



Visual outcome in diabetic retinopathy with macular oedema after combined therapy with intravitreal bevacizumab and retinal photocoagulation: An observational case series

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ABSTRACT

Purpose

To evaluate the Visual Outcome in Diabetic Retinopathy with Macular Oedema after Combined Therapy with Intravitreal Avastin (Bevacizumab) and Retinal Photocoagulation.

Material and Methods

The study included a total of 142 eyes in 142 patients with diabetic macular oedema. All eyes were treated with intravitreal bevacizumab followed by laser photocoagulation. Visual outcome was measured in terms of changes in visual acuity (logMAR) at 1 month and 3 months after treatment and central macular thickness using spectral domain Ocular Coherence Tomography (OCT) at 3 months after treatment.

Results

Visual acuity improved from the mean best corrected visual acuity (BCVA) log (MAR) of 0.9678 ± 0.2306 at baseline to 0.8928 ± 0.2516 at first visit and then 0.7831 ± 0.2866 at final visit in all 142 patients. OCT determined central macular thickness changed from a mean value of 624 ± 151 microns at first visit to 478 ± 141 microns at final visit in all studied subject.

Conclusion

Combined therapy with intravitreal bevacizumab and laser photocoagulation has a role in stabilizing the retinal anatomy and reducing retinal edema both in NPDR (Non proliferative diabetic retinopathy) and PDR (Proliferative diabetic retinopathy) with macular oedema. The decrease in the central macular thickness is also associated with a significant improvement in BCVA.

INTRODUCTION

Diabetic retinopathy (DR) is a vascular disorder affecting the microvasculature of the retina.¹ It has been shown that nearly all type 1 and 75 per cent of type 2 diabetes will develop DR after 15 yr duration of diabetes.^{2, 3} Diabetic retinopathy remains the major cause of blindness in developed countries in patients

under 55 years of age its early diagnosis and appropriate management are critically important.⁴

Retinal oedema or involving the macula is an important visual consequence of abnormal retinal vascular permeability in diabetic retinopathy.⁵ The Early Treatment Diabetic Retinopathy Study (ETDRS) showed the 3- year risk of moderate visual loss for

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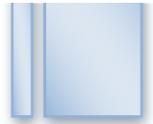
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diabetic patients with clinically significant macular oedema was 30%.⁶

Macular laser photocoagulation (MPC) is considered the standard treatment for focal and diffuse macular oedema.⁷ Although the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that immediate focal photocoagulation reduced moderate visual loss by 50% (from 24% to 12%, 3 years after initiation of treatment), 12% of treated eyes still lost 15 ETDRS letters at the 3-year follow-up interval.⁸

Development of DR is multifactorial but vascular endothelial growth factor (VEGF) has an important role in pathogenesis of diabetic retinopathy.⁹ In diabetic eyes, the upregulation of VEGF is associated with the breakdown of the blood–retinal barrier and an increase in retinal vessel permeability resulting in macular edema.¹⁰ Bevacizumab is a full length humanized monoclonal antibody that blocks all forms of VEGF. Intravitreal bevacizumab (IVB) injection has been reported to be effective in reducing DDME and improving the best-corrected visual acuity (BCVA).¹¹ Because IVB and MPC achieve their effect via different pathways, a combination therapy may yield more favorable results than either therapy alone.¹²

The purpose of this study is to evaluate the efficacy and safety of the combined effect of retinal photocoagulation and intravitreal bevacizumab in diabetic retinopathy with macular oedema. The aims of our study were to determine, using an interventional design, the efficacy of retinal photocoagulation and intravitreal injection of bevacizumab in terms of improvement in visual acuity, reduction in foveal thickness, and to evaluate the visual prognosis and anatomic alterations of macular edema using spectral domain OCT.

MATERIAL AND METHODS

This study was conducted in the Post Graduate Department of Ophthalmology, Government Medical College Srinagar, which is the sole referral tertiary care hospital for Kashmir Valley. This was an observational case series done from April 2013 to October 2014.

Inclusion criteria

Diabetic patients of either sex of more than 18 years of age were included if they had Diabetic retinopathy with macular oedema, defined according to the guidelines set forth by the ETDRS (Diabetic Retinopathy Study Research Group 1979; ETDRS Research Group 1991a). Patients with no previous treatment, media clarity and pupillary dilation sufficient for adequate fundus imaging were included.

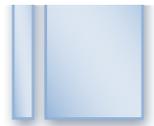
Exclusion Criteria

History of previous laser treatment, vitreoretinal surgery, or intravitreal injection, history of any thromboembolic event (including myocardial infarction or cerebral vascular accident), major surgery within the prior 6 months or planned within the next 28 days, uncontrolled hypertension (according to the guidelines of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC-7]), known coagulation abnormalities or current use of anticoagulative medication other than aspirin, any condition affecting documentation or follow-up, history of another ocular disease other than Diabetic Retinopathy and use of oral thiazolidinediones.

