

Effects of Intra-vitreous Injection of Bevacizumab as an Adjunct during Phacoemulsification in Diabetic Maculopathy

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ABSTRACT

Purpose: To study the effects of Intra-vitreous injection of Bevacizumab as an adjunct during phacoemulsification in patients with diabetic retinopathy.

Study Design: Quasi experimental study.

Place and Duration of Study: Multan Medical and Dental College and Bodla Eye Care, Multan, between March 2018 to February 2019.

Methods: The study included 108 eyes of 108 diabetic patients who were scheduled to undergo phacoemulsification. They were equally divided into two groups; Bevacizumab and control group. Complete ocular examination and macular thickness and volume were determined using an OPTOVUE-OCT machine. The patients in the Bevacizumab group were given intra-vitreous injection of 1.25 mg/0.05ml of Bevacizumab at the time of Phacoemulsification.

Results: The bevacizumab group manifested low value of central macular thickness (CMT) one-month post-surgery as compared to the control group (262.2 ± 32.2 and 288.5 ± 54.1 , respectively) with $P = 0.01$. The Total macular volume, and Best-corrected visual acuity in the two groups showed no significant difference one month after surgery. Two (4%) patients in the Bevacizumab group and five (10%) patients in the control group developed post-surgical macular edema one month after surgery which was not statistically significant ($P = 0.244$). We found no significant relationship between the post-surgical macula edema with the presence of mild Non Proliferative Diabetic Retinopathy. (Fisher's test, $P = 0.321$).

Conclusion: Ocular anti-VEGF therapy substantially reduces macular edema secondary to post-surgical inflammation in diabetic patients. It effectively reduces the central macular thickness although the results are not found to be statistically significant when compared with the control group.

Key Words: Diabetes mellitus; diabetic macular edema; diabetic retinopathy, Bevacizumab.

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INTRODUCTION

Subsequent to cataract surgery performed on diabetics, the most sight threatening retinopathy is gross and/or cystoid macular edema, which is indicated as fluid accumulation in the macula.¹⁻³ After cataract surgery there is a substantial increment in angiogenesis and inflammation, thereby surging cytokines, chemokines and vaso-permeability factors in the vascular

endothelium which trigger breakdown of blood retinal barrier, manifesting clinically as macular edema and resulting in visual loss.^{4,5} The pathophysiology encompasses between the vascular endothelial growth factor (VEGF) and inflammatory mediators.^{6,7} This study has been conducted to clinically investigate the potential therapeutic effects of Anti VEGFs in the control of macular edema in patients with non-proliferative diabetic retinopathy.

METHODS

In this study, we enrolled 108 eyes of 108 patients from hospital of Multan Medical and Dental College and Bodla Eye Care, Multan, between March 2018 to February 2019. A written Ethical Review statement was obtained before the beginning of study and the research was conducted according to the principles of Declaration of Helsinki. These patients had significant cataract but with visible posterior segment. At the first visit patients were divided into control (got phacoemulsification alone) and intervention group (who got intravitreal injection of 1.25 mg/0.05 ml of Bevacizumab at the end of surgery) depending upon their treatment choice. The inclusion criteria was diabetic patients (Diabetes Mellitus Type 2) with significant cataract and early diabetic retinopathy or moderate Non Proliferative Diabetic Retinopathy. The exclusion criteria were patients with preoperative central macular thickness (CMT) of $> 280 \mu\text{m}$ and/or any attestation of cystic spaces indicated by optical coherence tomography (optovue-OCT; OPTOVUE companies; USA), HbA1c greater than 6.8, intractable Non Proliferative Diabetic Retinopathy or Proliferative Diabetic Retinopathy, Diabetes Mellitus type 1, Uncontrolled persistent hypertension and Precedent retinal laser therapy. During the preliminary visit, the anterior and posterior segment examination was done using Slit lamp and 90 D lens. Goldmann Applanation tonometry was performed to determine the Intra Ocular pressure whereas OCT was used to assess retinal structures and macular thickness. ETDRS was employed to assess the degree of retinopathy. The complete post-operative ophthalmic examinations were performed at day one, day seven, and one month later. OCT was performed one month post-surgery on all patients.

