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STUDY OF EFFECT OF SINGLE INTRAOPERATIVE INTRAVITREAL INJECTION OF BEVACIZUMAB ON CENTRAL MACULAR THICKNESS IN PATIENTS WITH DIABETES MELLITES UNDERGOING PHACOEMULSIFICATION CATARACT SURGERY UNDER LOCAL ANAESTHESIA

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Abstract

Background: Cataract is a major problem for diabetic patients because it decreases the vision, prevents adequate fundus examination and interferes with the strategy of laser photocoagulation for diabetic retinopathy. Present study was aimed to study effect of single intraoperative intravitreal injection of bevacizumab on central macular thickness in patients with diabetes mellites undergoing phacoemulsification cataract surgery under local anaesthesia, **Material and Methods:** Present study was prospective interventional observational single centre study conducted in patients above 40 years of age with Diabetes underwent Phacoemulsification cataract surgery under Local anaesthesia, Bevacizumab 0.05 ml (1.25 mg) was injected intravitreal. **Results:** 30 eyes of 27 patients with PDR were studied. Mean age among the study population was 61.167 ± 8.77333 years. Majority of patients were in the age group of 61-70 yrs. (43.3 %), were male (66.67 %), left eye (66.67 %) & had diabetes for more than 10 years (63.37 %). At day one postoperatively 18 patients had central macular thickness < 250 and in 12 patients it was >250. In < 250µ CMT group 33.33 % cases showed decrease, another 33.33% cases showed no change and remaining 33.33 % cases showed increase in CMT which was <10%. While, in >250µ group 58.4% cases showed increase CMT , Out of which in 41.7% cases the increase was >10%, while 41.7% cases showed decrease in CMT at one month Postoperatively. **Conclusion:** Intravitreal administration of 1.25 mg bevacizumab at the time of cataract surgery is a safe and effective way in avoiding new onset maculopathy in diabetic retinopathy patients. It is also effective to treat preexisting CSME and prevent its progression to some extent in few cases.

Keywords: Intravitreal administration, bevacizumab, cataract surgery, diabetic retinopathy

Introduction

Cataract is a major problem for diabetic patients because it decreases the vision, prevents adequate fundus examination and interferes with the strategy of laser photocoagulation for diabetic retinopathy. Diabetic patients have been reported to have higher prevalence of cataract and develop it at an earlier age than non-diabetics.[1,2] It is well established that after cataract surgery, patients with preexisting diabetic retinopathy (DR)

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have a significant risk for progression of DR, diabetic maculopathy and anterior segmentneovascularization.[3]

The risk for progression of retinopathy after cataract surgery is related to these verity at the time of surgery. Patients with no retinopathy have an excellent prognosis while, those with retinopathy may have progression of DR and poor visual outcomes after surgery.[4,5] The pathogenesis of these complications may be related to the changes and rise in the concentration of angiogenic factors in response to surgical trauma and inflammation.[6] The most relevant angiogenic factor is vascular endothelial growth factor (VEGF) .[7]

Bevacizumab is a humanized monoclonal antibody that inhibits all is o-forms of VEGF-A. The low cost and ease of availability has made bevacizumab currently the most vigorously studied anti-VEGF medication for DME.[8] Present study was aimed to study effect of single intraoperative intravitreal injection of bevacizumab on central macular thickness in patients with diabetes mellites undergoing phacoemulsification cataract surgery under local anaesthesia,

Material And Methods

Present study was prospective interventional observational single centre study conducted department of ophthalmology in Mysore Race club Eye hospital, Mysore, India. Study duration was of One and a half year (December 2014 to June 2016). Study approval was obtained from institutional ethical committee.

