Original Article

Pars plana vitrectomy versus three intravitreal injections of bevacizumab for nontractional diabetic macular edema. A prospective, randomized comparative study

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Background: The aim of this study was to compare the effectiveness of pars plana vitrectomy (PPV) and removal of the internal limiting membrane (ILM) with three, monthly, intravitreal bevacizumab (IVB) injections for refractory diabetic macular edema. **Materials and Methods:** This was a prospective, randomized, comparative, interventional study. Forty-four patients were enrolled and randomized in two groups. Twenty-two eyes enrolled in Group I received three IVB injections at monthly interval. Twenty-two eyes were enrolled in Group II which underwent PPV with ILM removal. The primary outcomes measured were: (1) Best corrected logMAR visual acuity (BCVA) using Snellen's visual acuity chart. (2) Central macular thickness (CMT) on optical coherence tomography. The secondary outcome measures were: Complication rates like (1) progression of lens opacities, (2) high intraocular pressure needing further treatment/procedure, (3) development of vitreous hemorrhage related to the procedure employed, (4) retinal detachment and (5) severe inflammation/endophthalmitis. **Results:** In Group I (IVB): 3 (13.6%) eyes showed no change in BCVA; 3 (13.6%) eyes reported decrease in BCVA and 16 (72.8%) eyes showed improvement in BCVA; (P = 0.0181). In Group II (PPV): 4 (18.2%) eyes showed no change in BCVA; 5 (22.7%) eyes showed decrease and 13 (59.1%) eyes showed improvement in BCVA (P = 0.0281). Mean decrease in CMT in IVB group was 108.45 μ, whereas mean decrease in CMT in PPV group was 161.36 μ. No major complications were seen in either group. **Conclusion:** Posttreatment decrease in CMT was more in PPV group and vision improvement more in IVB group. However, no statistically significant difference between the two methods was found.

Key words: Internal limiting membrane peeling, intravitreal bevacizumab injection, pars plana vitrectomy, refractory diabetic macular edema

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Diabetic macular edema (DME) is a major cause of visual morbidity in diabetic patients.[1-3] In the early treatment diabetic retinopathy study (ETDRS) study, laser photocoagulation reduced the risk of moderate visual acuity loss for all eyes with DME by approximately 50%.[4,5] Since the results of the ETDRS, macular laser photocoagulation had been the mainstay of treatment for DME although visual outcomes were not satisfactory.[5]

Recently, many authors have stressed on the important role vascular endothelial growth factor (VEGF) plays in promoting vascular permeability and accumulation of intracellular and extracellular fluid by disrupting the intercellular tight junctions normally present between retinal endothelial cells.[6,7] Several anti-VEGF agents are being tried and used for treatment of refractory DME. Ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA, USA) is a recombinant, humanized antibody fragment that binds all isoforms of VEGF, whereas bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) is a recombinant, full-length, humanized antibody that also binds all VEGF isoforms. Lucentis is recently Food and Drug Administration-approved for DME while Avastin is used on an off-label basis for DME because of cost benefit. Several studies have documented the beneficial effect of anti VEGF intravitreal injections.[8-11] Advantages of pharmacological intervention are speed and ease of procedure and early benefit to the patient. The major drawback of anti-VEGF injections is its short term effect leading to multiple injections.

Another mode of treatment resorted to in refractory DME is pars plana vitrectomy (PPV). Several retrospective studies showed that vitrectomy leads to a reduction of central macular thickness (CMT) in most cases and improvement of visual acuity in 43–69% of study eyes.[12-18]

In the present study, our aim was to evaluate both the treatment methods (PPV vs. three intravitreal injections of anti-VEGF agent) as standalone procedure and to compare the final results in both the groups to ascertain if any one treatment method is superior to other in improving visual acuity and resolving CMT in patients with refractory nontractional DME.