By using the 512×128 scan pattern, OCT images were acquired and center of 6×6 -mm scanning area was fixed at the fovea centralis. Central macular

thickness (CMT) was measured which is the average thickness of retina in the central foveal 1 mm subfield. Total macular volume (TMV) was also determined. Phacoemulsification was performed by a single surgeon (Infinity® vision system; Alcon Laboratories). At the end of cataract surgery, an injection of 1.25 mg of Bevacizumab was injected intravitreally given in the inferotemporal quadrant, 3.5 mm away from limbus using a standard 1cc insulin syringe.

It was pre-defined that $\text{CMT} > 280 \mu\text{m}$ using OCT would be considered as a consequential postoperative macular edema. SPSS version 20 was employed to analyze the statistical data. The Variables found in the data were demonstrated in terms of mean \pm standard error of mean. The analysis was done by using Wilcoxon Mann – Whitney test. It was determined that P value less than 0.05 will be significant.

RESULTS

The study included 108 eyes from 108 patients. Three patients were omitted due to advancement of postoperative cystoid macular edema not secondary to diabetes as in accordance with guidelines suggested by Munk et al. Five of these patients were lost during follow up. After excluding the patients who were lost during follow-up, there were fifty eyes included in the Bevacizumab group and fifty eyes in the control group. The pre requisite criterion for the patients was Type 2 DM. The two groups were much the same in terms of age, male to female ratio, stage of diabetic retinopathy baseline CMT and TMV, HbA1c and blood pressure. The bevacizumab group manifested low value of CMT one-month post-surgery as compared to the control group (262.2 ± 32.2 and 288.5 ± 54.1 , respectively) with $P = 0.02$. The TMV and BCVA in the two groups showed no significant difference one month after surgery (Table 1). In the light of our definition in study set in accordance with DRCR. NET protocols, ($\text{CMT} > 280 \mu\text{m}$ using SD-OCT), two (4%) patients in the Bevacizumab group and five (10%) patients in the control group developed post-surgical macular edema one month after surgery. Although the frequency of macular edema was somewhat higher in the control group, this distinction was not statistically significant at one month after surgery ($P = 0.244$). We found no significant relationship between the post-surgical macula edema with the presence of mild Non Proliferative Diabetic Retinopathy. (Fisher's test, $P = 0.321$).

Table 1: Mean Central macular thickness (CMT) and total macular volume (TMV) before and at 1 month after cataract. CMT: Central Macular Thickness; TMV: Total Macular Volume; BCVA: Best Corrected Visual Acuity; PME: Postoperative macular edema.

	Bevacizumab Group	Control Group	P-value
CMT (pre-operative)	255.4 ± 24.3	262.5 ± 27.4	0.30
CMT (1 month post-operative)	262.2 ± 32.2	288.5 ± 54.1	0.01
TMV (pre operative)	8.29 ± 0.54	8.30 ± 0.51	0.93
TMV (1 month post-operative)	8.30 ± 0.62	8.53 ± 0.70	0.14
BCVA	0.58 ± 0.21	0.50 ± 0.09	0.13
BCVA (1 month post operative)	0.08 ± 0.06	0.11 ± 0.09	0.226
Post operative PME%	2 (%4)	5 (%10)	0.24

DISCUSSION

Vascular endothelial growth factor is one of the key agents responsible for causing macular edema. Anti-VEGF act as promising halts of this macular edema. In such patients a mono-therapy or combination of topical NSAIDs and corticosteroids can be employed right after the surgery as a prophylactic therapy or as treatment.^{8,9} However, there are other options which include intravitreal anti-VEGF and steroid therapy at the time of surgery.^{10,11} Multiple anti-VEGF drugs e.g. Aflibercept, Intravitreal Ranibizumab (IVR) or intravitreal Bevacizumab (IVB) are administered as an adjunct in cataract surgery for the management of macular edema in diabetic patients having danger of post-operative macular edema.¹²⁻¹⁶ These drugs are used widely and are effective in vision improvement and prevention of vision loss caused by diabetic macular edema. The effect of anti-VEGF is not enough sometimes and many patients do not show complete remission of fluid.