Inclusion criteria

- Patients above 40 years of age, Sight-limiting cataract in Diabetic patients (with Non-Proliferative Diabetic Retinopathy OR stable Proliferative Diabetic Retinopathy) with poor fundus view precluding adequate monitoring and/or laser therapy, with adequate metabolic control for at least two months (glycosylated hemoglobin $\leq$ 7), arterial blood pressure control (BP < 140/90 mmHg), underwent Phacoemulsification cataract surgery under Local anaesthesia, willing to participate in present study

Exclusion criteria

- Diabetic patients who have previously received rid/focal laser, steroid implants, Anti-VEGF etc. for diabetic retinopathy in last three months.
- Diabetic patients with tractional retinal detachment involving macula, active PDR, vitreous hemorrhage, etc.
- Other Macular pathologies affecting vision like Age-Related Macular Degeneration (wet ARMD), Choroidal Neovascular Membrane (CNVM), Macular edema secondary to vascular occlusion.
- Patients with inadequate metabolic control, kidney failure, uncontrolled arterial high pressure, recent myocardial infarction and cerebral vascular accident.
- Cases with Optic nerve diseases, Glaucoma, ocular hypertension, Uveitic patients.
- Cases complicated with posterior capsular tear and vitreous loss during cataract surgery.

Study was explained to patients in local language & written consent was taken for participation & study. A detailed history regarding the age, sex and residence of the patient, ocular complaints, treatment history (medical and/or surgical), family history of diabetes, diabetic status, diabetic age as well as their medications was taken. History of any associated hypertension or any other systemic illness was also noted. The Fasting and Postprandial blood sugar levels, Glycosylated hemoglobin level and blood pressure were recorded for all the patients.

All patients underwent a detailed ophthalmic evaluation including Snellen Best corrected visual acuity and Slit lamp evaluation of the anterior segment was done to know the Lenticular status of the eye and to rule out the presence of any rubeosis. Other details

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regarding the status of the cornea, iris, and anterior chamber were also noted. Applanation tonometry was done for all the patients to rule out the presence of raised intra ocular pressure. Gonioscopy using Goldman's three mirror gonio lens was performed to exclude the presence of neovascularization of the angle to rule out the presence of neovascular glaucoma.

Comprehensive dilated fundus examination was carried out using slit lamp biomicroscopy with the help of a 90D/78D lens and Indirect ophthalmoscopy using a20D condensing lens. Details regarding the fundus were noted and diagrams drawn for the same. Fundus photos were taken using Topcon TR50EX retinal camera if required in selected cases. In cases in which fundus details were obscured by the density of the cataract, retinopathy grading was based on the first postoperative day examination.

A-scan biometry noting axial length of eye and intraocular lens power calculation, measurement of macular thickness with Spectral Domain Optical Coherence Tomography. if macular thickness measurement was not possible by OCT because of hazy view secondary to the cataractous lens then OCT was done on the immediate first post-op day.

Surgical Technique- All phacoemulsification procedures were performed by the single surgeon using either 0.5%topical proparacaine eye drops or sub-Tenon local anesthesia as per the preference of the surgeon in individual case. The operative techniques included 3.5-mm Clear corneal incision and anterior chamber filled with an ophthalmic viscosurgical device (OVD) and a complete continuous curvilinear capsulorhexis created. After the nucleus was hydrodissected, it was emulsified using a cracking technique and the cortical material was removed. then, a foldable IOL was implanted in the capsular bag. Bevacizumab 0.05 ml (1.25 mg) was injected intravitreal using a 30-gaugeneedle through the pars-plana (3.0 to 3.5 mm from the limbus) into the vitreous cavity. The OVD was removed, and a subconjunctival injection of gentamicin+ dexamethasone was given at the completion of surgery.

All eyes were treated postoperatively with combination of gatifloxacin 0.3% and prednisolone acetate 1% eye drops 8 times daily for first week then 6 times daily for two weeks and then tapered as 4 times daily for two weeks and 2 times daily for next two weeks. Patients were followed postoperatively at day one then at one week and one month respectively for recording the central macular thickness and best corrected visual acuity at one month postoperatively.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

Results

30 eyes of 27 patients with PDR were studied. Mean age among the study population was 61.167 ± 8.77333 years. Majority of patients were in the age group of 61-70 yrs. (43.3 %), were male (66.67 %), left eye (66.67 %) & had diabetes for more than 10 years (63.37 %).