Study Size and Data Collection:

The patients selected as were diagnosed on the basis of detailed history, comprehensive eye examination and appropriate investigations.

Ophthalmologic evaluations performed, included anterior segment examination, best corrected visual acuity (BCVA) of logarithm of the minimum angle of resolution (logMAR) units, IOP measurement and fundus examination for baseline and follow-up data. Fundus photography and fluorescein angiography (FAG) and Ocular Coherence Tomography (OCT) to estimate macular thickness and the morphological pattern of diabetic macular oedema. Central macular thickness was measured with the Optos' OCT SLO, leading spectral OCT imaging using 1mm scans. Eyes with NPDR macular edema underwent one dose of intravitreal avastin followed by one session of Grid or focal laser. While as eyes with Macular oedema, and NVD or NVE received one dose injection Avastin



and one session of grid or focal laser and then two sittings of PRP.

Intravitreal Injections

Each eye was prepared using prophylactic antibiotic drops and 5% povidone iodine. Using a 30-gauge needle 1.25mg of bevacizumab in 0.01ml was administered 3.5mm posterior to the corneal limbus through the inferior pars plana.. All eyes were treated by the same surgeon.

Retinal Photocoagulation

Photocoagulation was performed under topical anaesthesia using a 532-nm green laser. One session of Grid Laser in eyes with macular edema and two sessions of Panretinal Photocoagulation (PRP) in eyes with NVD (Neovascularization at Disc) and NVE (Neovascularization Elsewhere), two weeks apart, was done. The spot size used was be $0.75\mu\text{m}$ for grid laser and $200\mu\text{m}$ for Panretinal Photocoagulation, the exposure time was be 0.1 sec, and the power was adjusted to produce a grey-white lesion. All eyes were treated by the same ophthalmologist.

Outcome Measures

Patients were scheduled for follow-up examinations at one, and three months after the treatment .The outcome measure included BCVA (Best Corrected Visual Acuity) changes measured at one, and three months after the treatment and changes in macular oedema measured at 3 months after treatment. Systemic and local adverse events, including changes in the intraocular pressure and lens status, were monitored throughout the study.

OBSERVATIONS AND RESULTS

In this study a total of 142 eyes of 142 patients with diabetic retinopathy with macular oedema were included. 81% (116) patients fell in the age group of 50-70 years with minimum age being 40 years and maximum age being 73 years. Mean age was 58.557 ± 7.008 years for males and 57.540 ± 6.7985 years for females (Table 1) .In our series 55.6% (79) patients were male and 44.4%(63) were female. The minimum duration of diabetes was 4 years and maximum duration was 25 years.

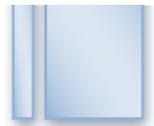
Table 1 Age and Gender Distribution, Duration of Diabetes and Type of Diabetes in Studied Subjects

Age and Gender Distribution							Duration of Diabetes in Years						Type of Diabetes							
Age (Years)	Male (79)		Female (63)		Total (142)		Duration (Years)	Male (79)		Female (63)		Total (142)		Type of Diabetes	Male (79)		Female (63)		Total (142)	
	N	%	N	%	N	%		N	%	N	%	N	%		N	%	N	%	N	%
≤50	12	15.18	12	19.05	24	16.91	≤5	4	5.06	4	6.35	8	5.63	Type I	7	8.86	8	12.69	15	10.5
51-60	31	39.25	27	42.85	58	40.84	6-10	30	37.97	29	46.04	59	41.55							
61-70	35	44.30	23	36.51	58	40.84	11-15	19	24.06	13	20.63	32	22.54							
≥71	1	1.26	1	1.59	2	1.41	16-20	16	20.25	13	20.63	29	20.42	Type II	72	91.13	55	87.30	127	89.4
							≥21	10	12.66	4	6.35	14	9.86							
Mean	58.557 Years		57.540 Years					13.051 Years		11.667 Years										
SD	7.0087 Years		6.7985 Years					5.730 Years		5.328 Years										
SEM	0.7885 Years		0.8565 Years					0.644 Years		0.67 Years										

Mean duration in males was 13.015 ± 5.7309 years and in females it was 11.667 ± 5.328 years (Table 2). In our series type II diabetes mellitus outnumbered type I diabetes mellitus in a ratio of 9:1 with 10%(15) patients suffering from type I diabetes mellitus and 90% (127) patients suffering from type II diabetes mellitus (Table 3). In this series patient suffered from 4 main co-morbidities with maximum number of patients suffering from hypertension 77.46% (110 patients). Other co-morbidities were hypothyroidism ,

hyperlipidemia and nephropathy .There was an almost equal distribution in male and female patients. The distribution was non-significant.

