Original Article

Comparison of anatomical and functional outcomes of vitrectomy with internal limiting membrane peeling in recalcitrant diabetic macular edema with and without traction in Indian patients

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Purpose: To study and compare the outcomes of pars plana vitrectomy (PPV) with the internal limiting membrane (ILM) peeling in the eyes with recalcitrant diabetic macular edema (DME) with and without vitreomacular traction. **Methods:** A comparative prospective interventional study was undertaken in which group 1 included 45 eyes of 45 patients with DME with vitreomacular tractional component and group 2 included 45 eyes of 45 patients with recalcitrant DME without a tractional component. Both groups underwent standard PPV with ILM peeling. All the patients were followed up for a minimum of 6 months. The parameters evaluated were changes in the best-corrected visual acuity (BCVA), central macular thickness (CMT), multifocal electroretinogram (mfERG) parameters, and occurrence of any intraoperative/postoperative surgical complication. **Results:** The mean CMT improved significantly from 540.6 and 490.2 µm at the baseline to 292.5 and 270.6 µm at 6 months in groups 1 and 2, respectively ($P < 0.001$). The mean BCVA logMAR improved from 0.78 ± 0.21 to 0.62 ± 0.22 in group 1 and 0.84 ± 0.19 to 0.65 ± 0.21 in group 2 at 6 months follow-up which was not statistically significant. The improvement in the mfERG was seen in group 2 as a significant increase in *P*1 wave amplitude in ring 2 (2–5°) ($P < 0.004$) and a significant decrease in *P* 1 wave implicit time in ring 1 (central 2°) ($P < 0.001$). None of the eyes suffered from the loss of BCVA or any major surgical complication in either group. **Conclusion:** PPV in recalcitrant DME provides good anatomical outcomes and the results are comparable in DME with and without a tractional component.

Key words: ILM peeling, recalcitrant diabetic macular edema, tractional diabetic macular edema, vitrectomy

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Diabetic retinopathy (DR) is a major public health problem in India and requires innovative solutions to tackle the menace.[1-3] Diabetic macular edema (DME) is one of the most important causes of visual impairment in DR. Intravitreal anti-vascular endothelial growth factor (VEGF) therapy has revolutionized the treatment of DME and has become the standard of care for patients presenting with this condition.[4-6] However, up to 23% of the patients with DME do not respond sufficiently to the anti-VEGF therapy.[7] Further, this treatment involves the need for repeated intravitreal injections which a poses great economical, psychological, and physical burden to the patients.[8] Pars plana vitrectomy (PPV) in cases of non-responding/persistent DME is a viable treatment option that has been shown to be a cost-effective alternative.[9] The efficacy of vitrectomy for tractional DME was first demonstrated by Lewis *et al*.[10] While favorable results of PPV have been shown in the cases of DME with vitreomacular traction, the results are still ambiguous in the cases of DME without a tractional component.[11-13] Hence, PPV is considered as an early option in the treatment of DME with vitreomacular traction and only as a terminal measure in cases without a tractional component. Studies comparing surgical outcomes between these two indications in the past have shown beneficial effects of surgery in the eyes with DME associated with vitreomacular traction, whereas limited improvement was observed in the eyes without traction.[8] As surgical instrumentation and techniques have evolved rapidly over the last few years and improved surgical outcomes are being observed in vitrectomy for DR, a relook into the comparative outcomes of PPV and internal limiting membrane (ILM) peeling for recalcitrant DME with traction on the retina and recalcitrant DME without any form of traction on the retina is warranted.

Methods

The present prospective interventional study was conducted at a government tertiary eye care hospital. The study was approved by the Institute Ethics Committee and adhered to the tenets of the Declaration of Helsinki. A total of 90 eyes of 90 patients were recruited. Written and informed consent was taken from all the patients. The inclusion criteria included patients over 18 years of age with well-controlled type 1 or type 2 diabetes mellitus and the center involving DME (central subfield thickness ≥300 µm) that is recalcitrant to the treatment.

