

# Prophylaxis of Macular edema with Per-operative Intravitreal Bevacizumab in Diabetic Retinopathy Patients Undergoing Phacoemulsification

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**Purpose:** To determine frequency of post-operative macular edema in patients with diabetic retinopathy receiving peroperative Intravitreal bevacizumab, as compared to controls after phacoemulsification cataract surgery.

**Study Design:** Randomized control trial.

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**Place and Duration of Study:** Ophthalmology Department Holy Family Hospital Rawalpindi from July, 2016 to January, 2017.

**Material and Methods:** Patients who reported at the health care facility with diabetic retinopathy were included in the study. Out of these 30 were kept as control (Group A) and 30 as cases (Group B). Every patient was examined clinically and using OCT pre-operatively and re-assessed at the completion of 1 month after surgery. Occurrence of macular edema was based on central macular thickness in both the study groups. Data was analyzed using SPSS version 19.0. Pearson's chi-square test at 5% level of significance was applied. A p- value of 0.05 was considered as statistically significant.

**Results:** There were 60 patients included out of which 33 (55%) were female. The participants of the study had mean age of  $61.97 \pm 5.7$  years. Analysis of both groups showed that macular edema was found in 4 (13.33%) patients in control group and 17 (56.67%) patients in group B. Most significant macular

edema was seen in 11 patients in age group of 61-70 years. Gender wise stratification showed that 9 (56.5%) female patients reported with macular edema.

**Conclusion:** Per-operative intravitreal bevacizumab is effective in prophylaxis of macular edema in patients with mild to moderate NPDR, as compared to controls.

**Keywords:** Intravitreal bevacizumab, Diabetic Retinopathy, Macular edema, Phacemulsification.

**M**acular edema (ME) is defined as abnormal thickening of the macula due to excessive accumulation of fluid in extracellular spaces of central retina.<sup>1</sup> It is a leading cause of irreversible vision loss, in the ocular conditions such as diabetic retinopathy, venous occlusion, uveitis, after cataract surgery, ocular inflammations, and branch retinal vein occlusion<sup>2</sup>. Diabetic macular edema (DME) is a noteworthy reason for loss of central vision in diabetic patients. Post cataract surgery visual outcomes can be negatively affected by diabetic maculopathy<sup>3</sup>.

It has been proposed that among diabetic patients undergoing uncomplicated cataract surgery 22% develop an increment of >30% in central macular thickness as quantified by optical coherence tomography (OCT)<sup>3</sup>. Another study showed an increment of maximum macular thickness of at least 11% was found in 25.7% of the diabetic retinopathy (DR) eyes undergoing cataract surgery, but no such increase occurred in the non-diabetic retinopathy control eyes<sup>4</sup>.

Increase in vascular permeability because of diabetes mellitus brings about extravasation of plasma constituents into the retina prompting DME; Vascular endothelial growth factor (VEGF) is documented to be basic underlying pathogenic factor for development and progression of macular edema auxiliary to Diabetes<sup>5</sup>. VEGF is produced by normal retinal pigment epithelial cells under hypoxic stress. Eyes with substantial spillage from retinal microvasculature leading to thickening of macula have altogether higher VEGF levels when contrasted with eyes with less spillage. Subsequently, anti VEGF agents are reflected as an adjunctive treatment for DME<sup>5</sup>. Anti VEGF therapy can lead to decreased leakage from blood vessels<sup>6</sup>

Bevacizumab is a full-length monoclonal humanized antibody that binds and blocks all isoforms of the VEGF-A family. Food and drug administration (FDA) has approved its use in the management of colorectal carcinoma<sup>5</sup>. Currently its use in ophthalmology is off-label. Numerous studies have suggested the prophylactic use of either anti VEGF or steroids as an intra-vitreous injection after phacoemulsification in patients with diabetic exudative maculopathy to improve the final surgical outcomes in terms of visual acuity and to keep the increase in thickness of macula<sup>3</sup>.

A study published in Korean journal of ophthalmology in 2011 showed that 18% of the diabetic patients undergoing cataract develop macular edema, with the highest incidence at the conclusion of 1 month after cataract surgery<sup>7</sup>, therefore outcome was measured at 1 month post-operatively. This study is used as reference study to calculate sample size.

Rationale of our study was to determine effectiveness of preoperative intra-vitreous bevacizumab in prophylaxis of macular edema in patients with mild to moderate diabetic retinopathy undergoing phacoemulsification so as to improve the visual outcomes. This was done by determining the frequency of macular edema in patients of mild to moderate non-proliferative diabetic retinopathy (NPDR) receiving per-operative intra-vitreous bevacizumab, as compared to controls 1 month after phacoemulsification cataract surgery. This study has not been previously done in Pakistani population.