Affected eyes chosen for intervention were right eyes in 55.63% (79) patients and left eyes in 44.37% (63) patients .Pre intervention slit lamp examination was NO (normal) in 38.03% (54) patients ,MIC (minimal cataractous changes) in 32.39%(46) patients ,C (cataract) in 13.39% (19) patients and PP (pseudophakia) in 16.19% (23) patients .Pre



intervention fundus showed NPDR with CSME in 71.13% (101) patients and PDR in 28.87% (41) patients. Pre intervention FFA showed NMI (mild NPDR) in 4.93% (7) patients, NM (moderate NPDR) in

40.84% (58) patients, NS (severe NPDR) in 25.36% (36) patients, PE (early PDR) in 21.13% (30) patients and PH (high risk PDR) in 7.74% (11) patients.

Table 2 BCVA Log (MAR) over Studied Period

	All studied subjects (n = 142)			NPDR WITH CSME			PDR WITH CSME		
	Baseline	First visit	Final visit	Baseline	First visit	Final visit	Baseline	First Visit	Final Visit
Mean	0.9678	0.8928	0.7831	0.9287	0.8068	0.6857	1.1525	1.1047	1.0230
SD	0.2306	0.2516	0.2866	0.2046	0.2177	0.2349	0.1834	0.2002	0.2620
SEM	0.1935	0.0211	0.2405	0.0203	0.0216	0.0234	0.0286	0.0312	0.0409

Table 3 Changes in Central Macular Thickness (microns)

	All studied subjects (n = 142)		NPDR WITH CSME		PDR WITH CSME	
	Baseline	Final visit	Baseline	Final visit	Baseline	Final Visit
Mean	624	478	563	422	775	618
SD	151	141	122	114	102	100
SEM	12	11	12	11	15	15

Age and gender distribution

T-test = .871, df = 141, P value < .05; not significant.

Duration of diabetes: t-test = .1475, df = 141, P value < .05 not significant

Chi Squared = 0.546, df = 1, P value = 0.460; not significant

Changes in BCVA

The mean BCVA log(MAR) changed from 0.9678 ± 0.2306 at baseline to 0.8928 ± 0.2516 at first visit and then 0.7831 ± 0.2866 at final visit showing an improvement of 0.075 from baseline to first visit (p value < 0.0001), 0.1847 from baseline to final visit (p value < 0.0001) and 0.1097 from first visit to final visit (p value < 0.0001).

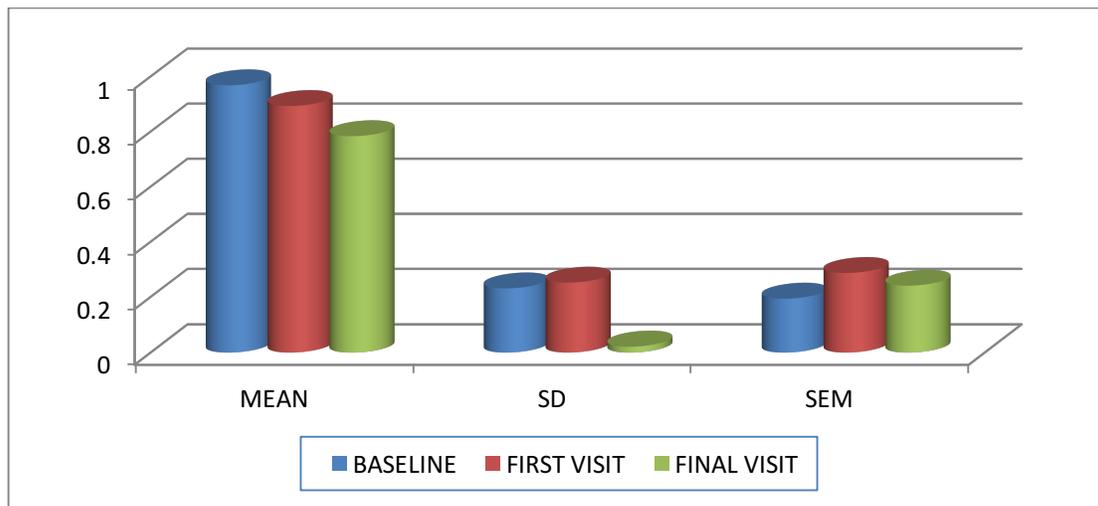


Figure 1 BCVA logMAR in all studied subjects

Changes in BCVA

The mean BCVA log(MAR) changed from 0.9678 ± 0.2306 at baseline to 0.8928 ± 0.2516 at first visit and then 0.7831 ± 0.2866 at final visit showing an improvement of 0.075 from baseline to first visit (p

value < 0.0001), 0.1847 from baseline to final visit (p value < 0.0001) and 0.1097 from first visit to final visit (p value < 0.0001). When assessed separately it was observed that in patients of NPDR with CSME the mean BCVA log(MAR) changed from 0.9287 ± 0.2046 at baseline to 0.8068 ± 0.2177 and then $0.6857 \pm$



