

ORIGINAL ARTICLE

Prophylaxis of Macular Edema with Preoperative Intravitreal Bevacizumab in Patients with Diabetic Retinopathy Undergoing Phacoemulsification

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ABSTRACT

Purpose: To determine frequency of post-operative macular edema in diabetic retinopathy patients having received preoperative intravitreal bevacizumab, after phacoemulsification cataract surgery while compared with the controls.

Study Design: Quasi experimental trial

Place and Duration of Study: Department of ophthalmology eye unit 3, KEMU /Mayo hospital, Lahore from March 2020 to August 2020.

Methods: A total of 60 patients were included in the study and randomly divided into two groups. Patients of study group were given 1.25mg bevacizumab injection by IV (intravitreal) in route two weeks prior to surgery while nothing was administered in the control group. Before one week of surgery ocular examination and OCT were performed and it was repeated after every month of performance of surgery. Allocation of patients was even not known to the researcher to avoid biasness. Components of monthly examination were best correct visual acuity, slit lamp examination and central macular thickness quantification with OCT. Standard cataract surgery was performed in all the patients (phacoemulsification and implantation of monofocal intraocular lens (IOL). Post-operatively, all patients were given standard treatment i.e moxifloxacin-dexamethasone). Follow up of all the patients was made for consecutive three months on monthly basis to assess outcome variables i.e macular edema was observed keeping in view central macular thickness.

Results: In patients of study group, 16.66% had developed macular edema while in control group it was observed in 46% patients. While comparing macular edema between side of eye, study group had 02 (13.33%) patients belonging to right eye while 03(20.0%) had left eye. However, in control group it was 08 (53.33%) and 06 (40.0%) for right and left eyes respectively. Group A had $230.23 \pm 32.16 \mu\text{m}$ central macular thickness while it was $274.21 \pm 25.34 \mu\text{m}$ in group B.

Conclusion: In macular edema prophylaxis, using preoperative intravitreal bevacizumab is efficacious in comparison with the controls in patients with mild-moderate NPDR with macular edema.

Keywords: NPDR, Macular edema, Intravitreal Bevacizumab, Phacoemulsification Surgery, Diabetic Retinopathy.

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by high blood sugar levels due to defective production and sensitivity of insulin.^{1,2} most common symptoms of diabetes are frequent urination and increased thirst. It may cause many complications if not treated. Accumulation of fluid in extracellular space resulting into thickening of macula is called diabetic macular edema^{3,4}.

Macula is part of the retina that controls our most detailed vision. In diabetic retinopathy, a major complication is diabetic macular edema which is among major causes of visual loss in patients at early stage. Though, it is reversible but as the disease progresses it becomes irreversible. In patients with diabetic retinopathy about 12% may have diabetic macular edema. Diabetic macular edema causes about 10,000 new cases of blindness per year.^{5,6} Duration and type of diabetes can affect the prevalence rate of diabetic macular edema. Following diagnosis of type 1 diabetes, diabetic macular edema can occur in first five years. The prevalence rate of DME gradually reaches up to 40% within 30 years^{7,8}. In patients with type 2 diabetes, the prevalence of diabetic retinopathy is 12%.⁹ After cataract surgery, visual outcomes are severely affected by diabetic macular edema. It has been found that the chances of increase in central macular thickness are elevated by 25-30% in patients undergoing cataract surgery and have already been diagnosed as diabetics.¹⁰

In hypoxic condition, vascular endothelial growth factor is a signal protein produced by cells and causes stimulus for formation of blood vessels. Vascular endothelial growth factor is a sub-family of platelet derived growth factor. They are important signaling proteins that are involved in both vasculogenesis and angiogenesis. A vital factor; vascular endothelial growth factor (VEGF) increases diabetic macular edema¹¹. Anti VEGF treatment decreases the leakage from blood vessels and helps to cure

diabetic macular edema.¹² Bevacizumab specifically binds to the VEGF-A protein and block it, so it stops the process of angiogenesis¹³. Prophylactic use of anti VEGF as intravitreal injection helps to improve diabetic macular edema.¹⁴ A study reported that in control group, 46% (14 eyes) were documented for diabetic retinopathy progression while it was 16% (5eyes) in intervention group with p-value=0.0008. In DR patients undergoing cataract surgery, to prevent diabetic maculopathy and progression of DR, intravitreal 1.25 mg bevacizumab injection two weeks before cataract surgery proved very efficient¹⁵. In 2011, a Korean study on ophthalmology where macular edema was witnessed in 18% of diabetic patients who had undergone surgery and its incidence was at its peak after completion of first month after surgery¹⁶, so in this study outcomes have been measured on monthly basis for consecutive three months post-operatively.