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Recalcitrant DME was defined as no response (<10% decrement in CMT) to (a) anti-VEGF therapy: previous 5 monthly injections of intravitreal anti-VEGF (aflibercept, ranibizumab, bevacizumab) including switchover between these agents, (b) intravitreal steroids (triamcinolone acetonide, dexamethasone implants), (c) laser photocoagulation based on fluorescein angiography (FA). Those patients who presented initially with tractional DME due to vitreomacular traction or epiretinal membrane were directly recruited for the study without waiting for the need of repeated doses of anti-VEGF drugs. Patients with Snellen BCVA at baseline worse than 3/60 and better than 6/12 were excluded. The patients having macular ischemia (confirmed on FA or optical coherence tomography [OCT] angiography) were also excluded. The patients with poor media clarity, poor glycemic control (HbA1C >8.0%), uncontrolled hypertension, overt diabetic nephropathy with coexistent optic nerve diseases like glaucoma, optic atrophy, or macular pathologies like age-related macular degeneration were excluded. Pseudophakic cystoid macular edema was excluded based on the history and fundus fluorescein angiography (FFA) investigation.

The patients were divided into two groups. Group 1 consisted of patients who had recalcitrant DME and had signs of traction on the retina in the form of vitreomacular or vitreofoveal traction, epiretinal membrane (ERM), or thick and taut undetached posterior hyaloid detected on OCT and/or clinical examination. Group 2 consisted of patients who had recalcitrant DME without any clinical or OCT evidence of traction on the retina. In this group, the posterior hyaloid was either completely detached from the posterior pole or was completely or partially adhered to the posterior pole without causing any traction on the retina. All the patients underwent a detailed ophthalmological examination including recording of the BCVA, intraocular pressures, slit-lamp biomicroscopy, and peripheral retinal examination with indirect ophthalmoscopy. The baseline fundus FA and OCT were performed in every patient.

The spectral-domain OCT (SDOCT) was performed with the Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany). The results were recorded with the fovea well-centered at the initial visit and on each of the follow-up visits. The CMT was measured as the thickness of the central subfield of the Early Treatment of Diabetic Retinopathy Study (ETDRS) grid centered on the fixation (automated, inbuilt).

Multifocal electroretinogram (mfERG) was done using Metrovision Monpack3™ (Vision Monitor, Perenchies, France). Standard mfERG recording was done in a fully dilated light-adapted state for 5 min with monocular stimulation (other eye occluded using occluder) following the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines.[14] It consisted of 61 regular hexagons at a viewing distance of 33 cm corresponding to a field of 30° horizontally and 24° vertically, flashed in a pseudorandom pattern on a dark background cover with a luminance of 30 cd/m^2 at a frequency of 17 Hz to optimize the amplitude of the responses.[14] Serial records were analyzed to check for any change in the parameters. The mfERG was recorded on the initial visit and at 6 months postoperatively.

All patients underwent standard 23 Gauge PPV performed by a single surgeon. In all the eyes, a core vitrectomy was done. The entire posterior vitreous was separated from the retina and any visible vitreous strands that were adherent to the retina were removed. Intravitreal triamcinolone was used in all the cases as a marker to facilitate visualization and removal of the adherent posterior cortical vitreous. Later, 0.025% brilliant blue G (BBG) (Fluoron GmbH, Neu-Ulm, Germany) dye was used to stain the ILM. The ILM peeling was initiated using the pinch and peel technique and the ILM peeling was done over the macula. In the cases with ERM, the negatively-stained ERM was first peeled. Using the double staining technique, ILM was peeled subsequently after the second application of BBG dye. In the cases with cystic macula, the center-sparing ILM peeling was done to avoid the deroofing of the fovea. After peeling, the foveal contour was confirmed using intraoperative OCT ensuring that there was no deroofing of the fovea or any residual vitreomacular traction. The fluid air exchange was done. Laser augmentation of the skip areas was also done in lasered proliferative diabetic retinopathy (PDR) eyes. Tamponade with sulfur hexafluoride (SF6) gas was achieved in all the cases to provide short-term retinal tamponade and prevent postoperative hypotony.

The patients were followed up at regular intervals for 6 months. The outcome measures included a change in the BCVA, CMT, mfERG parameters, and occurrence of any intraoperative or postoperative complications. All data were recorded and appropriate statistical tests were applied. The *P* value less than 0.05 was taken as statistically significant.