0.2349 at final visit showing an improvement of 0.1219 from baseline to first visit (p value <0.0001), 0.243 from baseline to final visit (p value <0.0001) and 0.1211 from first to final visit (p value <0.0001). In patients of PDR with CSME mean log(MAR) changed from 1.1525 ± 0.1834 at baseline to $1.1047 \pm$

0.2002 and then 1.0230 ± 0.2620 at final visit showing an improvement of 0.0118 from baseline to first visit (p value = 0.008), 0.1295 from baseline to final visit (p value <0.0001) and 0.0817 from first to final visit (p value = 0.001).

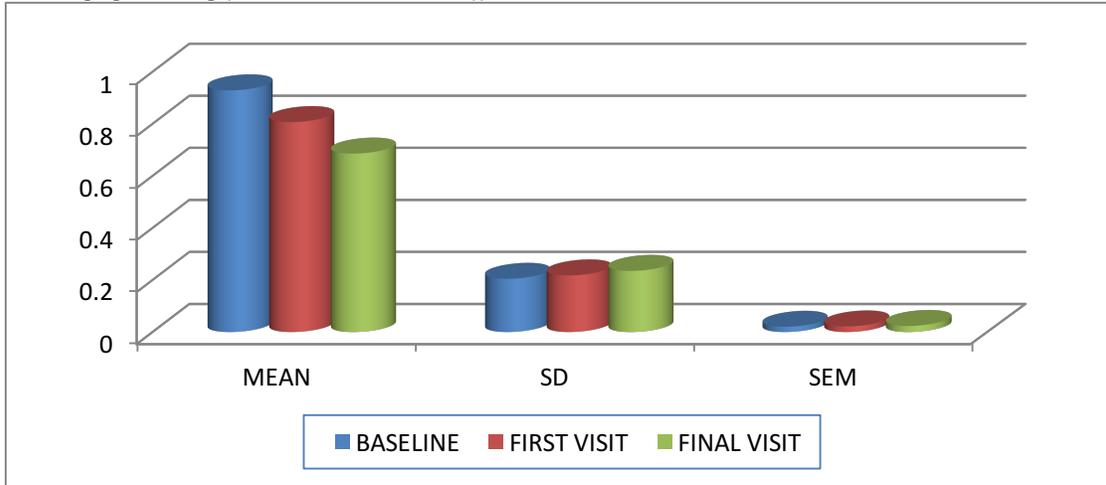


Figure 2 BCVA logMAR over studied period in patients with NPDR

Then mean line improvement in all patients changed from 0.430 ± 0.677 at first visit to 1.155 ± 1.168 at final visit (P value <0.0001). Then mean line improvement in patients of NPDR with CSME changed from 0.465 ± 0.609 at first visit to 1.218 ± 1.006 at final visit (P

value <0.0001). Then mean line improvement in patients of PDR with CSME changed from 0.341 ± 0.824 at first visit to 1 ± 1.5 at final visit (P value <0.0001).

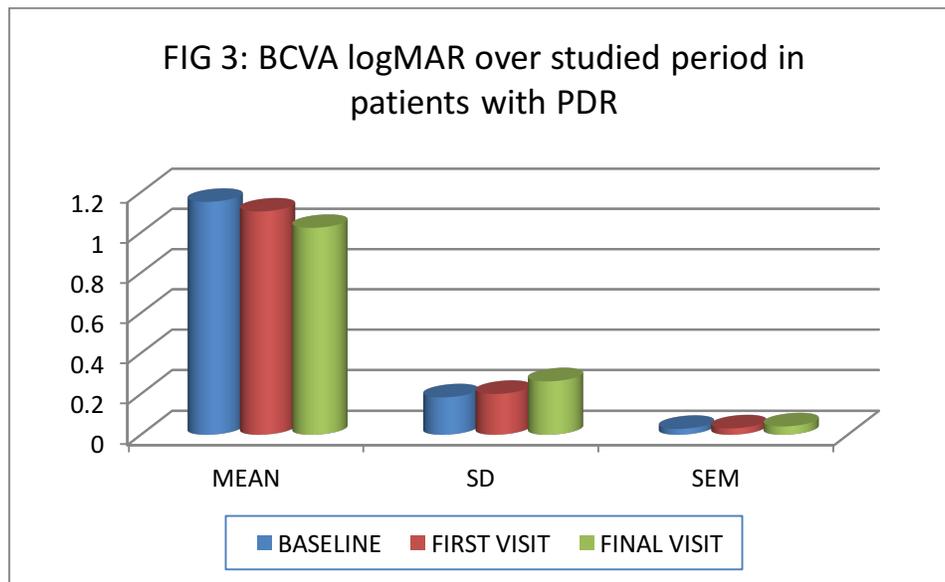
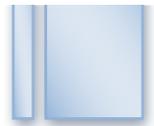


