Pars Plana Vitrectomy with Internal Limiting Membrane Peeling and Intravitreal Bevacizumab Injection for Refractory Diffuse Diabetic Macular Edema

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Research Article

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Abstract

Purpose: Evaluating the impact of pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling and intravitreal bevacizumab (IVB) injection to manage refractory diffuse diabetic macular edema (DME).

Methods: In the current prospective interventional clinical study, eyes with refractory diffuse DME with no response to a minimum of three times IVB injections, and best corrected visual acuity (BCVA) of equal or more than 20/200 and equal or lower than 20/60 were subjected to PPV with ILM peeling and intravitreal avastin injection. Pre- and post-operative assessments were a comprehensive ophthalmologic evaluation, fluorescein angiography, and optical coherence tomography (OCT). BCVA, central macular thickness (CMT) and contrast sensitivity (CS) were major outcomes.

Results: Fifteen eyes of 13 cases (mean age: 63±5.19 (range, 54-70) years) were subjected to operation and a follow-up of 3 months. Average BCVA at last test was 0.74 ± 0.19 LogMAR that showed no improvement compared with its value before intervention (0.84 ± 0.14 LogMAR) (P=0.073). Average CMT at last test was 328.26±129 µm that was significantly lower compared with its value before operation (450.8±114 µm) (P=0.002) and a significant improvement in CS was found (from 16.66 ± 8.99 mm to 18.13 ±1.22mm;p=0.003). CMT and BCVA (correlation coefficient =0.419,p=0.120), BCVA and CS (correlation coefficient =-0.336,p=0.221) , and CS and CMT (correlation coefficient =-0.07,p=0.979) were found with no significant correlation.

Conclusion: PPV with ILM peeling and IVB regarding refractory diffuse DME reduced macular width along with CS improvement, but does not significantly improve visual acuity.

Introduction

Macular edema has been the main etiology of vision-loss in diabetics.1 Macular edema reduces visual acuity and over 50% of the patients loss a minimum of 2 lines through 2 years.[2] The inner and outer blood-retina barrier breakdown causes diffuse diabetic macular edema (DME) that is difficult to treat compared with focal edema that is commonly treated with laser macular photocoagulation (MPC) of microaneurysms. In spite of MPC, diffuse DME has poor visual prognosis. [3–6] Following detaching the posterior hyaloid, tangential traction applied by residual cortical vitreous as well as the internal limiting membrane (ILM) is crucial in DME. Thus, pars plana deep vitrectomy (PPV) in combination with removing ILM has been considered.[7] This method can reduce or resolve DME and improve visual acuity.[7–14] The current prospective research aimed at evaluating the efficacy and immunity of PPV plus ILM peeling and IVB injection in cases with diffuse refractory DME with no respond to intravitreal bevacizumab (IVB).

Methods

In the current prospective case series, we assessed eyes with diffuse DME persistent to MPC and/or IVB referring to the Bina eye hospital, Tehran, between September 2018 and September 2019. All aspects of the study were approved by the ethics committee and Institutional Review Board of Bina eye Hospital for the procedures and the tenets of the Declaration of Helsinki were followed. An informed consent was signed by the study participants.Refractory diffuse DME was considered as central macular thickness (CMT) of equal or over 300 µm with a background of a minimum of three IVB sessions or a session of every modality carried out over four months before PPV and the best corrected visual acuity (BCVA) ≥ 20/200 and ≤ 20/60 were inclusion criteria. Exclusion criteria were: Those with uncontrolled ocular diseases (except DME or cataract), angiographic macular ischemia, systemic conditions along with unacceptable high surgical complications, major perioperative complications, a history of vitreoretinal surgery; monocular cases and missing follow-up examinations three months after surgery.

Preoperative evaluation included determination of Snellen BCVA, Contrast sensitivity test measurement using Melbourne edge test, biomicroscopic assessment of the anterior and posterior segments, fluorescein angiography (FA), and OCT (3D OCT-1000, Topcon Corporation, Japan) to measure CMT. The participants signed the written informed consent.

The eyes were subjected to the 23-gauge triamcinolone acetonide-assisted pars plana vitrectomy. In the presence of significant cataract, phacoemulsification by implementing intraocular lens in capsular bag was carried out before vitrectomy. After removing epiretinal membrane as well as staining with brilliant blue G (MembraneBlue-Dual, DORC), ILM peeling was done. We did not use tamponade after the operation. Following vitrectomy and ILM peeling, injection of avastin (1.25 mg) was done. After surgery, visiting the patients was as follows: a day, one and four weeks, and every 2–3 months after the surgery. After the procedure, Chloramphenicol, betamethasone, and cycloplegic drops were used followed by tapering off betamethasone over four weeks. At all follow-up visits, we calculated Snellen BCVA along with a comprehensive ophthalmologic assessment and also complete ocular examination as well as SD-OCT. When the lens opacity was severe to prevent FA and/or OCT, cataract surgery was considered. BCVA before and after surgery was converted to Log MAR comparing through Wilcoxon signed-rank test (also for comparing the CMT and CS before and after surgery).