Materials and Methods

This was a prospective, interventional, comparative study in which patients were randomized into two groups. Patients who met the eligibility criteria and agreed to participate in the study were randomized either to receive three intravitreal injections of bevacizumab (IVB) or to undergo PPV. Treatment allocation for each patient was determined by the opening of a sealed envelope. The randomization sequence was on a 1:1

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basis in blocks of an unknown and variable size. Only 1 patient was lost from the study after randomization (but before treatment protocol could be started). This patient was listed for PPV but did not turn up for surgery due to acute cardiac ailment. All the patients enrolled in the study were explained the procedures employed in detail and an informed consent was obtained from them. Ethical approval was obtained from the Institutional Review Board. The study has been conducted in accordance with the ethical standards laid down in the 1964 declaration of Helsinki. Forty-four patients were registered in the study and were randomized into two groups. All patients underwent complete eye examination along with pretreatment fluorescein angiography and spectral domain optical coherence tomography (OCT) (Topcon three-dimensional OCT 2000; Topcon Medical Systems, Inc., Oakland, NJ, USA). The following inclusion criteria were applied: (1) A confirmed diagnosis of diabetes mellitus, (2) clinical and angiographic evidence of DME refractory to laser photocoagulation (last laser session at least 3 months before being enrolled). Patients were excluded on the basis of the following: (1) Co-existing eye disease liable to affect visual outcome, (including axial or capsular lens opacity, glaucoma, amblyopia and nondiabetic macular disease), (2) ischaemic maculopathy evident on fluorescein angiography (3) active proliferative diabetic retinopathy, (4) vitreous hemorrhage, (5) vitreo macular traction (VMT) syndrome evident on biomicroscopic examination and OCT, (6) history of receiving laser or intravitreal injection of any anti-VEGF agent or steroids within last 3 months.

All eyes in the bevacizumab group (Group I) underwent three injections of 1.25 mg/0.05 ml bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) given on day 1, day 30 and day 60. The PPV group (Group II) underwent standard 23 gauge three port PPV with induction of a posterior vitreous detachment followed by 0.5 mg/ml indocyanine green (ICG) (IC-Green™ Akorn, Inc., USA) assisted internal limiting membrane (ILM) peeling. The extent of ILM peeling was approximately in an area of about two disk diameter centered at the fovea. The primary outcomes measured were: (1) Best-corrected logMAR visual acuity (BCVA) using Snellen's Visual acuity chart. (2) CMT on OCT. The secondary outcome measures were: Complication rates like (1) progression of lens opacities, (2) high intraocular pressure (IOP) needing further treatment/procedure, (3) development of vitreous hemorrhage related to the procedure employed, (4) retinal detachment and (5) severe inflammation/endophthalmitis. BCVA and CMT were analyzed on day 30, day 60, day 90 and day 120. The final analyses were done taking the preoperative BCVA and CMT and comparing it with the BCVA and CMT at day 120; which corresponded to 60 days after the third (last) bevacizumab injection.

Statistical analysis

The BCVA was converted to logMAR units for statistical purposes. Data were expressed as mean ± standard deviation, as a percentage of patients with the characteristic, or as means (95% confidence interval [CI]). $P < 0.05$ were considered statistically significant. Statistical analysis was performed using SPSS 19.0 (SPSS®, Chicago, IL, USA).

Results

Forty-four patients were enrolled and randomized into two groups in this study. Twenty-two eyes of 22 patients were enrolled in Group I and received three intravitreal injection of bevacizumab. Twenty-two eyes of 22 patients were enrolled in Group II in which all eyes underwent PPV and ICG enhanced ILM peeling. Table 1 describes the baseline characteristics of the all the patients. All eyes enrolled in the study had clinically significant macular edema (CSME). In Group I (PPV group); 8 eyes (36.4%) had moderate nonproliferative diabetic retinopathy (NPDR), whereas 14 eyes (63.6%) had severe NPDR. In Group II (IVB group); 6 eyes (27.3%) had moderate NPDR, whereas 16 eyes (72.7%) had severe NPDR. Table 2 enumerates the change in BCVA and CMT in Group I, after three IVB injection. Both were taken into account after 120 days which corresponded to 60 days after last (third) injection. Out of 22 eyes in Group I, 16 (72.8%) eyes showed improvement in vision; 3 (13.6%) showed no change and 3 (13.6%) eyes reported decrease in vision. Improvement in vision after IVB was statistically significant ($P = 0.0181$).When CMT was analyzed it was noted that all 22 (100%) eyes showed decrease when compared with the preinjection status. Decrease in CMT postinjection was statistically significant ($P < 0.0001$). Table 3 gives the detail of pre- and post-procedure vision and CMT in Group II. Both vision and CMT were taken into account after 120 days of PPV. Out of 22 eyes in this group: 13 (59.1%) eyes showed improvement in vision, 4 (18.2%) eyes showed no change from the preoperative status and 5 (22.7%) eyes showed decrease in BCVA when compared with preoperative visual status. Improvement in vision after PPV was statistically significant ($P = 0.028$).