Figure 3 BCVA logMAR over studied period in patients with PDR



Macular oedema patterns and changes according to OCT

The pattern of macular oedema according to OCT was divided into four groups diffuse macular oedema, cystoid macular oedema, serous retinal

detachment and mixed macular oedema which were present in 71 (50%) patients, 39 (28%) patients, 15 (10.60%) patients and 17 (11.40%) patients respectively.

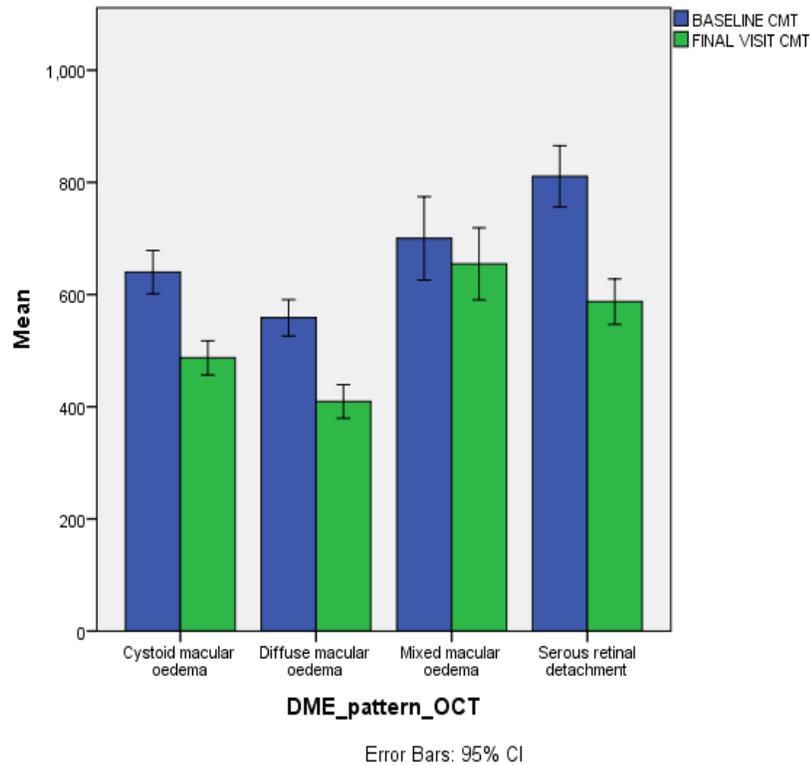


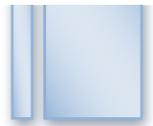
Figure 4 DME Pattern on Oct 1

In this study mean CMT in all studied subjects changed from 624.5 ± 151.81 microns at first visit to 478.9 ± 141.58 microns at final visit showing a decrease of 145 microns (P value < 0.0001). In patients with NPDR, the mean CMT changed from 563.1 ± 122.96 microns at first visit to 422.4 ± 114.33 microns at final visit, showing a decrease of 140.7 microns (P

value < 0.0001). Patients with PDR also demonstrated a statistically significant improvement. In these patients, the mean CMT changed from 775.9 ± 102.10 microns at first visit to 618.0 ± 100.33 microns at final visit showing a difference in the CMT by 157.9 microns (P value < 0.0001).

Table 4 Changes in Central Macular Thickness (microns) in Different Morphological Patterns of Macular Oedema

	DIFFUSE MACULAR OEDEMA		CYSTOID MACULAR OEDEMA		SEROUS RETINAL DETACHMENT		MIXED MACULAR OEDEMA	
	Baseline	Final Visit	Baseline	Final Visit	Baseline	Final Visit	Baseline	Final Visit
Mean	558.59	409.30	640	487.18	810.67	587.33	700	654.71
SD	136.521	126.585	119.009	93.554	98.740	73.238	144.871	124.605
SEM	16.202	15.023	19.057	14.981	25.494	18.910	35.136	30.221
	p value < 0.001		p value < 0.001		p value < 0.001		p value = 0.262	



When analyzed according to different morphological patterns the mean CMT changed from 558.59 ± 136.521 microns at baseline to 409.30 ± 126.585 microns at final visit, thus showing a decrease by 149.559 microns (p value < 0.001) in patients with diffuse macular oedema. In patients categorised as cystoid macular oedema the mean CMT decreased from a baseline value of 640 ± 119.009 microns to a final value of 487.18 ± 93.554 microns showing a

decrease in CMT by 153 microns (p value < 0.001). In patients with serous macular detachment mean CMT decreased from a baseline value of 810.67 ± 98.740 microns to a final value of 587.33 ± 73.238 microns, showing decrease by 223.34 microns (p value < 0.001). The mean CMT changed from 700 ± 144.871 microns to 654.71 ± 124.605 microns showing a decrease by 45.29 microns (p value $= 0.262$).