Results

We studied fifteen eyes (13 patients (6 males)). The patients' characteristics and BCVA and CMT before and after surgery are presented in Table 1. The cases' average age was 63.38 ± 5.15 (range: 54–70) years and they had type 2 diabetes. Seven eyes were found with severe NPDR 5 eyes had moderate NPDR, and 3 eyes had regressed PDR. Macular edema of the eyes was assessed by biomicroscopy, and fluorescein angiography showed diffuse fluorescein leakage. The eyes were subjected to three sessions of IVB. An average interval 4 (range, 4–9) months was found between the latest IVB and PPV. Mean BCVA at the last follow-up was 0.74 ± 0.19 Log MAR that showed no significant improvement compared with its value before surgery (0.84 ± 0.14 Log MAR) (P = 0.073). An improvement of 2 lines was detected in visual acuity in 7 eyes (46%), whereas 7 eyes (46%) remained unchanged and it reduced by at least 2 lines in 1 eye (8%).

Average CMT of 328.26 ± 129 µm was recorded at final follow-up that showed a significant reduction compared with its value before surgery (450.8 ± 114 µm; Wilcoxon test, P = 0.002). CMT at the last examination showed a decrease of over 80% in 14 of 15 eyes (86%). Moreover, a significant improvement in CS was found (from 16.66 ± 8.99 mm to 18.13 ± 1.22 mm; p = 0.003).

No patient was reported with major intraoperative complications. Vitreous hemorrhage was reported in 2 eyes postoperatively that resolved 3 months post-operation and did not required repeat deep vitrectomy. Preoperatively, four eyes were pseudophakic, whereas the others were found with mild/no lens opacity. Following vitrectomy, there was no need for cataract surgery until 6 months of follow-up.

Discussion

DME is still an important reason for visual impairment in diabetics and may be refractory to conventional therapies.[26]

Eyes categorized as diffuse DME do not properly respond MPC visual .[15] Lee and Olk[5–6] assessing 302 eyes categorized as diffuse DME after treatment with MPC, announced an improvement in vision identical to three Early Treatment of Diabetic Retinopathy Study (ETDRS) charts or over in just 13.7% of eyes after a year, and decline of visual function in 25% at three years. Visual rehabilitation in such cases with no respond to laser photocoagulation, is challenging. vitrectomy is suggested for VMT or a tractional ERM cases.[29]

Different data have been reported on the vitrectomy effect on BCVA. However, vitrectomy for DME is recommended due to the association between PVD and a lower prevalence of DME. Nasrallah et al[16] showed that just 20% of DME eyes showed PVD, while 55% of eyes with no DME showed PVD. Vitrectomy is effective for eyes characterized by detectable hyaloid thickening or contraction, however, the outcomes are controversy regarding eyes with no hyaloidal abnormality. In the current study, a significant improvement was found in foveal thickness. Nonetheless, no significant improvement was detected in visual acuity. Different studies have revealed a significant improvement in BCVA[9–11]. For example, an improvement of two or over lines in 43–92% of eyes subjected to PPV with ILM removal.[7–11, 17] PPV with ILM peeling can reduce retinal thickness with no visual improvement .[18–20] The rate of eyes experiencing a minimum of 2 lines of improvement (45%), was at the same rate or over than those reported earlier [7–11, 17].

Our results are in contrast with those by Kim et al 28 who announced that BCVA significantly improved (from 0.44 ± 0.15 logMAR to 0.34 ± 0.22 logMAR after six months) and BCVA decreased at 3 months that was reported to be due to cataract progression. Accordingly, two points should be considered. 1) In Kim et al [28] research the baseline average BCVA was significantly higher compared with ours as well as in Dehghan et al[27] research. 2) Kim et al studied (28 eyes) more eyes compared with the current research as well as Dehghan et al[27] (12 eyes) study.

Such discrepancies may be due to variations in inclusion criteria, past therapies, chronicity level, previous MPC and/or IVB, diabetic retinopathy level, macular ischemia severity that are not commonly detectable on FA, and follow up period.

PPV with ILM peeling can cause a significant reduction in macular width,7–12,14 however, it is uncorrelated precisely with improvement in visual acuity,[18–20](as our research). Such disagreement between anatomic and visual results is possibly because of the increased lens opacity as well as deteriorate of diabetic retinopathy.