When we compare the difference between pre- and postoperative CMT after PPV and ILM peel it was observed that all the 22 (100%) eyes showed decrease in CMT postoperatively. Decrease in CMT postsurgery was statistically significant ($P < 0.0001$). Table 4 calculates Group statistics showing the relationship between the two methods (PPV vs. IVB). Table 4a shows the comparative group statistics for vision in both treatment groups and Table 4b shows comparative group statistics for CMT in both treatment groups. The mean of vision difference in IVB Group between pretreatment levels from posttreatment level was 0.203 (95% CI: 0.0364–0.369). The mean of vision difference in PPV group between pretreatment levels from posttreatment level was 0.189 (95% CI: 0.0210–0.356). The mean of CMT in pretreatment minus posttreatment eyes equals 108.46 in IVB group (95% CI: 62.20–154.71). In PPV group; the mean of CMT in pretreatment minus posttreatment equals 161.37 (95% CI: 03.28–219.45).

As is evident from the data presented; the group difference in CMT between the eyes after treatment in both the groups is 52.91 μ, which looks substantial but on calculation is not found

Table 1: Baseline characteristics of the cases enrolled in the study

	Group I (PPV)	Group II (bevacizumab)	*P*
Age (years)	54±4.33	53.8±5.57	0.894
HbA1C	9.4±0.97	9.9±1.37	0.169
Baseline BCVA (logMAR)	0.871±0.273	0.894±0.303	0.792
Baseline CMT (μ)	410.18±127.16	432.77±86.04	0.439
Follow-up (months)	5.36±1.60	5.81±1.46	0.335

PPV: Pars plana vitrectomy, CMT: Central macular thickness, BCVA: Best corrected logMAR visual acuity, HbA1C: Hemoglobin A1c

Table 2: Vision and CMT in Group I (bevacizumab group)

Case	Preoperative BCVA	Preoperative OCT	Postoperative BCVA	Postoperative OCT
1	0.477	284	0.602	270
2	1.301	330	0.602	267
3	1.0	368	0.698	288
4	1.301	400	1.176	245
5	1.176	346	1.0	331
6	0.698	411	1.0	399
7	1.176	567	1.176	300
8	0.602	497	0.544	335
9	0.544	466	0.544	358
10	0.602	495	0.477	307
11	1.0	390	0.698	329
12	0.698	432	0.544	347
13	1.301	509	0.698	300
14	0.602	524	0.301	267
15	1.176	483	0.544	309
16	0.544	472	0.301	289
17	0.602	577	0.698	500
18	0.698	513	0.602	486
19	1.0	464	0.698	345
20	1.176	335	0.602	309
21	0.698	369	0.698	293
22	1.301	289	1.0	261
(mean)	(0.849)	(432.7)	(0.691)	(324.3)

CMT: Central macular thickness, BCVA: Best corrected logMAR visual acuity, OCT: Optical coherence tomography

Table 3: Vision and CMT in Group II (vitrectomy group)

Case	Preoperative BCVA	Preoperative OCT	Postoperative BCVA	Postoperative OCT
1	1.0	508	0.544	276
2	1.301	623	0.698	314
3	0.698	566	0.698	227
4	1.176	496	0.602	295
5	1.0	457	1.0	328
6	1.301	685	0.544	258
7	1.176	414	1.176	227
8	0.602	285	0.301	190
9	0.698	305	0.544	208
10	0.477	284	0.544	197
11	1.0	334	0.301	204
12	0.602	274	0.477	227
13	0.698	260	1.0	183
14	0.544	338	0.477	231
15	0.698	411	1.0	284
16	1.0	365	0.602	211
17	1.176	348	1.301	276
18	0.698	295	0.602	198
19	1.0	364	1.0	312
20	1.176	648	0.602	297
21	0.544	406	0.698	288
22	0.602	358	0.301	243
(mean)	(0.871)	(410.1)	(0.682)	(248.8)

CMT: Central macular thickness, BCVA: Best corrected logMAR visual acuity, OCT: Optical coherence tomography

Table 4a: Comparative group statistics for vision

Vision	Method	*n*	Mean	SD	*t*	Significant (two-tailed)	df
Difference in posttest minus pretest	Bevacizumab (group I)	22	−0.20	0.26	0.164	0.871	42
	PPV (group II)	22	−0.19	0.32			

PPV: Pars plana vitrectomy, SD: Standard deviation

Table 4b: Comparative group statistics for CMT

CMT	Method	*n*	Mean	SD	*t*	Significant (two-tailed)	df
Difference in posttest minus pretest	Bevacizumab (group I)	22	108.45	79.64	1.87	0.068	42
	PPV (group II)	22	161.36	105.94			