## MATERIAL AND METHODS

After taking approval from institutional research forum of Rawalpindi medical college a randomized

control trial study was carried out to highlight that the per-operative intra-vitreous bevacizumab is effective in prophylaxis of macular edema in patients with mild to moderate NPDR, when compared to controls. Study population included patients who reported at hospital with cataract and diabetic retinopathy. Sample size for the study was taken by non-probability, consecutive sampling from a total of 60 participants divided into two groups, The allocation was done through simple random sampling technique by formulating a list of randomly allocated 60 numbers in random number list generated through SPSS, 30 to group A or study group and 30 to control group B. The study was carried out for a period of 6 months (20<sup>th</sup> July 2016 to 19<sup>th</sup> January 2017).

For the procedure all participants were randomly allocated in a 1:1 ratio to either have an injection of bevacizumab (1.25 mg in 0.05 ml) through intravitreal route on the conclusion of surgery (study group, Group A) or not (control group, Group B). A thorough ocular examination and OCT was done 1 week prior to the surgery and then 1 month post surgery by the same researcher in all cases. The researcher was not aware of the allocation of the patients to the study groups. The standard ocular examination at each visit comprised of slit lamp examination, uncorrected and best corrected visual acuity, and quantification of the central macular thickness with OCT as an average of three consecutive measurements. Patients underwent standard cataract surgery (phacoemulsification and monofocal intraocular lens (IOL) implantation). One surgeon performed all the surgeries and intra-vitreous injections. Postoperatively all patients were prescribed moxifloxacin-dexamethasone eye drops two hourly for two weeks followed by tapering over 1 month. Every patient was followed-up and was re-assessed at completion of 1 month after baseline. Occurrence of macular edema based on central macular thickness was the outcome variable.

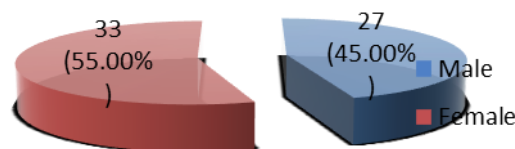
Results of the collected data were entered into SPSS version 22.0. Numerical variables were described as mean and standard deviation. While qualitative variables that included the macular edema, diabetic maculopathy, central macular thickness and side of eye were reported in the form of frequency and percentages.

**RESULTS**

Sample was calculated from a total of 60 patients. Mean age of the study participants was reported as

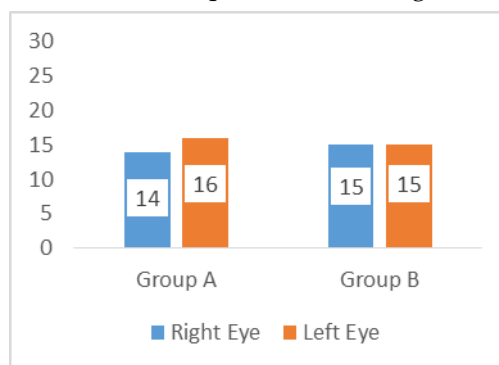
61.97 ± 5.70 years. Out of the 60 participants 33 (55.0%) were females while female to male ratio was 1.2:1. Macular edema was seen in 4 (13.33%) patients in study group and 17 (56.67%) patients in control group. Sample selected showed that 2 (12.50%) patients reported with right eye macular edema and 2 (14.29%) noticed with left eye in group A while in group B for the right eye macular edema was reported in 8 (53.33%) patients and 9 (60.0%) reported with left eye. The Gender wise sample collection of patients is described in Fig. 1.

**Fig. 1:** Gender wise distribution of the patients.



The Central Macular thickness in group A was 233.23 ± 30.16 µm and in group B was 253.21 ± 22.34 µm. Macular edema was seen in 4 (13.33%) patients in study group and 17 (56.67%) patients in control group (p-value = 0.0001). Distribution of patients according to side of eye is shown in figure 2 below.

