Int Ophthalmol (2018) 38:2709–2714
https://doi.org/10.1007/s10792-017-0761-6

REVIEW

ILM peeling in nontractional diabetic macular edema: review and metanalysis

M. Rinaldi · R. dell'Omo · F. Morescalchi · F. Semeraro · E. Gambicorti · F. Cacciatore · F. Chiosi · C. Costagliola

Received: 23 January 2017 / Accepted: 23 October 2017 / Published online: 31 October 2017

Abstract
Purpose To evaluate the effect of internal limiting membrane (ILM) peeling during vitrectomy for nontractional diabetic macular edema.
Methods PUBMED, MEDLINE and CENTRAL were reviewed using the following terms (or combination of terms): diabetic macular edema, nontractional diabetic macular edema, internal limiting membrane peeling, vitrectomy, Müller cells. Randomized and nonrandomized studies were included. The eligible studies compared anatomical and functional outcomes of vitrectomy with or without ILM peeling for tractional and nontractional diabetic macular edema. Postoperative best-corrected visual acuity and central macular thickness were considered, respectively, the primary and secondary outcomes. Meta-analysis on mean differences between vitrectomy with and without ILM peeling was performed using inverse variance method in random effects.
Results Four studies with 672 patients were eligible for analysis. No significant difference was found between postoperative best-corrected visual acuity or best-corrected visual acuity change of ILM peeling group compared with nonpeeling group. There was no significant difference in postoperative central macular thickness and central macular thickness reduction between the two groups.
Conclusions The visual acuity outcomes in patients affected by nontractional diabetic macular edema using pars plana vitrectomy with ILM peeling versus no ILM peeling were not significantly different. A larger prospective and randomized study would be necessary.

Keywords Internal limiting membrane peeling · Diabetic macular edema · Vitrectomy · Müller cells · Diabetic retinopathy · Meta-analysis

M. Rinaldi
Department of Ophthalmology, Second University of Naples, Naples, Italy

R. dell'Omo · F. Chiosi (✉) · C. Costagliola
Department of Medicine and Health Sciences, University of Molise, Via Francesco De Sanctis 1, 86100 Campobasso, Italy
e-mail: flaviachiosi@yahoo.it

F. Morescalchi · F. Semeraro · E. Gambicorti
Department of Medical and Surgical Specialties, Radiological Specialties and Public Health, Eye Clinic, University of Brescia, Brescia, Italy

F. Cacciatore
Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy

F. Cacciatore
UOSD- Cardiac Transplantation and Mechanical Assistance, Monaldi Hospital, Naples, Italy

Introduction

Macular edema is the major cause of visual loss in patients with nonproliferative diabetic retinopathy (NPDR) [1]. The pathogenesis of DR is complex, and several vascular, inflammatory and neuronal mechanisms are involved. Inflammation mediates structural and molecular alterations associated with DR. Tissue hypoxia and dysregulation of immune responses associated with diabetes mellitus can induce increased expression of numerous vitreous mediators (cytokines, chemokines and other factors) responsible for DR development [2]. The breakdown of the tight junctions of endothelial retinal cells (which constitute the inner blood–retinal barrier) and of the pigment epithelial cells (which constitute the outer blood–retinal barrier) is responsible for the accumulation of plasma within the retina. The leakage of fluid and plasma constituents is due to oxidative damage caused by hyperglycemia. The thickening of the retina (namely the diabetic macular edema or DME) and subsequent ischemia causes the progressive loss of vision [3]. DME is stimulated and supported both by inflammatory factors that accumulate in the vitreous [2–4] and by vitreomacular traction forces exerted by contraction of posterior hyaloid over the internal limiting membrane (ILM) [5]. ILM is the site of adhesion between retina and vitreous; thus, the role exerted by ILM in the pathogenesis of tractional DME is surely worthwhile. Cortical vitreous of diabetic patients contains enzymes able to cross-link vitreous fibers, with subsequent stiffening of collagen over the ILM. The posterior hyaloid stiffens and becomes shorter, causing retinal traction and the loss of the physiological concavity of the macula [6]. The thickening of ILM in diabetic patients depends on the accumulation of extracellular matrix (i.e., collagen type I, III, IV, V, proteoglycans and adhesion molecules such as laminin and fibronectin) and immune cells, such as macrophages and fibroblasts [7]. The thickened ILM impedes the outflow of fluids accumulating into the retina and hinders the diffusion of oxygen from the vitreous. The accumulation of inflammatory cells increases inflammation and provokes the breakdown of blood–retinal barrier, whereas the accumulation of fibroblasts may be responsible of the epiretinal membranes formation.