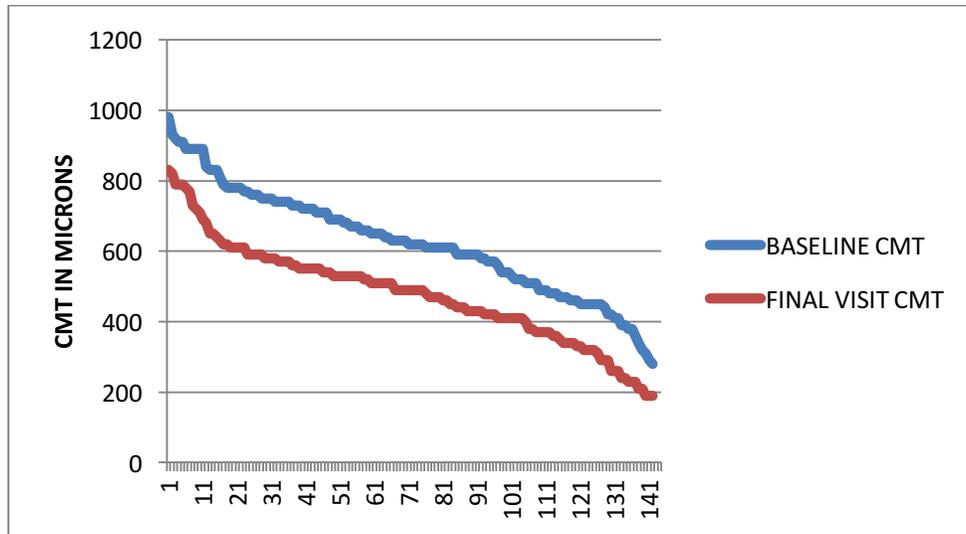


Figure 5 Changes in CMT over studied period

Post intervention OCT in studied subjects showed persistent macular oedema 8.45% (12 patients), persistent macular oedema with taut posterior

hyaloids in 1.49% (2 patients) but majority of patients 90.14% (95 patients) showed resolving macular oedema.

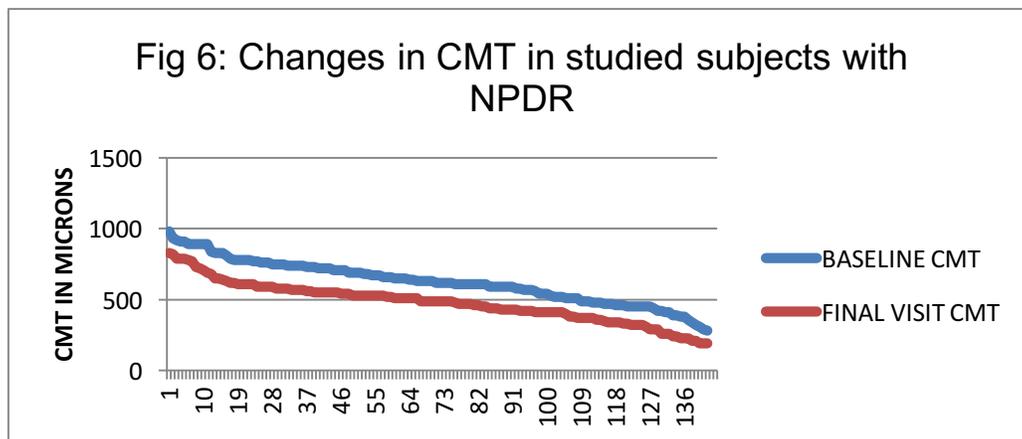
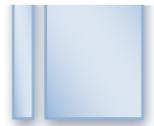


Figure 6 Changes in studied subjects with NPDR



In our study the mean IOP at was 17.211 ± 1.5296 mmHg at baseline, 17.706 ± 1.8325 mmHg at first visit and 17.794 ± 1.8614 at final visit. There was no significant change in the intra-ocular pressure during the course of study ($p = 0.012$). In our study mild anterior chamber cellular reaction was observed in 14

eyes (9.86%), however the inflammation resolved within a week with topical steroids. No other systemic or ocular complication was noted in 90.14% (128) other patients.