PPV: Pars plana vitrectomy, CMT: Central macular thickness, SD: Standard deviation

to be statistically significant. The secondary outcome measured were; progression of lens opacities, high IOP needing further treatment/procedure, development of vitreous hemorrhage related to the procedure employed, retinal detachment, and severe inflammation/endophthalmitis. In our series 16 (72.7%) eyes in Group II (PPV) were already pseudophakic and the rest did not show any significant increase in cataract after 4 months of PPV. In 7 (31.8%) eyes peripheral breaks were observed during induction of posterior vitreous detachment in PPV group. Gas tamponade was used in these cases. No other complications like high IOP requiring a further procedure, vitreous hemorrhage, retinal detachment or endophthalmitis was observed in either group.

Discussion

Refractory nontractional DME is a difficult condition to treat and several treatment modalities are used in its management. Though there are reports which suggest that the use of bevacizumab in patients with center-involving CSME without advanced macular ischemia is superior to laser,[19] but not much evidence is available comparing IVB to PPV. In present study we compared three IVB injections with PPV. Intravitreal Anti VEGF agents are reported to be beneficial in DME, but there is no agreement on how many injections should be given and when the treatment should be stopped or re-instated. Several dosage schedules have been described in literature. Recently, the effect of IVB on DME was evaluated retrospectively in 78 eyes of 64 patients.[20] This treatment resulted in stability or improvement of visual acuity, OCT, and fluorescein angiography at 6 months. A second injection was required in 20% and a third injection was needed in 8% of eyes.[20] In some other prospective randomized placebo-controlled studies, three consecutive injections of bevacizumab were found to be beneficial in refractory macular edema.[11,13] It was reported that, 3 monthly bevacizumab injections can be used for chronic DME regardless of BCVA, CMT, or foveal avascular zone dimensions, especially in cases with milder retinopathies.[21] In the present study, we used 1.25 mg/0.05 ml bevacizumab and gave three, monthly injections. Considering the severity of DME and in the attempt to maximize the potential effect of bevacizumab, we decided to perform three consecutive injections as a loading dose in our treatment strategy. Only 4 eyes included in the study received anti VEGF injections previously. All 4 eyes received only one anti-VEGF injection. They got this injection elsewhere (not in our hospital) and that also more than 3 months before being enrolled in the study. In the present study, our aim was to evaluate PPV versus three intravitreal injections of bevacizumab. We wanted to assess the final vision and CMT after three IVB at a point when both the parameters stabilize. We know by published reports in literature that it takes 4–6 weeks for the eye to stabilize after IVB.[11] Final assessment after 1-month of last injection seemed a bit early for final assessment; so 2 months after last injection (corresponding to 4 months after start of study period) was taken as an end point in both the groups in our study. When we planned this study longer follow-up was not decided because by experience we know that bevacizumab group may need further intravitreal injections after three initial loading dose injections. That would have interfered with our main aim of comparing PPV with Three IVB injections.

As shown in Fig. 1 Line Graph A; the vision progressively improved after subsequent intravitreal injections of bevacizumab, and it remained stable after 60 days of last injection. Similar improvement in final vision was recorded in the PPV group though the improvement in vision was much earlier (in about 30 days after the procedure) when compared with IVB group. In Fig. 1 Line Graph B, we can see that CMT improved in both groups but more in eyes that underwent PPV. The CMT increased marginally in IVB group when analyzed after 60 days of last bevacizumab injection whereas in the PPV group it dropped sharply after the procedure and then remained stable. Usually, maximum therapeutic effects of anti-VEGF injections are seen within 4–6 weeks postinjections. We analyzed vision and CMT in IVB group at 30 days and 60 days after injection to give us a better idea how CMT behaves with time. Figs. 2 and 3 show pre- and post-injection OCT picture of two representative cases enrolled in the Group I of the study. The intravitreal injection is an invasive procedure and not without complications. There are inherent complications of the intravitreal injection procedure and also side effects of the drug (bevacizumab). In one large retrospective study, records of 1173 patients were analyzed who received IVB and were followed for 12 months to review ocular and systemic side-effects.[22] This study reported seven cases of acute elevation of blood pressure, six cases of cerebrovascular attacks, five cases of myocardial infarctions, five deaths, seven cases of bacterial endophthalmitis, seven cases of tractional retinal detachment, and four cases of uveitis. Mason *et al*. retrospectively studied their series of 5233 IVB treatments for the incidence of acute postinjection endophthalmitis.[23] The authors reported just one case of endophthalmitis. There are also concerns regarding the effect of bevacizumab on the