The treatment for DME involves rigorous glycemic control, macular laser treatment, as indicated by the Early Treatment Diabetic Retinopathy Study, intravitreal pharmacotherapy, especially with anti-VEGF, and surgical treatment [8–10]. Also considering the inflammatory impact of diabetic retinopathy, currently the use of slow-release dexamethasone (Ozurdex; Allergan, Irvine, CA) or fluocinolone acetonide (Iluvien®) intravitreal implant has been investigated in the literature as second-line therapy for DME refractory to anti-VEGF therapy [11, 12]. Otherwise surgical treatment with pars plana vitrectomy is indicated when other approaches have not been found useful in reducing the edema. The main goal of vitrectomy in NPDR is the reduction in retinal vitreous traction. Other possible benefits are that the removal of the vitreous gel increases the availability of oxygen, with a partial reduction in the inner retina ischemia. Moreover, vitrectomy removes the inflammatory mediators, which further increases the leakage. Finally, the removal of the ILM improves exchanges with the oxygen-rich vitreous and promotes the discharge of liquid from the retina, ensuring the absence of any residual traction. Although the atraumatic removal of ILM seems to play a role also in chronic diabetic macular edema without evidence of traction [13], its efficacy in the improvement of visual acuity is controversial. In fact, some studies have reported that reduction in macular edema does not lead to noticeable functional improvement in vision [14, 15]. However, despite the removal of macular ILM has yielded good anatomical outcome in the surgical treatment of macular hole and epiretinal membrane [17–19], the adverse effects potentially related to this procedure could interfere with good functional recovery in medium- and long-term follow-ups.

The objective of this study was to investigate the functional and anatomical effect of ILM peeling in nontractional diabetic macular edema.

Methods

An extensive Medline, Embase and Cochrane search was performed including the following words "diabetic macular edema," "internal limiting membrane peeling," "diabetic retinopathy," "vitrectomy" and "Muller cells." The search accrued data from January 1, 1988, up to November 31, 2016. In addition, completed but still unpublished RCTs evaluating the

effects of ILM peeling on diabetic macular edema on different outcomes were identified through a search on the www.clinicaltrials.gov Web site. The identification of relevant studies was performed independently by two of the authors (MR, FC), and conflicts resolved by the third investigator (CC).

Eligible studies included randomized or nonrandomized studies comparing the visual outcomes with and without ILM peeling in the management of DMR. There was only one RCT from Poland (NCT01218750), without study results posted. A period of up to 12 months was considered an appropriate duration of follow-up for the evaluation of surgical outcomes. We extracted data on outcome measures including best-corrected visual acuity (BCVA) before and after surgery, and central macular thickness (CMT) before and after surgery, along with the study design, diagnosis, surgical procedures and laser treatment. The primary outcome of our study was BCVA measure, whereas CMT was the secondary outcome.

The quality of trials was assessed using the Cochrane criteria (Cochrane Handbook for Systematic Reviews of Interventions, available at: www.cochrane-handbook.org). For each study, we also assessed how the population was selected, the duration and the adequacy of study follow-up [20].