Table 1- General characteristics

	No. of patients	**Percentage**
Age groups (in years)		
41-50	4	13.3%
51-60	10	33.3%
61-70	13	43.3%
71-80	2	6.7%
>80	1	3.3%
Mean age (mean ± SD)	61.16 ± 8.77	

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Gender		
Male	20	66.66%
Female	10	33.33%
Laterality		
RE	10	33.33%
LE	20	66.67%
Duration of diabetic (in years)		
<10	11	36.63
≥10	19	63.37
Mean duration	12.00 ± 8.60633	
Type of cataract		
NS2 + PSCC	8	26.7
NS2 + CC	6	20.0
NS2	5	16.7
NS3 + PSCC	4	13.3
Near mature	2	6.7
PSCC	1	3.3
CC + PSCC	1	3.3
NS1 + PSCC	1	3.3
Dense PSCC + NS4	1	3.3
Dense PSCC	1	3.3

Moderate Non- Proliferative diabetic retinopathy(NPDR) was most frequent both overall and in >10 year diabetic age group. Mild NPDR was the most common type of retinopathy in < 10 years diabetic age group. Stable Proliferative Diabetic Retinopathy are seen in > 10 year diabetic age group only.

Table 2- Duration of diabetes Vs grades of retinopathy distribution

Diabetic age (years)	**Grade of diabetic retinopathy**				
	Mild NPDR	**Moderate NPDR**	**Severe NPDR**	**Very severe NPDR**	**Stable PDR**
<10	6	4	3	0	0
≥10	3	9	1	0	4
Total	9	13	4	0	4

Hypertension was the most common comorbidity associated with diabetes. Nephropathy was seen in only two (6.7%) of cases.

Table 3- Distribution of other comorbidities

Comorbidity	**Grade of retinopathy**					**Total**
	Mild NPDR	**Moderate NPDR**	**Severe NPDR**	**Very severe NPDR**	**Stable PDR**	
Hypertension	5	7	1	0	2	15
IHD	1	0	0	0	0	1
Nephropathy	0	0	0	0	2	2
None	3	6	2	0	1	12

At day one postoperatively 18 patients had central macular thickness < 250 and in 12 patients it was >250.

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Table 4- Central macular thickness

Central macular thickness (CMT)	No. of patients	%
<250 microns	18	60.0
>250 microns	12	40.0

In < 250µ CMT group 33.33 % cases showed decrease, another 33.33% cases showed no change and remaining 33.33 % cases showed increase in CMT which was <10%. While, in >250µ group 58.4% cases showed increase CMT , Out of which in 41.7% cases the increase was >10%, while 41.7% cases showed decrease in CMT at one month Postoperatively.

Table 5- Change in mean CMT at one month in

CMT	< 250 µ CMT group (Mean ± SD)	> 250 CMT group (Mean ± SD)	(Mean ± SD)
Day one	193.72 ± 30.30	404.33 ± 151.68	277.96 ± 142.40
Month one	194.22 ± 32.05	432.41 ±158.83	289.50 ± 155.74
P value	0.179	0.194	0.272

Both the diabetic age group showed significant gain in post operative BCVA.≥ 10 year diabetic age group out of 19 cases 2 cases showed loss of at least one line and 2 more cases there was no change in VA and the rest cases showed improvement of ≥2 lines of VA While diabetic age < 10 year gained ≥ 3 lines.

Table 6- Diabetic age Vs BCVA at one month

Diabetic age (years)	Mean BCVA		P value
	Day1	Month one	
<10	1.09	0.26	0.01
≥ 10	0.99	0.34	

Preoperatively, in 2/3rd of the cases the visual acuity was ≤ 6/60. In 3 cases (10%) BCVA was 6/18 and no case had BCVA better than 6/18. At one month, in 56.7 % of the cases BCVA improved to 6/9 and above. In two patients there was reduction in BCVA while in another 2 cases the BCVA remained unchanged at one month follow-up. In all these 4 cases the central macular thickness at day one postoperatively was found to be > 250µ. In one case despite mild increase in CMT the vision showed improvement of more than 3 lines. There was significant gain in postoperative BCVA as is evident from p value.

