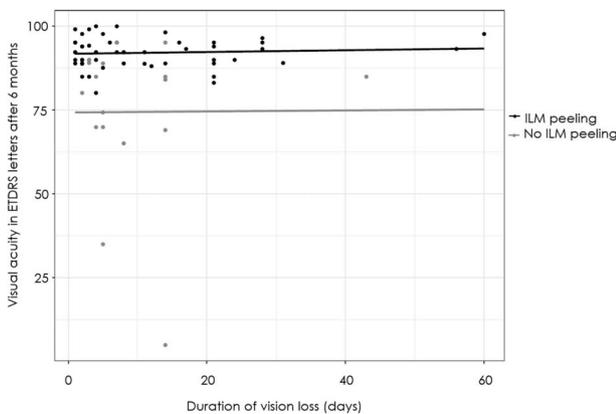

Fig. 2. Relationship between the duration of the visual loss before surgery and the visual acuity 6 months later. A Spearman coefficient of r = 0.14 excludes a correlation between final visual acuity and the duration of vision loss in our series for both groups (P = 0.24).

argues against the much discussed but unproven contention that it exerts a negative one. Inner limiting membrane peeling has a positive impact on the anatomical outcome of revision surgery for recurrent PVR-associated retinal redetachment, reducing the need for retinectomy. This finding argues in favor of its performance in cases of primary RD.[26,27] We are of course aware that our cohort of patients was too small to justify any definitive conclusion respecting the impact of the undertaking on the risk of redetachment. Last but not least, our results indicate that the duration of macular detachment has no marked influence on the final visual outcome after ILM peeling. This finding contrasts with published experience in the repair of macula-involving RD without ILM peeling.[8,32,33,35] Hence, we attribute the positive effect to ILM peeling, which would justify its performance at least in cases with visual losses that had endured for more than 3 to 7 days. However, since an extended period of detachment may be associated with a higher risk of redetachment, we would still advocate rapid surgical intervention.[9]

Highly myopic eyes, which usually have a poor functional prognosis, were excluded from our analysis. Hence, the observed improvement in visual outcome does not hold for RD with macular holes in these cases.[19,22,36] We are well aware that peeling of the ILM could impair the physiological function of the inner retina, which is supported by the footplates of Müller cells.[11] However, its removal induces no relevant structural neuroretinal damage or atrophy during a follow-up period of 12 months.[37] The ILM affords a structural boundary between the vitreous and the inner retina.[12,13] This circumstance may have a relevant bearing on the risk of development of secondary macular edema after silicone oil tamponade, which is a consequence of an interaction between the oil and the tissue. During vitrectomy for ERMs, cells and cellular fragments on the retinal side of the ILM are removed when this structure is peeled away, which could account for the rather high incidence of secondary ERM formation if the ILM is not peeled off.[38] The observed benefits of ILM peeling were so marked as to render a total misinterpretation of this effect unlikely,

despite the limited number of eyes that were analyzed in our study. In patients that had undergone no ILM peeling, secondary surgery for ERMs was necessary in 35% of the eyes, as against <2% in those that had. Inner limiting membrane peeling would thus relevantly reduce the burden of the disease for the patients and caregivers. This possibility would justify a prospective evaluation of the risk and the benefits of the demanding but obviously safe procedure although re-vitrectomy with secondary ILM peeling for ERMs is rewarded as an alternative with functional success.[39]

In conclusion, because ILM peeling has been greatly facilitated and enhanced by the intraoperative use of vital stains,[40] we believe that the procedure should be considered in cases of macula-off RD that are associated with severe loss of vision. To substantiate this recommendation and to ascertain the degree to which eyes with a higher visual acuity would benefit there from, we are now designing a prospective randomized clinical trial.

Key words: macular involvement, inner limiting membrane, visual recovery, rhegmatogenous retinal detachment, vitrectomy.

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