Statistical analysis

Meta-analysis was performed using CMA software (comprehensive meta-analysis). For each study, the odds ratio and 95% confidence interval were considered. In the Forest plot, the studies are represented by symbols whose area is proportional to the study's weight in the analysis. However, a random-effects model was applied for all analyses and used to estimate the difference in the outcomes between the vitrectomy group with ILM peeling and that without ILM peeling. The Z value and p value were calculated for each study and for the cumulative effect.

Results

The first database query yielded 507 articles. Of these, we screened titles and abstracts for relevant reports and selected 9 articles for which we obtained full articles. Within these reports, we excluded 3 articles because, to our opinion, were of lower level evidence. Two other reports were also excluded because they were noncomparative studies [21, 22]. The remaining four studies selected evaluated the visual and anatomical outcomes of patients affected by diffuse, nontractional diabetic macular edema, who underwent pars plana vitrectomy with and without ILM peeling [23, 24]. Among these studies, three were randomized trials and one was a retrospective observational study. Table 1 shows the main characteristics of the 4 studies included. The prevalence of proliferative diabetic retinopathy, duration of diabetes mellitus type 2, previous macular laser therapy were well balanced preoperatively between the groups, along with the main baseline characteristics of patients (age, preoperative lens status, preoperative absence of PVD, etc.). Between studies ILM peeling was performed using indocyanine green (ICG) in just one [23] out of three studies, while Patel el al did not specify if ICG was used during surgery. Posterior hyaloid face was always removed by surgeons in all eyes, even in the groups where ILM peeling was not performed.

The results obtained comparing the postoperative BCVA between the ILM peeling and nonpeeling groups did not show a significant statistical superiority between the two groups on a long-term follow-up. The meta-analysis evaluating the change in BCVA before and after surgery showed that there was no statistical difference ($p = 0.16$) in terms of visual improvement between the groups analyzed (Fig. 1). Unfortunately it was not possible to perform a meta-analysis over the CMT data due to lack of the pre- and postoperative CMT values per group, along with the indispensable standard deviation. Anyhow the results obtained from each study did not show a statistical difference in macular thickness reduction between vitrectomy with and without ILM peeling even on a long-term follow-up.

The differences in the BCVA between the two groups were not statistically significant.

Discussion

The role of ILM peeling in the treatment of nontractional diabetic macular edema is controversial, and no sufficient data are available to clarify the utility of this procedure in this condition.

Table 1 Characteristics of the studies included for review

Study	Design	No.	Age	Phakia	Surgical procedure	Follow-up (months)
Kumagai et al. [23]	RO	318	60	496	PPV alone	12
		178			PPV + ILM peeling	
Kumagai et al. [24]	PC	58	61	114	PPV alone	80.4
		58			PPV + ILM peeling	
Patel et al. [25]	PC	8	57	NR	PPV alone	12
		10	73		PPV + ILM peeling	
Figueroa et al. [26]	PC	11	71	29	PPV + ILM peeling	12
		11	68		PPV + IVTA	
		20	65		PPV + ILM peeling + IVTA	

NR not reported, *PC* prospective comparative, *RO* retrospective observational, *PPV* pars plana vitrectomy, *IVTA* intravitreal triamcinolone acetonide