**Fig. 2:** Distribution of patients according to side of eye.



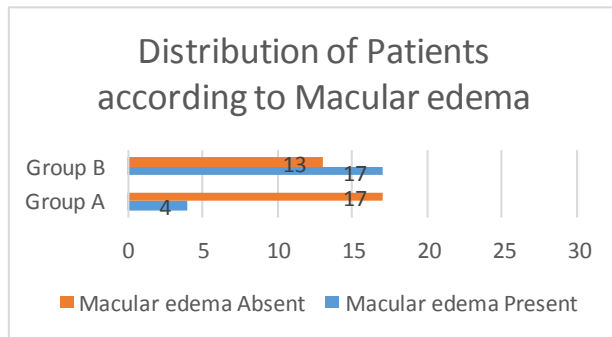
Stratification of macular edema with respect to age groups showed significant difference in macular edema in all age groups among both groups. Similarly, statistically significant difference was found in

macular edema in female among both groups. Stratification of macular edema with respect to side of eye has shown in Table 1. The details of Macular edema found in both groups are graphically shown in figure 3.

**Table 1:** Stratification of macular edema according to side of eye.

Side of eye	Group A (n = 30) Macular Edema		Group B (n = 30) Macular Edema		P-value
	Yes	No	Yes	No	
Left	02 (14.29%)	12 (85.71%)	09 (60.0%)	06 (40.0%)	0.0001
Right	02 (12.50%)	14 (87.50%)	08 (53.33%)	07 (46.67%)	0.015

**Fig. 3:** Distribution of patients according to macular edema in both Groups



**DISCUSSION**

Diabetic maculopathy is a foremost cause of loss of visual acuity in diabetic population<sup>8,9</sup>. It is well-known fact that outcomes of cataract surgery in terms of visual acuity can be negatively affected by DME.<sup>10</sup> It was suggested by some authors that any clear evidence is lacking to show that phacoemulsification cataract surgery causes advancement of DME, specifically in low-risk population; i-e, those with mild diabetic retinopathy or with controlled retinal disease. However, it was established by Kim et al<sup>11</sup> that 22% of the diabetic patients undergoing uncomplicated phacoemulsification show > 30% increase in central retinal thickness as quantified by optical coherence tomography (OCT). Numerous studies have proposed the prophylactic use of intra-vitreous injection of either bevacizumab or steroids in patients with DME that are undergoing phacoemulsification to improve the final anatomical and physiological outcome of intervention in terms of retinal thickness and visual acuity.<sup>12-15</sup> This

study was conducted to determine the frequency of macular edema in patients of mild to moderate non-proliferative diabetic retinopathy (NPDR) receiving per-operative intra-vitreous bevacizumab, as compared to controls.

The purpose of this study was to assess adequacy of bevacizumab given as an intravitreal injection at the conclusion of cataract surgery on the postoperative outcomes of surgery in terms of diabetic retinal changes. For this purpose all the participants were randomly allocated in a 1:1 ratio to either have an intravitreal injection of bevacizumab (1.25 mg in 0.05 ml) at the completion of surgery (study group) or not (control group). Visual acuity with and without correction, optical coherence tomography (OCT), and dilated fundoscopic examination were the efficacy parameters checked. Noteworthy contrast was not seen in central macular thickness (CMT), BCVA, or foundational condition between the control and IVB groups at baseline. Progression of diabetic retinopathy was documented in 15 among 30 eyes (50%) in the control group and 2 among 27 eyes (7.4%) in the intervention group (P = 0.0008). Age range in this study was from 50 to 70 years with mean age of 61.97 ± 5.70 years. The participants in group A (study group) had a mean age of 61.60 ± 5.75 years while that of participants in group B was 62.33 ± 5.71 years. Majority of the patients 38 (63.33%) were between 61 to 70 years of age. Out of 60 patients 33 (55.0%) were females and 27 (45.0%) were males with female to male ratio of 1.2:1. Macular edema was seen in 4 (13.33%) patients in the study group and 17 (56.67%) patients in control group (p-value = 0.0001).

In a study<sup>16</sup>, 42 patients with diabetic macular edema were randomly allocated to either phacoemulsification only or combined with intravitreal injection of bevacizumab. Macular thickness (MT) as quantified by optical coherence tomography was >300µm in all patients. The eyes with

PDR or those that had received laser treatment at least 1 year before surgery were excluded. Reassessment of CMT at first and third month after surgery, demonstrated a substantial decrease in the intra-vitreous bevacizumab group in comparison to no bevacizumab group in which it increased significantly. Likewise bevacizumab group showed significantly higher improvement in VA as compared to the control group; which was correlated to be due to the reduction in MT in the bevacizumab group<sup>16</sup>.