Results

Baseline demographic profile

Ninety patients were recruited in the study. A majority of the participants were males (67/90). The mean age of the patients recruited in group 1 was 60.8 years and in group 2 was 61.8 years (range from 51–69 years). All the patients were pseudophakic. The baseline characteristics are depicted in Table 1 and are comparable between the two groups. In group 1, 35 eyes had broad-based vitreomacular traction (>1,500 μm) due to thick taut posterior hyaloid or epiretinal membrane and 10 eyes had focal vitreomacular traction (<1500 μm). In group 1, 18 (40%) eyes had associated PDR changes. In group 2, 21 eyes (46%) had PDR changes. These eyes were lasered preoperatively to tackle neovascularization. The other cases had associated non-PDR changes with no evidence of neovascularization. All the patients were reportedly treatment-naive before the anti-VEGF injections/laser therapy. All the patients in group 1 and group 2 had received anti-VEGF injections as the first line of treatment; 35 eyes of group 1 and all eyes of group 2 received intravitreal steroids as the second-line therapy after anti-VEGF. Further details are provided in Table 1. Laser therapy was performed in 18 eyes in group 1 and 21 eyes in group 2 which presented with PDR.

Postoperative outcomes

Change in the Foveal contour

Foveal contour was restored in a majority of the eyes (40/45 in group 1 and 36/45 in group 2) at 6 months of follow-up [Figs. 1 and 2]. In group 1, the mean CMT improved significantly from 540.6 ± 112.9 μm at the baseline to 292.5 ± 48.8 μm at 6 months of follow-up visit ($P < 0.01$). In group 2, the mean CMT improved significantly from 490.2 ± 84.3 μm at the baseline to 270.6 ± 20.8 μm at 6 months of the follow-up visit ($P < 0.01$). The mean change in the CMT after 6 months was 248.1 and

Table 1: Baseline characteristics of the study participants in two groups

Parameter	Group 1 (± SD)	Group 2 (± SD)	*P*
Age (years)	60.8±1.5	61.8±2.4	0.155
HbA1C (%)	7±0.9	7±1.3	0.169
Baseline visual acuity (logMAR)	0.78±0.21	0.84±0.19	0.424
Baseline CMT (μm)	540.6±112.9	490.2±84.3	0.177
Number of intravitreal anti-VEGF injections (range)	4.8 (3-6)	6.2 (5-6)	0.232
Number of intravitreal steroid injections (range)	1.2 (0-2)	1.8 (1-3)	0.414

*SD - Standard deviation

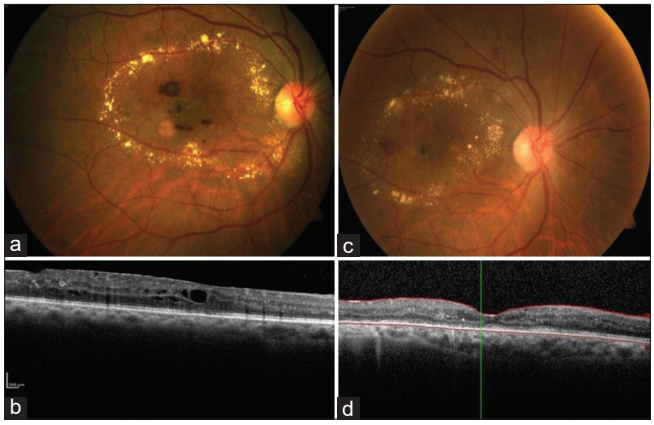

Figure 1: (a and b) Preoperative fundus photograph and SDOCT of a patient with recalcitrant DME with epiretinal membrane. (c and d) Postoperative fundus photograph and SDOCT showing resolution of DME and restoration of foveal contour after PPV

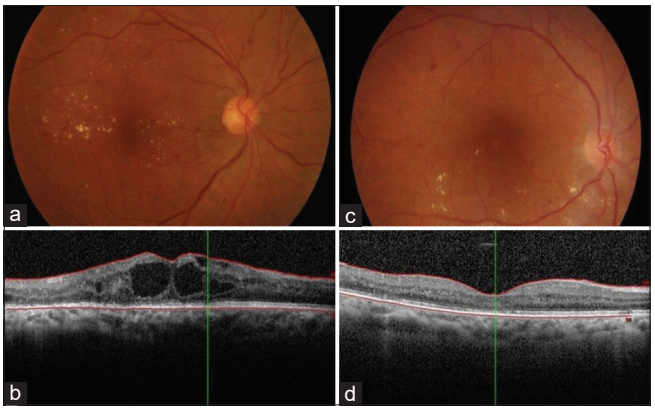

Figure 2: (a and b) Preoperative fundus photograph and SDOCT of a patient with recalcitrant DME without any traction (c and d) Postoperative fundus photograph and SDOCT showing resolution of DME and restoration of foveal contour after PPV

219.6 μm in group 1 and group 2, respectively. The mean change in the CMT was not statistically significant when group 1 was compared with group 2 (*P*: 0.128).