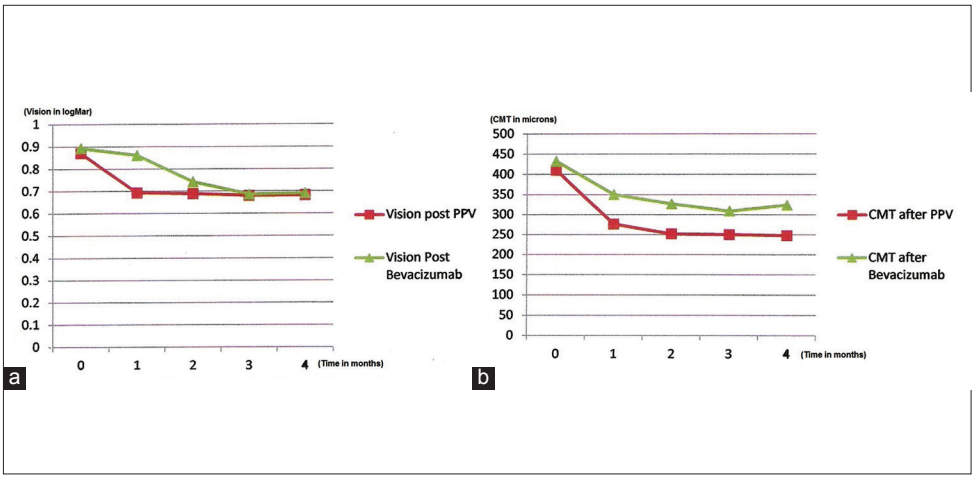

Figure 1: Line Graph A: Comparison of Vision change in both Groups. Line Graph B: Comparison of Central macular thickness change in both Groups

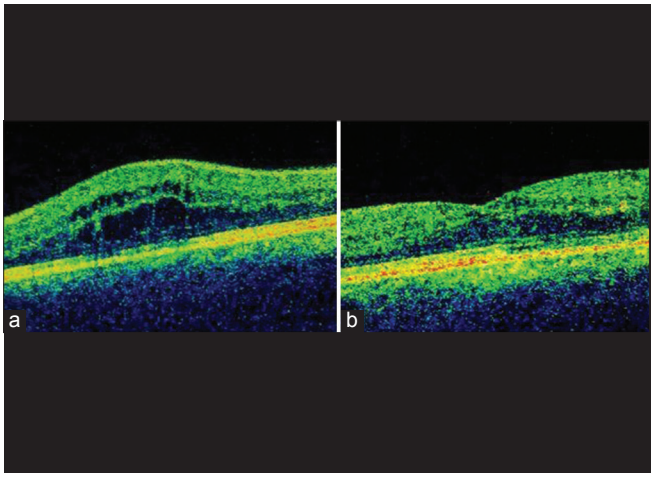

Figure 2: (a) Preinjection optical coherence tomography (OCT) picture showing diffuse diabetic macular edema along with cystic changes. (b) OCT picture 1-month after 3 injections of bevacizumab

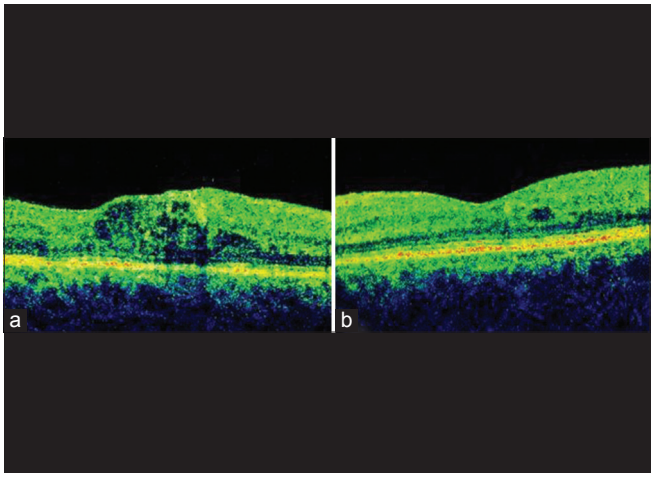

Figure 3: (a) Preinjection optical coherence tomography (OCT) picture showing diffuse diabetic macular edema. (b) OCT picture one after three injections of bevacizumab. Note the residual cystic edema

capillary perfusion in the macular area. In one such study, the authors concluded that bevacizumab may improve CMT in DME but leads to capillary loss.[21] On the other hand, there are reports which suggest that IVB may be beneficial even in cases where the severe capillary loss is already present.[23] It was reported that fluorescein angiography demonstrated no change in the extent of macular capillary loss or reduced dye leakage when compared with baseline in all patients who received IVB injections.[24]