Cheema and colleagues<sup>17</sup> investigated as to whether intra-vitreous bevacizumab injection with cataract surgery prevents postoperative diabetic macular edema (PME) in patients with stable DR with no notable ME. Eighty patients each with visually significant lenticular opacity, steady pre-proliferative DR, and no substantial ME were randomized to a sham group (cataract surgery only), or a study group undergoing cataract surgery with bevacizumab injection at the end of procedure. Best-corrected visual acuities, central subfield foveal thickness, and macular volume were measured by means of optical coherence tomography at baseline and then 1 week, 1, 3, and 6 months postoperatively. Clinically significant postoperative macular edema (PME) was defined as  $>60\mu\text{m}$  increase in central subfield thickness as compared to baseline. There was no significant difference in measured parameters at baseline. The sham group showed significantly larger increment in central subfield thickness at 1 week and 1 month postoperatively as compared to baseline, larger increases in total macular volume at all follow ups, greater development of PME at 1 month follow up, and poorer best-corrected visual acuities outcome from baseline to 6 months post intervention. It was concluded from the study that, intravitreal injection of bevacizumab given at the time of surgery in patients with stable DR without significant ME, undergoing cataract surgery might be effective in preventing the postoperative worsening of ME and it might improve the concluding visual outcome of cataract surgery<sup>17</sup>.

In another study<sup>18</sup>, participants were randomly allocated to a control group undergoing standard procedure of cataract extraction followed by intraocular lens implantation alone or intervention group to get an intravitreal injection of standard dose of bevacizumab on the conclusion of cataract surgery. Patients were monitored postoperatively up to duration of 6 months specifically for the development and progression of any retinal and macular changes attributed to diabetes. In total sixty-eight eyes were

enrolled in the study. Diabetic retinal changes progressed in 15 (45.45%) among 33 eyes in the cataract surgery only group and 4 (11.42%) among 35 eyes in the cataract surgery plus bevacizumab group ( $P = 0.002$ ). 17 eyes (51.51%) in the control group showed progression of maculopathy as compared to only 2 eyes (5.71%) in the intervention group ( $P = 0.0001$ ). But visual acuities did not show any significant contrast between the 2 groups postoperatively ( $P = 0.772$ ); however, two eyes in the control group progressed to neovascular glaucoma as compared to none in intervention group. No significant difference was seen between the mean postoperative central macular thickness and mean macular thickness between the 2 groups ( $P = 0.874$  and  $0.942$ , respectively)<sup>18</sup>.

An interventional, randomized, open-label and control study<sup>19</sup> of two parallel groups of already diagnosed patients with pre-proliferative diabetic retinopathy without macular edema was done. The study included sixty eyes of sixty patients, having non-proliferative diabetic retinopathy without macular edema and lens opacity (grade 1 to 3). One group ( $n=30$ ) received intra-vitreous injection of Bevacizumab and the control group ( $n = 30$ ) did not receive intra-vitreous injection of Bevacizumab during standard phacoemulsification. Best-corrected visual acuity (BCVA) on the conclusion of two months compared with the baseline visual acuity recorded along with central macular thickness (CMT) measured on optical coherence tomography (OCT) was the key outcome measured. The mean age of the patients was also similar in the control ( $55.2 \pm 9.66$  years) and Bevacizumab groups ( $56.47 \pm 9.13$  years) ranging from 40 to 75 years. All of the patients in Bevacizumab group had visual acuity of 6/6 postoperatively except one eye (3.33%) had 6/12 due to CSME that was evident on OCT as increase in macular thickness. While in control group 10 (33.33 %) eyes out of 30 had BCVA of 6/12 or less (evident on OCT as increase in macular thickness)<sup>19</sup>.

Another study carried out by Lanzagorta et al<sup>12</sup> has shown improvement in the vision and decrease in the retinal thickness in the Bevacizumab group in contrast to control group. Mason et al<sup>20</sup> described noticeable improvement of visual acuity in 2 patients with persistent CME which has been effectively treated with Bevacizumab. On the whole, it was concluded that per-operative intravitreal bevacizumab is effective in prophylaxis of macular edema in patients with mild to moderate NPDR, as compared to

controls, at completion of 1 month after phacoemulsification cataract surgery.

## CONCLUSION

The study concluded that the per-operative intra-vitreous bevacizumab is effective in prophylaxis of macular edema in patients with mild to moderate NPDR, as compared to controls, at completion of 1 month after phacoemulsification cataract surgery. So, we recommend that pre-operative intra-vitreous bevacizumab should be used as a prophylaxis of macular edema in patients with mild to moderate NPDR after phacoemulsification cataract surgery.

**Conflict of interest: none**

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### Author's contribution

Dr. Sidra Jabeen  
Corresponding author, planning of research including data collection, collection methods, setting, collection of data, drafting.

Dr. Rizwan Khan

All surgical interventions done, analysis and interpretation of data.

Dr. Ali Raza

Critical revision of all work, supervisor of research project.

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