Rationale of this was determining efficacy of preoperative intra-vitreous bevacizumab in prophylaxis of diabetic macular edema diabetic retinopathy patients who were undergoing phacoemulsification for visual improvements. This study compared frequency of macular edema in non-proliferative diabetic retinopathy (NPDR) patients who had received intra-vitreous Bevacizumab preoperatively in comparison with the controls after three months of emulsification.

MATERIAL AND METHODS

This quasi experimental trial was conducted at "The Department of ophthalmology eye unit 3, KEMU /Mayo hospital, Lahore from March 2020 to August 2020. Approval from "Institutional Ethical Committee" was acquired. Informed written consent was taken from patients of all study participants. Simple random sampling probability technique was used to calculate sample size and two groups of equal size 30 eyes each were made by lottery method. Patients having cataract and diabetic retinopathy were included in

this study and they belonged to both genders. Allocation of patients was even not known to the researcher to avoid biasness. Alone intraocular monofocal lens implantation group was declared as study group and the control group was given 1.25mg Intravitreal Bevacizumab prior to two weeks of performing extraction procedure.

In macular edema prophylaxis, effectiveness of intravitreal Bevacizumab mild-moderate NPDR patients has been probed in this quasi experimental trial. Patients of study group were given 1.25mg bevacizumab injection by IV route two weeks prior to surgery while nothing was administered in the control group. Before one week of surgery ocular examination and OCT were performed and it was repeated after every month of performance of surgery. Components of monthly examination were best correct visual acuity, slit lamp examination and central macular thickness quantification with OCT. Standard cataract surgery was performed in all the patients (phacoemulsification and implantation of monofocal intraocular lens (IOL). Post-operatively, all patients were given standard treatment i.e moxifloxacin-dexamethasone). Follow up of all the patients was made for consecutive three months on monthly basis to assess outcome variables i.e macular edema was observed keeping in view central macular thickness.

Table 1: Macular edema stratified as per 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	03 (20%)	12 (80%)	06 (40.0%)	09 (60.0%)	0.0001
Right	02 (13.33%)	13 (86.67%)	08 (53.33%)	07 (46.67%)	0.015

DISCUSSION

In diabetic patients, a vital factor in loss of visual acuity is diabetic maculopathy. DME may affect visual acuity during cataract surgery in diabetic patients. Kim et al.¹⁷ exhibited that central retinal thickness was increased > 30% by uncomplicated phacoemulsification in 22% of diabetic patients when measured with OCT. visual acuity and retinal thickness can be improved in DME patients by using intravitreal injection of steroids or bevacizumab as prophylactic use.¹⁸

Another study showed that macular edema were quantified as >300µm by OCT. Patients with PDR or having administered laser treatment during last one year were excluded from the study. CMT reassessments were made after 1st and 3rd month of surgery and intravitreal bevacizumab group showed substantial decrease in comparison with the group where bevacizumab was not administered. In VA significantly high improvement was seen in bevacizumab group in comparison with the controls and it was associated with decreased MT in bevacizumab group.²⁰

Whether postoperative diabetic macular edema (PME) can be prevented postoperatively in stable patients having no macular edema with the help of intravitreal bevacizumab injection or not; was evaluated by Cheema and colleagues.²¹ Two random groups of forty patients in each group were created from patients having steady pre-proliferative, significant visual lenticular opacity and no substantial ME, who were administered bevacizumab injection at the end of cataract surgery. Preoperative macular volume, central subfield foveal thickness and best corrected visual acuities were measured with the help OCT and then postoperative week 1 & 3 and at 6 months. PME was explained clinically significant where central subfield thickness increase >60µm in comparison with the baseline was observed. A significantly high increase was seen in sham group in terms of thickness of subfield at week 1 and one month post-operative from the baseline.

Comprised of two parallel groups, an open label randomized interventional control study in patients who had pre-proliferative diabetic retinopathy and in which macular edema had not been performed. In this study, sixty patients were included who had 60 eyes to be studied and two random groups were made. One group was given standard phacoemulsification without any intravitreal intervention of bevacizumab injection. After two months of cataract

SPSS version 22.0 was used for collection of results and data analysis. Mean and standard deviation was calculated for numerical variables while qualitative variables were calculated in terms of frequency and percentage.