Pars plana vitrectomy is another treatment modality reported to be useful in treating refractory DME. Several studies published in peer reviewed literature have shown that vitrectomy leads to a reduction of CMT in most cases and improvement of visual acuity in 43–69% of study eyes.[14-17] One important prognostic factor affecting the final visual acuity is the presence of VMT. DRCR.net study reported results of visual acuity outcomes after vitrectomy for DME in which 71% eyes had some sort of macular traction.[25] In that series 64% eyes underwent ILM removal. They reported that median central subfield thickness decreased from 412 μm to 278 μm at 6 months, but median visual acuity remained unchanged. Several studies have documented good anatomical and functional results after PPV in refractory DME even without macular traction.[15,26,27] In one retrospective study; results of PPV with ILM peel were analyzed in 60 eyes with DME without macular traction. The authors reported that 55 (93%) eyes showed a decrease in macular thickening. Better postoperative vision was seen in 26 (43%).[15] In another retrospective study analyzing results of PPV and ILM peel in refractory DME without VMT, the authors reported that 13 (50%) eyes showed improvement in postoperative visual acuity.[26] In our study vision improved in 13 (59.1%) eyes. Figs 4 and 5 show pre- and post-vitrectomy, OCT pictures of two representative cases enrolled in the Group II of the study. In our series presence of VMT was an important exclusion criterion. None of our cases had macular traction. Another important decision when planning PPV is whether to remove ILM or not. Some studies have reported a beneficial effect of ILM removal in chronic DME[28] where as others have reported no added advantage of ILM removal.[29] There are concerns for further photoreceptor damage in an already damaged macula by removing ILM. The

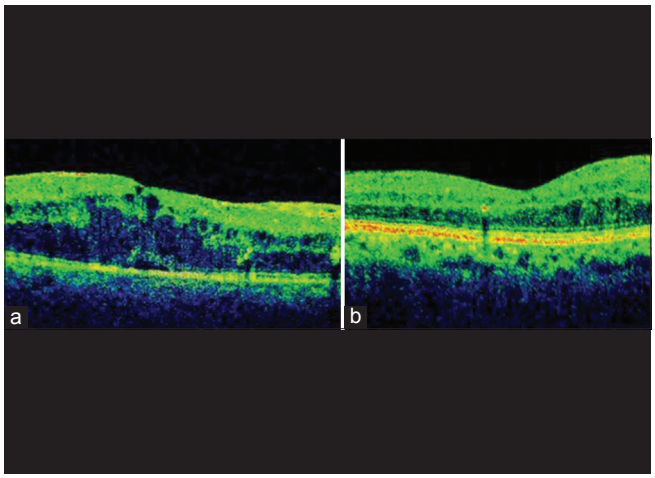

Figure 4: (a) Optical coherence tomography (OCT) picture showing diffuse diabetic macular edema (DME) before vitrectomy. (b) Postsurgical OCT showing resolving macular edema

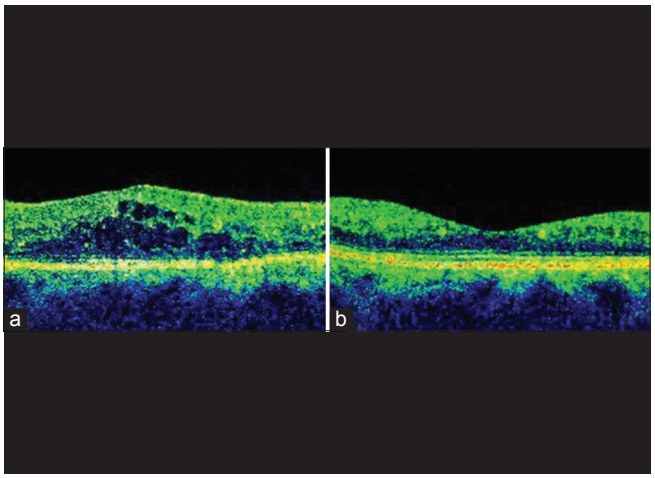

Figure 5: (a) Optical coherence tomography (OCT) picture showing diffuse DME before vitrectomy. (b) Postsurgical OCT showing resolving macular edema

reason of persistence of chronic edema and how ILM could improve outcomes in some patients remains unknown. The significant role of the ILM in the pathogenesis of persistent diffuse DME might be explained by stressing the importance of colloid and protein accumulation and retention in the retinal interstitial space. Furthermore, ILM removal may also have a beneficial effect in preventing postoperative epiretinal membrane formation by removing the scaffold for proliferating cells. In our series, all eyes underwent ILM peel after staining with ICG.