The optical coherence tomography (OCT) is used for the clinical assessment of diabetic macular edema that discerns visual loss by objective evaluation of macular thickness and evaluates the vitreo-macular interface.^{17,18} The most certain rationale of poor vision in diabetics after cataract surgery is Cystoid and/or gross macular edema. It has been demonstrated that aqueous VEGF levels are greatly responsible for clinically remarkable changes in Central Macular Thickness. The pre-operative VEGF levels play a pivotal role in causing post-operative macular edema.¹⁹ Therefore, it is hypothesized that controlling this VEGF would productively play a crucial role in impeding postoperative elevation in central macular thickness and thereby refining the visual outcomes in the patients. The present study showed that patients who had no or mild diabetic retinopathy had an insignificant decrease in macular thickness

subsequently after the administration of intravitreal Bevacizumab injection at the time of surgery.

Takamura et al. appraised the effects of intravitreal Bevacizumab supplemented shortly after phacoemulsification in diabetics with pre-existing macular edema.¹² While in first month post-surgery macular edema decreased proficiently by Bevacizumab, it somehow was increased in the control group. Likewise, best corrected visual acuity (BCVA) was significantly lower in the control group than in the bevacizumab group. Conducive to the hypothesis stating that total Macular Volume is a better reflection of changes in macular status rather than Central Macular Thickness, we measured both TMV and CMT in order to observe any change with the use of intravitreal Bevacizumab.

Often quoted, post-op macular edema was taken as an increase of CMT ≥ 60 μm in relation to the preoperative baseline. Interestingly, CMT changes until 1 month after surgery were depicted differently in these two groups. Fard et al. in their study, found a significant increase in the control group one month post-operative as compared to the Bevacizumab group while evaluating the effect of intravitreal Bevacizumab in patients with CMT < 200 μm . They concluded that intravitreal administration of 1.25 mg bevacizumab was effective in reducing macular thickness.²⁰

It is apparent that progression of diabetic retinopathy or development of subsequent macular edema after surgery occurs more commonly in patients with moderate to severe NPDR and/or macular edema prior to phacoemulsification as compared to patients with no or mild NPDR.²¹

There are a few limitations to our study. First, sample size of each group was small and perhaps not considerable enough to explicate the beguiling differences particularly of post-operative cystoid

macular edema between the control and the Bevacizumab group. Second, the follow up period was small. It is possible that some change would be imminent in further follow-ups. Third, macular edema was defined as CMT > 280 μ m using SD-OCT. A comparable conclusion might have been drawn by considering an increase of \geq 60 μ m.

CONCLUSION

The ocular anti-VEGF therapy substantially reduces central macular thickness secondary to post-surgical inflammation in diabetic patients. However, the results are not found to be statistically significant when compared with the control group.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board. (MMDC/B-24-418)

Conflict of Interest

Authors declared no conflict of interest

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Authors' Designation and Contribution

Ali Afzal Bodla; Associate Professor: *Concepts, Design, Manuscript editing, Manuscript review.*

Syeda Minahil Kazmi; Consultant Ophthalmologist: *Data acquisition, Data analysis, Statistical analysis, Manuscript review.*

Noor Tariq; Consultant Ophthalmologist: *Literature search, Data analysis, Manuscript preparation, Manuscript editing.*

Ayema Moazzam; Consultant Ophthalmologist: *Data acquisition, Statistical analysis, Manuscript preparation, Manuscript editing.*

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