Change in the visual acuity

Postoperatively, the visual acuity improved in all the cases when compared to baseline. There was no deterioration of the visual acuity in any operated case when compared to the baseline visual acuity. In group 1, the mean BCVA logMAR improved from 0.78 ± 0.21 to 0.62 ± 0.22 at 6 months of follow-up. In group 2, the mean BCVA logMAR improved from 0.84 ± 0.19 to 0.65 ± 0.21 at 6 months of follow-up. The mean postoperative change in BCVA was statistically insignificant in both group 1 (*P*: 0.238) and group 2 (*P*: 0.462) at 6 months of follow-up.

Change in mfERG responses

The analysis of mfERG in the cases showed improvement at 6 months in group 2 as noted by a statistically significant decrease in *P*1 wave implicit time in ring 1 (central 2°) (from 48.6 to 38.4 ms, $P = 0.001$). This was associated with an increased P1 wave amplitude in ring 2 (2–5°) (from a baseline median of 317–376 nV/deg^2 at 6 months, $P = 0.044$) and ring 3 (5–10°) (from a baseline median value of 101–216 nV/deg^2 at 6 months, $P = 0.131$). In group 1, there was a non-significant decrease in the *P*1 wave median amplitude. The changes in P implicit time in group 1 were also not significant.

Intraoperative/postoperative complications

There was no major intraoperative complication like the formation of iatrogenic macular hole, retinal breaks, retinal detachment, retinal bleeding, etc., in any of the operated cases in both groups. It was further confirmed by the intraoperative OCT which showed that there is no iatrogenic deroofing of the macula or any remnant/persistent traction over the macula.

Postoperatively, there was no case of vitreous bleed or retinal detachment till 6 months of follow-up. The retina remained attached in all the cases. The postoperative spike in the intraocular pressure was noted in 12/45 eyes in group 1 and 10/45 eyes in group 2 which were managed medically with topical medications. The incidence of Intraocular pressure(IOP) spike was statistically insignificant between the two groups. As all our patients were pseudophakic, we could not assess the progression of the cataracts after vitrectomy.

Recurrence of DME was noted in 5/45 eyes in group 1 and 7/45 eyes in group 2. It recurred after an average duration of 3 months (range, 3–5 months) in group 1 and 2.6 months (range, 2–3 months) in group 2 after surgery. They were successfully managed with an intravitreal injection of anti-VEGF or steroid implants based on the discretion of the treating ophthalmologist. The DME resolved in all these eyes after therapy. At 6 months follow-up, CMT was comparable to other cases.

Discussion

Traction in DME has evolved through various meanings over the years. Before the advent of OCT, traction in cases of DME was defined as the presence of a thick, taut, and glistening posterior hyaloid. This was a biomicroscopic finding and was seen in less than 5% of the patients with DR.[15] With the

advent of OCT, vitreofoveal traction, vitreomacular traction, and epiretinal membrane proliferation along with a thick taut posterior hyaloid came to be referred to as traction. These entities caused various amounts of anteroposterior and tangential traction on the retina.[16,17] In this study, we defined tractional DME as any DME with one or more of the above-described tractional components.

The favorable anatomical outcomes obtained in our tractional DME group are consistent with those of the DRCR.net prospective study.[18] The anatomical results of vitrectomy in the non-tractional DME group were also favorable. There was no statistically significant result between the two groups. This result is consistent with the recent reports, which have shown the long-term efficacy of vitrectomy with or without ILM peeling for diffuse nontractional DME.[13,19,20] There are some studies which showed that the results of vitrectomy in nontractional DME were quite similar to those of the studies in which the patients had been treated with anti-VEGF monotherapy or with anti-VEGF therapy combined with deferred laser.[4,8,18] However, there are also a set of published studies that have not reported beneficial anatomical outcomes after vitrectomy in the eyes with nontractional DME.[21-24] This discrepancy may be due to the heterogeneity in the studies in terms of the definition and duration of recalcitrance, the status of ILM peeling, follow-up period, and nature of intervention.