Table 6- Comparison of Preoperative BCVA Vs BCVA at one month postoperatively

Visual acuity	Distribution					
	Preoperative		Mean ±SD	Month one		Mean ±SD
	No.	%		No.	%	
1.30 (<6/60)	14	46.7	1.03 ±0.29	2	6.7	0.31 ±0.35
1.0 (6/60)	6	20.0		0	0.0	
0.78 (6/36)	5	16.7		1	3.3	
0.70 (6/30)	1	3.3		0	0.0	
0.60 (6/24)	1	3.3		3	10.0	
0.48 (6/18)	3	10.0		1	3.3	
0.40 (6/15)	0	0.0		5	16.7	
0.30 (6/12)	0	0.0		1	3.3	
0.18 (6/9)	0	0.0		1	3.3	
0.10 (6/7.5)	0	0.0		11	36.7	
0.0 (6/6)	0	0.0		5	16.7	

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P value	0.000

In both groups there was significant gain in postoperative BCVA but particularly in < 250 µ CMT group.

Table 7- Mean BCVA Pre-op Vs one month in < 250 µ and > 250 µ CMT group.

BCVA	**<250µCMT**		**>250µCMT**	
	Pre-op	**One month**	**Pre-op**	**One month**
Mean± SD	1.03 ± 0.31	0.14 ± 0.16	1.03 ± 0.29	0.56 ± 0.40
P value	0.000		0.014	

In mild NPDR and stable PDR group no significant worsening occurred in CMT thickness. While in moderate NPDR 4 (i.e.13.33 %) out of 13 cases showed significant increase in CMT (>10%) at one month. In severe NPDR out of 4 cases 1 case showed significant increase in CMT while other 3 cases showed modest reduction of CMT.

Table 7: Levels of retinopathy Vs mean CMT at one month

Level of retinopathy	**Mean CMT**		**P value**
	Day one	**Month one**	
Stable PDR	172.5	166	0.716
Mild NPDR	282.7	282.7	
Moderate NPDR	256.46	286.23	
Severe NPDR	496	491	

In mild NPDR and stable PDR group all showed improvement in visual acuity of ≥3 lines on Snellen visual acuity chart at one month. While in moderate NPDR in 2 patients visual acuity deteriorated by > 2 lines, one patient there was no change while in one case despite increase in CMT the vision showed improvement of more than 3 lines. In severe NPDR out of 4 cases 1 case showed no change in the visual acuity atone month and other 3 cases showed gain in VA of ≥ 2 lines.

Table 8: Levels of retinopathy Vs mean BCVA at one month

Level of retinopathy	**Mean BCVA**		**P value**
	Day one	**Month one**	
Stable PDR	0.995	0.375	0.00
Mild NPDR	1.10	0.25	
Moderate NPDR	0.97	0.30	
Severe NPDR	1.1	0.45	

Discussion

Diabetic patients pose a challenge due to their early formation of cataracts and propensity to develop macular edema after cataract surgery. Macular edema is a leading cause of an unfavourable visual outcome in patients with diabetes, especially in patients with preexisting diabetic retinopathy. The pathogenesis of these complications may be related to the changes and rise in the concentration of angiogenic factors in response to surgical trauma and inflammation. The most relevant angiogenic factor is vascular endothelial growth factor (VEGF).

According to Patel *et al.*,[9] raised VEGF levels in aqueous sample obtained from diabetic patients one day after surgery approximately was noted to be 10- times higher than those of controls. Blockage of the VEGF surge with anti-VEGF therapy at the time of cataract surgery may prevent these complications. Bevacizumab is a humanized monoclonal antibody that inhibits all isoforms of VEGFA.