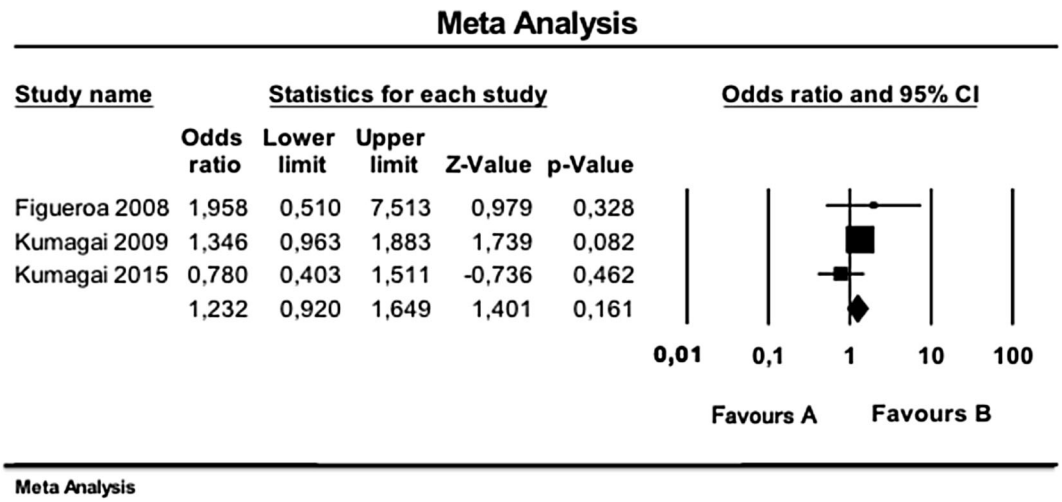

Fig. 1 BCVA before and after surgery is showed. The columns include the odds ratio and 95% confidence interval for each study. The last row in the spreadsheet shows the summary data. The same information is captured by the Forest plot. This plot shows each study as a point estimate with its lower and upper limit and provides a sense of the study-to-study dispersion. In the Forest plot, the studies are represented by symbols whose area is proportional to the study's weight in the analysis. *A* non-ILM peeling, *B* ILM peeling

Data obtained in this review showed that vitrectomy with ILM peeling does not offer clear advantages. There was no significant difference in visual acuity outcomes and reduction in macular edema among patients undergoing vitrectomy with or without ILM peeling.

The role of vitrectomy in the treatment of nontractional DME has not been fully addressed, although represents a therapeutic choice for several surgeons.

Vitrectomy is performed to release the pathological influence of the vitreous on the retina and is useful in restoring the normal anatomical shape of the macula and improving visual acuity.

ILM peeling during the vitrectomy was suggested to yield a better anatomical and functional result [27–33], and its effectiveness was sustained long term with less recurrence [34]. However, the surgical removal of the ILM is also challenging because it can compromise the already affected retinal tissue. Poor visibility of the thin transparent membrane, the sensitivity of the macular tissue and the small dimensions must be considered during the procedure.

Anyway several studies demonstrated an accelerated absorption of DME, improved anatomy but not necessarily improved VA [16, 29]. The addition of ILM peeling to vitrectomy was based on the benefit obtained by the removal of the scaffold used by astrocytes to proliferate on the retinal surface and by the elimination of all tractional forces at the vitreo-retinal interface. When no tractional adherences are observable, such as in nontractional DME, vitrectomy with ILM peeling does not offer a clear advantage from the clinical data now available. However, there are many variables that can affect the data in each study. Treated patients hardly are similar and the general conclusions are difficult. The main problem today is that it is not yet possible to assess the real vitreous morphology, its relationship with the macula and the presence of pockets of liquid in front of the retina. The state of the vitreous can only be assessed during surgery using vital dyes suitable. OCT instruments can evaluate the thickness of the retina, but are not yet able to distinguish intracellular edema from that extra cellular one; thus, they cannot determine whether the damage is irreversible or not. Furthermore, the OCT frames are not able to evaluate the impairment of retinal micro circulation. The surgery is only effective if performed before irreversible damage occurs to the photoreceptors layer. Other variables useful to determine the reversibility of visual impairment are the duration of macular edema, the presence of glucose control, the extent of ischemic damage and the age of patients. Because the asset of ILM peeling might reveal only later after vitrectomy, in this study we analyzed postoperative results from 12 up to 80 months.