Less is known regarding ILM removal function in DME. PPV with no ILM removal has been demonstrated influential like surgery with ILM removal regarding reduced retinal width and visual acuity improvement .12,21 In contrast, PPV could successfully reduce DME, however, better outcomes were achieved in eyes with ILM removal compared with cases with no ILM removal.[17] Gandorfer et al[7] found that diffuse DME that is able to progresse in spite of PPV along with posterior hyaloid and epiretinal membrane removal for non-clearing vitreous hemorrhage, is resolved quickly following ILM removal. Kimura et al[14] introduced rapid resolution of DME in eyes subjected to PPV with no epiretinal membrane. Residual cortical vitreous can be connected to the macula following the posterior hyaloid removal through triamcinolone-assisted PPV.[22] Eyes with diabetic maculopathy are found with ILM thickening and cell frequency on the vitreous direction of the ILM.[23] Thus, ILM peeling is effective in DME through the removal of the tangential traction due to the ILM and residual cortical vitreous. Also, it possibly is effective to prevent epiretinal membrane generation after surgery via the removal of the scaffold for proliferating cells. We consistent with other studies [7–12] did not find epiretinal membrane generation after surgery reported in 10.2% – 13.8% of eyes following PPV with no ILM peeling,[24–26], however, a research announced epiretinal membrane generation in 5% of eyes.[14]

Complications after surgery were subconjunctival hemorrhage in 4 eyes, hyphaema in 4 eyes and vitreous hemorrhage in 2 eyes that resolved 3 month post operation.

The power of our study are the prospective, PPV along with ILM peeling and IVB injection, Contrast sensitivity measurement and independent, unsponsored study. However, our study has some limitation such as small sample size, short term follow-up and randomization deficiency. Also, systemic parameters, particularly HbA1c and lipid levels, can be confounding factors however, we did not evaluate them.

It can be concluded that vitrectomy with ILM removal and IVB injection for persistent diffuse DME is able to decrease macular thickness, however, causes no significant improvement in visual acuity through a 3-month follow. A large, multicenter, randomized controlled trial is needed to compare PPV with/without ILM removal as well as IVB injection using longer follow-up for establishing the ILM removal effect on treating DME.

Declarations

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Consent for publication

Not available

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available since all relevant data are included in the manuscript. The datasets are available from the corresponding author on reasonable request.

Authors' contributions

AA ,KJ and HT were responsible for the conception and design of the study. SAM acquired the data. KJ,SAM and H T analyzed and interpreted the data. SAM wrote the draft. AA and KJ revised the manuscript critically. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The research protocol was in accordance with the Helsinki's Declaration and approved by the Ethics Committee in Human Research at Bina Eye Hospital Research Center. The registered number is **ir.bmsu.rec.1396.479**

Informed consent was taken to participate the study from all cases

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Demographic characteristics, visual acuity before and after surgery, central macular thickness and contrast sensitivity in eyes with refractory diffuse diabetic macular edema

	BCVA (logMAR)	CMT (μm)	CS

Case	Age (years)	Sex	Eye	Lens status	IVB injection(n)	Grade (NPDR)	Baseline	Final	Baseline	Final	Baseline	Fina
1	60	F	OD	PCIOL	9	Moderate	0.7	0.5	336	252	16	19
2	54	M	OS	PCIOL	5	Severe	1	1.2	319	267	16	18
3	54	M	OD	PHAKIC	4	Severe	1	0.9	324	231	16	16
4	60	M	OS	PHAKIC	4	Moderate	0.7	0.7	508	362	18	17
5	67	F	OS	PCIOL	8	Moderate	0.8	0.9	492	449	14	16
6	67	F	OD	PCIOL	10	Moderate	0.9	0.6	537	542	16	18
7	58	M	OD	PHAKIC	6	Regress PDR	0.7	0.6	654	392	18	19
8	65	F	OD	PCIOL	6	Severe	0.6	0.4	389	191	16	19
9	70	F	OS	PCIOL	5	Severe	0.9	0.9	376	215	17	15
10	65	M	OS	PCIOL	7	Regress PDR	0.7	0.8	338	226	15	18
11	66	M	OS	PCIOL	3	Severe	1	0.8	457	548	17	19
12	64	F	OD	PCIOL	4	Severe	1	0.8	548	238	17	19
13	59	F	OS	PHAKIC	4	Regress PDR	0.8	0.7	485	409	14	16
14	69	M	OD	PCIOL	5	Severe	1	0.7	652	392	15	18
15	67	F	OS	PCIOL	4	moderate	0.9	0.6	357	184	17	17

HM, hand motions; F, female; M, male; NPDR, non-proliferative diabetic retinopathy; CMT, central macular thickness; F/U, follow-up; BCVA, best corrected visual acuity; OS, left eye; OD, right eye;