How PPV helps in resolving macular edema and improvement of vision is not entirely known but it is postulated that increased macular blood flow in DME gets normalized after vitrectomy, which leads to resolution of macular edema in diabetic eyes.[30] Another factor affecting final visual acuity after PPV is the presence of a cataract. Several studies have showed that the presence of preexisting cataract or simultaneous phacoemulsification affects the final visual status. In our series 16 (72.7%) eyes in Group II (PPV) were already pseudophakic, and the rest did not show any significant increase in cataract after 4 months of PPV. We used short-acting gas - sulfur hexafluoride (SF6) in 7 (31.8%) eyes out of which only three were phakic. In these cases, peripheral breaks were observed during induction of posterior vitreous detachment. No other complication of the vitrectomy procedure like recurrent vitreous hemorrhage, retinal detachment or endophthalmitis was observed in our series. In IVB group also we did not encounter any complications like vitreous hemorrhage, retinal tear/detachment, lens touch or endophthalmitis.

We observed in our series that vision improved earlier in PPV group though the difference in final vision achieved, and the number of patients reported improvement of vision in either group were not statistically significant. When changes in CMT were analyzed, it was observed that the decrease in CMT was more in PPV group when compared to a decrease in CMT in IVB group. If we combine the data from both the groups, we find that CMT decreased in 44 (100%) eyes but vision improved only in 29 (65.9%) eyes. Both IVB and PPV are effective treatment modalities for nontractional DME refractory to laser therapy. PPV has the advantage of being a one time procedure. Also, the decrease in CMT is more and vision is stabilized early when compared to IVB injections. The disadvantages of PPV are that it is a difficult and long procedure needing specialized instruments, personnel, and setup. Moreover, the final visual result is affected by many variables like the dexterity of surgeon, dye used for ILM peel, the extent of ILM peel and cataract progression. The advantages of intravitreal anti-VEGF are that it is a simple procedure, can be done quickly in the outpatient clinic and does not require a large setup, specialized equipment or personnel. Disadvantages of IVB are delayed response in the improvement of vision and need for multiple injections.

Limitations

Our study is limited by the small number of cases, and short follow-up period. Development of cataract affects the final vision outcome, but it requires a longer follow-up. This study was also not powered to assess either the systemic side-effects of bevacizumab or the toxicity of staining material used to assist ILM peeling.

References

1. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91:1464-74.
2. Klein R, Klein BE, Moss SE. Visual impairment in diabetes. Ophthalmology 1984;91:1-9.
3. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1991;98:766-85.
4. Akduman L, Olk RJ. Laser photocoagulation of diabetic macular edema. Ophthalmic Surg Lasers 1997;28:387-408.
5. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 1. Early Treatment Diabetic Retinopathy Study Research Group. Arch Ophthalmol 1985;103:1796-806.
6. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, *et al.* Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480-7.
7. Gardner TW, Antonetti DA, Barber AJ, LaNoue KF, Levison SW.

Diabetic retinopathy: More than meets the eye. Surv Ophthalmol 2002;47 Suppl 2:S253-62.