In conclusion, the visual acuity and CMT outcomes using pars plana vitrectomy with or without ILM peeling in patients affected by nontractional diabetic macular edema were not statistically different. In our opinion, the better way to treat a nontractional diabetic macular edema is a personalized approach involving an increased collaboration between ophthalmologists and primary care providers, considering the ILM anatomy together with data on the microcirculatory state of the retina to perform the better surgical strategy, customized on the personal risk factor. Also a larger prospective and randomized study would be necessary to appropriately address the effectiveness of ILM peeling on visual acuity outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Klein R, Klein BE, Moss SE, Cruickshanks KJ (1995) The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long term incidence of macular edema. Ophthalmology 102:7–16
2. Semeraro F, Cancarini A, dell'Omo R, Rezzola S, Romano MR, Costagliola C (2015) Diabetic retinopathy: vascular and inflammatory disease. J Diabetes Res 2015:582060
3. Stehphen J. Ryan. Non proliferative diabetic retinopathy, Chap 67. In: Retina, Vol II, 4th edn. pp 1275–1276
4. Dell'Omo R, Semeraro F, Bamonte G, Cifariello F, Romano MR, Costagliola C (2013) Vitreous mediators in retinal hypoxic diseases. Mediators Inflamm 2013:935301
5. Agarwal D, Gelman R, Prospero Ponce C, Stevenson W, Christoforidis JB (2015) The vitreomacular interface in diabetic retinopathy. J Ophthalmol 2015:392983
6. Bandello F, Lattanzio R, Zucchiatti I, Del Turco C (2013) Pathophysiology and treatment of diabetic retinopathy. Acta Diabetol 50:1–20
7. Abari E, Kociok N, Hartmann U, Semkova I, Paulsson M, Lo A, Joussen AM (2013) Alterations in basement membrane immunoreactivity of the diabetic retina in three diabetic mouse models. Graefes Arch Clin Exp Ophthalmol 251:763–775
8. Semeraro F, Parrinello G, Cancarini A et al (2011) Predicting the risk of diabetic retinopathy in type 2 diabetic patients. J Diabetes Complications 25:292–297
9. Rinaldi M, Chiosi F, dell'Omo R et al (2012) Intravitreal pegaptanib sodium (Macugen®) for treatment of diabetic macular oedema: a morphologic and functional study. Br J Clin Pharmacol 74:940–946
10. Bressler SB, Liu D, Glassman AR, Blodi BA, Castellarin AA, Jampol LM, Kaufman PL, Melia M, Singh H, Wells JA, Diabetic Retinopathy Clinical Research Network (2017) Change in diabetic retinopathy through 2 years: secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. JAMA Ophthalmol 135(6):558–568
11. Khan Z, Kuriakose RK, Khan M, Chin EK, Almeida DR (2017) Efficacy of the intravitreal sustained-release dexamethasone implant for diabetic macular edema refractory to anti-vascular endothelial growth factor therapy: meta-analysis and clinical implications. Ophthal Surg Lasers Imaging Retina 48(2):160–166
12. Syed YY (2017) Fluocinolone acetonide intravitreal implant 0.19 (ILUVIEN(®)): a review in diabetic macular edema. Drugs 77(5):575–583
13. Yamamoto T, Naoko A, Takeuchi S (2001) Vitrectomy for diabetic macular oedema: the role of posterior vitreous detachment and epimacular membrane. Am J Ophthalmol 132:369–377
14. Diabetic retinopathy clinical research network writing committee, Haller JA, Qin H, Apte RS et al (2010)

Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. Opthtalmology 117:1087–1093
15. Ikeda T, Sato K, Katano T, Hayashi Y (1999) Vitrectomy for cystoid macular oedema with attached posterior hyaloid membrane in patients with diabetes. Br J Opthtalmol 83:12–14
16. Hartley KL, Smiddy WE, Flynn HW Jr, Murray TG (2008) Pars plana vitrectomy with internal limiting membrane peeling for diabetic macular edema. Retina 28:410–419
17. Ternent L, Vale L, Boachie C, Burr JM, Lois N, Full-Thickness Macular Hole and Internal Limiting Membrane Peeling Study (FILMS) Group (2012) Cost-effectiveness of internal limiting membrane peeling versus no peeling for patients with an idiopathic full-thickness macular hole: results from a randomised controlled trial. Br J Ophthalmol 96:438–443
18. Hasegawa T, Emi K, Ikeda T, Watanabe M, Takaoka G (2004) Long-term prognosis of internal limiting membrane peeling for idiopathic epiretinal membrane. Nihon Ganka Gakkai Zasshi 108:150–156
19. Park DW, Dugel PU, Garda J et al (2003) Macular pucker removal with and without internal limiting membrane peeling: pilot study. Ophthalmology 110:62–64
20. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50:1088–1101
21. Bonnin S, Sandali O, Bonnel S, Monin C, el Sanharawi M (2015) Vitrectomy with internal limiting membrane peeling for tractional and non tractional diabetic macular edema: long-term results of a comparative study. Retina 35:921–928
22. Ghassemi F, Bazvand F, Roohipoor R, Yaseri M, Hassanpoor N, Zarei M (2016) Outcomes of vitrectomy, membranectomy and internal limiting membrane peeling I patients with refractory diabetic macular edema and non-tractional epiretinal membrane. J Curr Ophthalmol 28:199–205
23. Kumagai K, Furukawa M, Ogino N, Larson E, Iwaki M, Tachi N (2009) Long-term follow-up of vitrectomy for diffuse nontractional diabetic macular edema. Retina 29:464–472
24. Kumagai K, Hangai M, Ogino N, Larson E (2015) Effect of internal limiting membrane peeling on long-term visual outcomes for diabetic macular edema. Retina 35:1422–1428
25. Patel JI, Hykin PG, Schadt M et al (2006) Pars plana vitrectomy with and without peeling of the inner limiting membrane for diabetic macular edema. Retina 26:5–13
26. Figueroa MS, Contreras I, Noval S (2008) Surgical and anatomical outcomes of pars plana vitrectomy for diffuse non tractional diabetic macular edema. Retina 28:420–426
27. Gandorfer A, Messmer EM, Ulbig MW, Kampik A (2000) Resolution of diabetic macular edema after surgical removal of the posterior hyaloids and the inner limiting membrane. Retina 20:126–133
28. Diabetic Retinopathy Clinical Research Network Writing Committee, Haller JA, Qin H, Apte RS et al (2010) Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. Ophthalmology 117(1087–1093):e3
29. Kumagai K, Ogino N, Furukawa M et al (2002) Internal limiting membrane peeling in vitreous surgery for diabetic macular edema. Nihon Ganka Gakkai Zasshi 106:590–594
30. Ikeda T, Sato K, Katano T, Hayashi Y (2000) Improved visual acuity following pars plana vitrectomy for diabetic cystoid macular edema and detached posterior hyaloid. Retina 20:220–222
31. La Heij EC, Hendrikse F, Kessels AG, Derhaag PJ (2001) Vitrectomy results in diabetic macular oedema without evident vitreomacular traction. Graefes Arch Clin Exp Ophthalmol 239:264–270
32. Yanyali A, Bozkurt KT, Macin A, Horozoglu F, Nohutcu AF (2011) Quantitative assessment of photoreceptor layer in eyes with resolved edema after pars plana vitrectomy with internal limiting membrane removal for diabetic macular edema. Ophthalmologica 226:57–63
33. Bahadir M, Ertan A, Mertoğlu O (2005) Visual acuity comparison of vitrectomy with and without internal limiting membrane removal in the treatment of diabetic macular edema. Int Ophthalmol 26:3–8
34. Yanyali A, Horozoglu F, Celik E, Nohutcu AF (2007) Long-term outcomes of pars plana vitrectomy with internal limiting membrane removal in diabetic macular edema. Retina 27:557–566