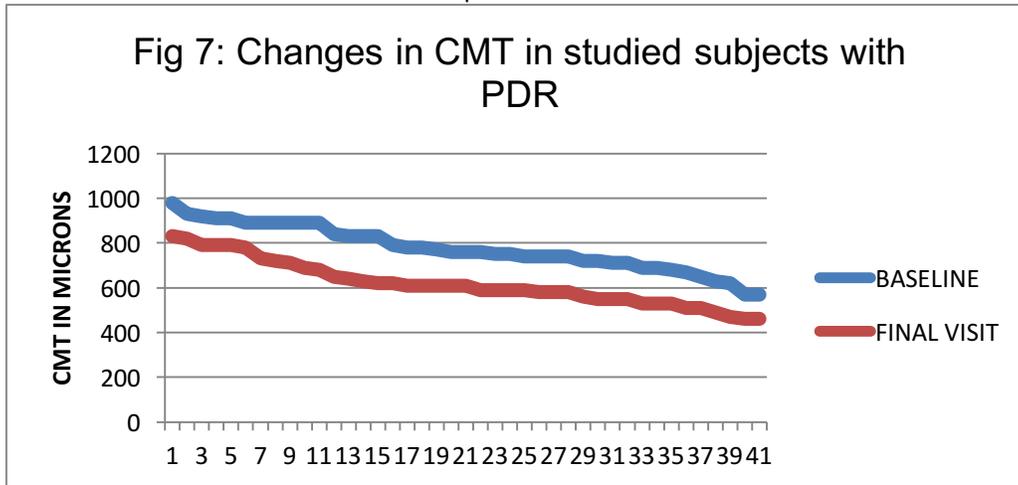


Figure 7 Changes in CMT in studied subjects with PDR

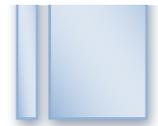
DISCUSSION

Diabetic macular edema is a manifestation of diabetic retinopathy that produces loss of central vision.⁸ The existence of substantial group of patients with DME whose vision has failed to improve following laser photocoagulation has prompted clinicians to seek more effective treatment modalities. It has also been stated in previous studies that laser coagulation of macular region often does not lead to increase in vision and that macular edema especially in diffuse type may persists despite laser treatment.¹³ Pharmacotherapy is a treatment modality that has generated considerable interest in vitreoretinal diseases such as choroidal neovascularization in age-related macular degeneration or DME.⁹

Lee et al (2011)¹⁴ reported that macular laser photocoagulation after decreasing macular edema with bevacizumab injection can reduce the recurrence of macular edema and maintain the visual acuity. It is known that intravitreal application of anti-VEGF leads to quick but short-term reduction of DME, while the effect of MPC comes later and lasts longer Telbizova-Radovanova et al (2014).¹⁵

This was also reflected in this series, where the mean Log BCVA changed from 0.9678 at baseline to 0.8928 at first visit and then 0.7831 at the final visit. The improvement from baseline to first visit, baseline to final visit and first to final visit all were statistically significant. At first visit the BCVA improved in 47.88% (68) patients, remained static in 46.47% (66) patients and deteriorated in 5.63% (8) patients. At final visit BCVA improved in 82.39% (117) patients, remained static in 8.45% (12) patients and deteriorated in 9.15% (13) patients. Then mean line improvement changed from 0.430 at first visit to 1.155 at final visit, which was statistically significant. Our findings were consistent with Solaiman et al (2010).¹² Barteselli et al (2014)¹⁶ also demonstrated improvement in visual acuity with bevacizumab and laser photocoagulation. It appears that laser therapy applied to an oedematous retina made thin by serial bevacizumab injections provides excellent visual improvement.

When evaluated separately, the patients with NPDR showed statistically significant improvement with the combination therapy. The mean log (MAR) BCVA changed from 0.928 at baseline to 0.806 at first visit and then 0.685 at final visit. At first visit the BCVA improved in 23.76% (24) patients, remained static in 73.26% (74) patients and deteriorated in 2.97% (3) patients. At final visit, the BCVA improved in 84.15%



(85) patients, remained static in 7.92% (8) patients and deteriorated in 7.92% (8) patients. Then mean line improvement changed from 0.465 at first visit to 1.218 at final visit, which was statistically significant as shown by, Faghihi et al (2008).¹⁷

Cho et al (2009)¹⁸ demonstrated that intravitreal bevacizumab appears to stabilize or improve PDR in conjunction with retinal photocoagulation, at least in the short term. This study demonstrated a significant improvement in the visual acuity in patients with PDR from baseline to final visit (p value < 0.0001). However the change in visual acuity from baseline to first visit (p value = 0.008) and first to final visit (p value = 0.001). At first visit, the BCVA improved in 51.21% (21) patients, remained static in 36.58% (15) patients and deteriorated in 12.19% (5) patients. At final visit, the BCVA improved in 78.04% (32) patients, remained static in 9.75% (4) patients and deteriorated in 12.19% (5) patients. The mean line improvement changed from 0.341 at first visit to 1 at final visit (p value < 0.0001).