Several pathophysiologic mechanisms have been suggested to explain the favorable results obtained with vitrectomy in nontractional DME. Improved retinal oxygenation after removal of the vitreous adjacent to the retina and ILM peeling has been suggested.[25,26] It has also been speculated that the vitreous cortex of the diabetic eyes could serve as a reservoir for accumulating proangiogenic factors and cytokines, thereby mediating macular edema.[27]

The results of our study show that even though visual acuity improved in both groups, there was no significant postoperative change in the BCVA despite a significant reduction in CMT in either group. This has also been shown in two recent meta-analysis studies which have found no significant functional improvement in the eyes after vitrectomy for DME.[28,29] This can be due to the presence of permanent changes in the retina due to long-standing ischemia such as photoreceptor atrophy and disorganization of inner retinal layers which are difficult to reverse even after successfully restoring the macular contour.

The functional effects of ILM peeling for DME are heterogeneously reported in comparative studies.[21,30,31] A meta-analysis of the effects of ILM peeling during vitrectomy for DME found no significant change in the anatomic or functional outcomes in the surgery when compared to vitrectomy without ILM peeling.[32] In this study, the surgeon has consistently peeled the ILM during surgery to ensure complete removal of posterior hyaloid and to remove tractional effects of the thickened ILM seen in diabetics. The rationale for this procedure is justified by the oncotic theory proposed by Saravia.[33] ILM peeling also ensured complete removal of the overlying residual vitreous cortex and the inflammatory cells adherent to the inner surface of the ILM in the eyes with diffuse DME.[34] Iatrogenic deroofing of the cystic macula was avoided by adopting center-sparing ILM peeling in such cases. Intraoperative OCT also proved to be of help in providing real-time feedback and helping us to visualize vitreoschisis, remnant persistent traction over the macula, and occurrence of the macular hole if any.[35]

The functional assessment of the macula after PPV for recalcitrant DME using mfERG has not been reported in the past. In our study, all the patients underwent a mfERG at the baseline and 6 months after the surgery. The results showed that there was an insignificant decrease in the *P*1 wave amplitude in all the rings and no significant change in the *P*1 wave implicit times in patients in group 1. However, in patients in group 2, there was a statistically significant decrease in the *P*1 wave implicit time within ring 1 and a statistically significant increase in the *P*1 wave amplitude within ring 2. There was also a statistically insignificant increase in the *P*1 wave amplitude within ring 3 as compared to the preoperative values. These are novel findings which have not been described in the published literature. These results indicate improvement in the functional state/functional recovery of the retina after PPV in Indian patients. These bring strength to the notion that PPV can be tried in cases of recalcitrant DME even without any traction.

Only 10–15% of the patients required anti-VEGF therapy or steroids for the recurrence of DME after PPV. India is a low-middle income country where frequent intravitreal injections can pose a great economic burden and other difficulties for the patient. It got amplified during the current Coronavirus disease 2019 crisis where issues like mobility, management of comorbidities, and financial distress were faced by many patients.[36,37] Advising timely vitrectomy in the cases of recalcitrant edema can help in restoring anatomical integrity and will also reduce the undue burden of intravitreal injection therapy to the patient.

The present study has various limitations including a limited sample size. Post-vitrectomy complications like the rate of progression of the cataracts could not be assessed as all the participants were pseudophakic. The cases with poorer visual acuity (<3/60) were also excluded. Future studies with a large sample size and long-term follow-up (2–3 years) could be planned in Indian settings. Other visual functions like microperimetry and quality of life indicators can also be assessed which can aid in suggesting a functional recovery in the absence of an improvement in visual acuity.

Conclusion

Vitrectomy is safe and effective in restoring the macular thickness in both the groups of DME with and without traction. Functional improvement after vitrectomy in cases of DME without traction is supported by improved responses in multifocal electroretinogram though improvement in the visual acuity was not statistically significant.

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Conflicts of interest

There are no conflicts of interest.

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