Optical Coherence Tomography (OCT) is a powerful tool for detecting and monitoring a

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variety of macular diseases including macular edema. It is non-contact and noninvasive imaging technique that uses infrared optical illumination. The use of optical rather than acoustic waves enables higher resolution, cross sectional retinal imaging with a measurement approaching 10μm which enables OCT of quantifying retinal thickness in eyes with macular edema.[10] OCT has now added an other quantitative dimension in the assessment of DME and could lead to better visual outcomes via earlier detection and more targeted therapeutic approaches. OCT is the single most important diagnostic and prognostic tool in the management of DME.[11]

In the present study sixth decade (60-70) was the most common age group who underwent cataract surgery & mean age was 61.16 ± 8.77 years. Also, a male preponderance was noted. In another study done by Kim *et al.*,[11] the mean age was 68.3. Similar findings were noted by R. Cheema *et al.*,[12] with mean age of 66.14 years

Kim *et al.*,[11] found that those with diabetes duration of ≥10 years had an increase of center point thickness at 1 month of 83 μm, whereas the group with <10 years' duration had an increase of only 18 μm at one month postoperatively. Similar findings were noted in present study.

In the present study those with≥ 10 year diabetic age group out of 19 cases 2cases showed loss of at least one line and 2 more cases there was no change in VA and the rest 15 cases showed improvement of ≥2 lines of VA (with P value < 0.05). While all patients with diabetic age <10yeargained ≥3 lines(P=0.00).

Kim *et al.*,[11] also showed that the group with diabetes of ≥10 years had a modest gain of 1 line (0.10 log MAR units) of VA at 1 month, whereas the group with duration <10 years gained more than 2 lines (0.24 logMAR units) of VA (P=0.04).

In the present study in mild NPDR and stable PDR group no significant worsening occurred in CMT thickness and all showed improvement in visual acuity of ≥3 lines on Snellen visual acuity chart at one month. While in moderate NPDR 4 (i.e.13.33%) out of 13 cases showed significant increase in CMT (>10%) at one month. Out of these 4 cases in 2 patients visual acuity deteriorated by ≥ 2 lines, one patient there was no change while in one case despite increase in CMT the vision showed improvement of more than 3 lines. in severe NPDR out of 4 cases 1 case showed significant increase in CMT but no change in the visual acuity at one month while other 3 cases showed modest reduction of CMT and gain in VA of≥ 2 lines. The findings of this study agrees with the published reports of Pollack A *et al.*,[13] and Malecaze F. *et al.*,[14] who showed that level of diabetic retinopathy is a risk factor for thickening of the retina after cataract surgery.

Kim *et al.*,[11] in their study showed that the group with moderate or severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy had the largest increase in center point thickness of 145 μm at 1 month after surgery, which was correlated inversely with VA improvement thus patients in these groups showed least improvement from baseline, of <1 line (0.08) of VA at 1 month after surgery.

In present study progression of maculopathy occurred in 16.65% of the eyes at the end of one month. Romero-Aroca *et al.*,[15] report diabetic macular edema in 6.6%of eyes with nonproliferative DR after phacoemulsification and Dowler *et al.*,[16] in 44%of eyes6 months after cataract surgery. R. Cheema *et al.*,[12] have reported that progression of diabetic maculopathy occurred in 51.51% of eyes that did not receive intravitreal bevacizumab (control group) and 5.71% of eyes that did receive intravitreal bevacizumab (intervention group) after cataract surgery with IOL implantation.

Kim *et al.*,[11] demonstrated that 22% of diabetic patients developed increases incenter point thickness of >30% at 4 weeks after uncomplicated phacoemulsification. While in the present study in <250μ CMT group 2/3rdcases showed either reduction or no change and in remaining 1/3rd of the cases the increase was < 10% at one month postoperatively. This

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finding of present study also agrees the findings of Dowler *et al.*,[16] who reported that prior CSME is a strong risk factor for subsequent thickening of the macula on OCT after cataract surgery. As in present study all the 5 cases (16.7%) who showed increased thickening at one month had baseline CMT value of>250µm.

Limitations of the study were small sample size and short duration of follow-up, which precludes the determination of the long term safety and efficacy of prophylactic use of Bevacizumab combined with phacoemulsification & control group was not included.

Conclusion

Intravitreal administration of 1.25 mg bevacizumab at the time of cataract surgery is a safe and effective way in avoiding new onset maculopathy in diabetic retinopathy patients. It is also effective to treat preexisting CSME and prevent its progression to some extent in few cases.

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