Intravitreal bevacizumab and laser photocoagulation by decreasing the capillary permeability can decrease the macular edema thereby decreasing the CMT. This was reflected in this study where the mean CMT changed from 624.5 ± 151.81 microns at first visit to 478.9 ± 141.58 microns at final visit showing a decrease of 145 microns. This study was consistent with Barteselli et al (2014)¹⁶ where the mean CMT decreased by 139 ± 106 microns

In this series, in patients with NPDR and CSME, the mean CMT changed from 563.1 ± 122.96 microns at first visit to 422.4 ± 114.33 microns at final visit, showing a decrease of 140.7 microns which was statistically significant (P value < 0.0001). Our results were consistent with Sulaiman et al (2010)¹² where the macular oedema after combination therapy decreased by 110.30 microns.

Patients with PDR also demonstrated a statistically significant improvement. In these patients, the mean CMT changed from 775.9 ± 102.10 microns at first visit to 618.0 ± 100.33 microns at final visit showing a difference in the CMT by 157.9 microns. The

difference was statistically significant (P value < 0.0001).

In this study the pattern of DME was classified as diffuse macular oedema (50%), cystoids macular oedema (28%), serous retinal detachment (10.60%) and mixed macular oedema (11.40%). Our study was consistent with Lee et al (2011)¹⁴ who reported a similar pattern with a similar incidence. Patients with diffuse macular oedema mean CMT changed from 558.59 ± 136.521 microns at baseline to 409.30 ± 126.585 microns at final visit showing a decrease by 149.294 microns. The difference was statistically significant (p value < 0.001). In patients with cystoid macular oedema mean CMT changed from 640.00 ± 119.009 microns at baseline to 487.58 ± 93.554 microns at final visit showing a decrease in CMT by 152.42 microns (p value < 0.001). Patients with serous retinal detachment showed a change in CMT from 810.67 ± 98.740 microns at baseline to 587.33 ± 73.238 microns at final visit, there by showing a decrease by 223.34 microns (p value < 0.001). However in patients with mixed macular oedema in CMT decreased from 700 ± 144.871 microns to 654.71 ± 124.605 microns showing a decrease by 45.29 microns which was statistically insignificant (p value = 0.262). Our study was consistent with Lee et al (2011)¹⁴ where the macular thickness after treatment significantly decreased in patients with diffuse macular oedema, cystoid macular oedema and serous retinal detachment. However in mixed macular oedema group showed no improvement or even deterioration.

Post intervention OCT in studied subjects showed persistent macular oedema 8.45% (12 patients), persistent macular oedema with taut posterior hyaloids in 1.49% (2 patients) but majority of patients 90.14% (95 patients) showed resolving macular oedema. Arevalo et al (2013)¹⁹, support our results.

In this study the mean IOP at was 17.211 ± 1.5296 mmHg at baseline, 17.706 ± 1.8325 mmHg at first visit and 17.794 ± 1.8614 at final visit. (p value = 0.012). Our study was consistent with Jahangir et al (2011)²⁰ where the baseline, 1 month and 3 month IOP was 16.2 ± 2.6 mmHg, 16 ± 2.3 mmHg and 16.1 ± 2.2 mmHg respectively.



In our study mild anterior chamber cellular reaction was observed in 14 eyes (9.86%), however the inflammation resolved within a week with topical steroids. Our findings were consistent with Soo Joeng et al (2011)¹⁴ who reported a similar set of complications with a similar incidence. Similar results were also reported by Fernando, (2007).²¹

CONCLUSIONS

Diabetic retinopathy is fast becoming one of the major causes of vision loss worldwide. Timely and proper intervention is needed to prevent any visual morbidity from the disease or its associated complications.

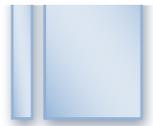
The positive results of this study are quite promising and demonstrate that combined therapy with intravitreal bevacizumab and laser photocoagulation has a role in stabilizing the retinal anatomy and reducing retinal edema both in NPDR and PDR with macular oedema. The decrease in the central macular thickness is also associated with a significant improvement in BCVA.

Also with the help of OCT morphological patterns of macular oedema can be determined. Reduction in macular oedema was significant in all patterns of macular oedema except mixed macular oedema and hence will help us to decide the appropriate time of treatment.

It is a safe procedure with low incidence of complications. However it is short term, nonrandomized, and uncontrolled, which precludes any estimation of the long-term efficacy or safety. In addition, because no control group is present we cannot rule out the possibility that some of the improvement in macular edema might be associated with improvement in systemic health. However, the results are very promising and suggest the need for further investigation.

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