8. Cunningham ET Jr, Adamis AP, Altaweel M, Aiello LP, Bressler NM, D'Amico DJ, *et al*. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005;112:1747-57.
9. Lam DS, Lai TY, Lee VY, Chan CK, Liu DT, Mohamed S, *et al.* Efficacy of 1.25 MG versus 2.5 MG intravitreal bevacizumab for diabetic macular edema: Six-month results of a randomized controlled trial. Retina 2009;29:292-9.
10. Fang X, Sakaguchi H, Gomi F, Oshima Y, Sawa M, Tsujikawa M, *et al.* Efficacy and safety of one intravitreal injection of bevacizumab in diabetic macular oedema. Acta Ophthalmol 2008;86:800-5.
11. Ahmadieh H, Ramezani A, Shoeibi N, Bijanzadeh B, Tabatabaei A, Azarmina M, *et al*. Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial. Graefes Arch Clin Exp Ophthalmol 2008;246:483-9.
12. Stefaniotou M, Aspiotis M, Kalogeropoulos C, Christodoulou A, Psylla M, Ioachim E, *et al.* Vitrectomy results for diffuse diabetic macular edema with and without inner limiting membrane removal. Eur J Ophthalmol 2004;14:137-43.
13. Kralinger MT, Pedri M, Kralinger F, Troger J, Kieselbach GF. Long-term outcome after vitrectomy for diabetic macular edema. Ophthalmologica 2006;220:147-52.
14. Yamamoto T, Hitani K, Sato Y, Yamashita H, Takeuchi S. Pars plana vitrectomy with and without peeling of the inner limiting membrane for diabetic macular edema. Ophthalmologica 2005;219:206-13.
15. Dillinger P, Mester U. Vitrectomy with removal of the internal limiting membrane in chronic diabetic macular oedema. Graefes Arch Clin Exp Ophthalmol 2004;242:630-7.
16. Jahn CE, Töpfner von Schutz K, Richter J, Boller J, Kron M. Improvement of visual acuity in eyes with diabetic macular edema after treatment with pars plana vitrectomy. Ophthalmologica 2004;218:378-84.
17. Yanyali A, Horozoglu F, Celik E, Ercalik Y, Nohutcu AF. Pars plana vitrectomy and removal of the internal limiting membrane in diabetic macular edema unresponsive to grid laser photocoagulation. Eur J Ophthalmol 2006;16:573-81.
18. Stolba U, Binder S, Gruber D, Krebs I, Aggermann T, Neumaier B. Vitrectomy for persistent diffuse diabetic macular edema. Am J Ophthalmol 2005;140:295-301.
19. Michaelides M, Kaines A, Hamilton RD, Fraser-Bell S, Rajendram R, Quhill F, *et al.* A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: Report 2. Ophthalmology 2010;117:1078-86.e2.
20. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M, *et al*. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: Results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. Ophthalmology 2007;114:743-50.
21. Erol N, Gursoy H, Kimyon S, Topbas S, Colak E. Vision, retinal thickness, and foveal avascular zone size after intravitreal bevacizumab for diabetic macular edema. Adv Ther 2012;29:359-69.
22. Wu L, Martínez-Castellanos MA, Quiroz-Mercado H, Arevalo JF, Berrocal MH, Farah ME, *et al.* Twelve-month safety of intravitreal injections of bevacizumab (Avastin): Results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol 2008;246:81-7.
23. Mason JO 3rd, White MF, Feist RM, Thomley ML, Albert MA, Persaud TO, *et al.* Incidence of acute onset endophthalmitis following intravitreal bevacizumab (Avastin) injection. Retina 2008;28:564-7.
24. Bonini-Filho M, Costa RA, Calucci D, Jorge R, Melo LA Jr, Scott IU. Intravitreal bevacizumab for diabetic macular edema associated with severe capillary loss: One-year results of a pilot study. Am J Ophthalmol 2009;147:1022-30, 1030.e1.
25. Flaxel CJ, Edwards AR, Aiello LP, Arrigg PG, Beck RW, Bressler NM, *et al*. Factors associated with visual acuity outcomes after vitrectomy for diabetic macular edema: Diabetic retinopathy clinical research network. Retina 2010;30:1488-95
26. Rosenblatt BJ, Shah GK, Sharma S, Bakal J. Pars plana vitrectomy with internal limiting membranectomy for refractory diabetic macular edema without a taut posterior hyaloid. Graefes Arch Clin Exp Ophthalmol 2005;243:20-5.
27. Kumagai K, Furukawa M, Ogino N, Larson E, Iwaki M, Tachi N. Long-term follow-up of vitrectomy for diffuse nontractional diabetic macular edema. Retina 2009;29:464-72.
28. Gandorfer A, Messmer EM, Ulbig MW, Kampik A. Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane. Retina 2000;20:126-33.
29. Kamura Y, Sato Y, Isomae T, Shimada H. Effects of internal limiting membrane peeling in vitrectomy on diabetic cystoid macular edema patients. Jpn J Ophthalmol 2005;49:297-300.
30. Park JH, Woo SJ, Ha YJ, Yu HG. Effect of vitrectomy on macular microcirculation in patients with diffuse diabetic macular edema. Graefes Arch Clin Exp Ophthalmol 2009;247:1009-17.

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