RESULTS

The sample population comprised of 60 patients who had mean age of 50.38 ± 5.20 years and belong to both the genders. In study sample, number of male patients was dominant 35 (58.0%) while females were lesser in number i.e 25 (32%). In patients of study group, 05 (16.66%) had developed macular edema while this figure was 14 (46%) in control group patients. While comparing macular edema between side of eye, study group had 02 (13.33%) patients belonging to right eye while 03(20.0%) had left eye. However, in control group it was 08 (53.33%) and 06 (40.0%) for right and left eyes respectively. Group A had 230.23 ± 32.16 µm central macular thickness while it was 274.21 ± 25.34 µm in group B. In study group 05 (16.66%) patients had macular edema while in control group 14 (46%) patients were found to have macular edema with p-value=0.0001.

surgery, best corrected visual acuity was recorded for comparison with the base figures and OCT was used to measure central macular thickness (CMT). Controls group had mean age of 55.2 ± 9.66 years while it was 56.47 ± 9.13 years in bevacizumab group; however patients age was between 40-75 years. Post-operative visual acuity was 6/6 in patients of bevacizumab group with the exception of one eye where it was 6/12 owing to CSME and it appeared on OCT in the shape of increased macular thickness. However, BCVA was observed in 10 patients as 6/12 or even low in control group.²²

From above discussion, it is concluded that administration of intravitreal bevacizumab is preoperatively effective as prophylaxis in mild-moderate NPDR patients in comparison with the controls when observed for three monthly consecutively after cataract surgery on monthly basis.

CONCLUSION

In macular edema prophylaxis, using preoperative intravitreal bevacizumab is efficacious in comparison with the controls in patients with mild-moderate NPDR with macular edema. Therefore, use of intravitreal bevacizumab as prophylaxis of macular edema is recommended pre-operatively in mild-moderate NPDR for cataract surgery.

REFERENCES

1. Asmat U, Abad K, Ismail K. Diabetes mellitus and oxidative stress—a concise review. *Saudi Pharm J*. 2016;24 (5):547-53.
2. Ateeq A, Tahir MA, Cheema A, Dahri A, Tareen S. Intravitreal injection of bevacizumab in diabetic macular edema. *Pak J Med Sci*. 2014;30 (6):1383.
3. Song W, Conti TF, Gans R, Conti FF, Silva FQ, Saroj N. Prevention of macular edema in patients with diabetic retinopathy undergoing cataract surgery: The Promise Trial. *Ophthalm Surg Laser Imaging Retina*. 2020; 51 (3): 170-8.
4. Wang Z, Wang E, Chen Y. Transient reduction in macular deep capillary density on optical coherence tomography angiography after phacoemulsification surgery in diabetic patients. *BMC Ophthalmol*. 2020;20 (1):1-9.
5. Feng L, Azhati G, Li T, Liu F. Macular vascular density changes following cataract surgery in diabetic patients: an optical coherence tomography angiography study. *J Ophthalmol*. 2021;26(7):20-27.

6. Campos A, Beselga D, Mendes S, Campos J, Neves A, Sousa P. Deferred intravitreal triamcinolone in diabetic eyes after phacoemulsification. *J Ocular Pharmacol Therap.* 2014; 30 (9):717-28.
7. Paulus YM, Gariano RF. Diabetic retinopathy: a growing concern in an aging population. *Geriatrics (Basel, Switzerland).* 2009;64(2):16-20.
8. Zhang X, Zeng H, Bao S, Wang N, Gillies MC. Diabetic macular edema: new concepts in patho-physiology and treatment. *Cell Biosci.* 2014;4(1):27-31.
9. Martinell M, Dorkhan M, Stålhammar J, Storm P, Groop L, Gustavsson C. Prevalence and risk factors for diabetic retinopathy at diagnosis (DRAD) in patients recently diagnosed with type 2 diabetes (T2D) or latent autoimmune diabetes in the adult (LADA). *J Diabetes Compli.* 2016; 30(8):1456-61.
10. Moshfeghi AA, Shapiro H, Lemmon LA, Gune S. Impact of cataract surgery during treatment with ranibizumab in patients with diabetic macular edema. *Ophthalmol Retina.* 2018; 2(2):86-90.
11. Chae JB, Joe SG, Yang SJ, Lee JY, Sung KR, Kim JY, Kim JG, Yoon YH. Effect of combined cataract surgery and ranibizumab injection in postoperative macular edema in nonproliferative diabetic retinopathy. *Retina.* 2014;34(1):149-56.
12. Bonnin S, Dupas B, Lavia C, Erginay A, Dhundass M, Couturier A, Gaudric A, Tadayoni R. Anti-vascular endothelial growth factor therapy can improve diabetic retinopathy score without change in retinal perfusion. *Retina.* 2019;39(3):426.
13. Galvano A, Guarini A, Iacono F, Castiglia M, Rizzo S, Tarantini L, Gori S, Novo G, Bazan V, Russo A. An update on the conquests and perspectives of cardio-oncology in the field of tumor angiogenesis-targeting TKI-based therapy. *Expert Opin Drug Safety.* 2019;18(6):485-96.
14. Boscia F, Giancipoli E, Ricci GD, Pinna A. Management of macular oedema in diabetic patients undergoing cataract surgery. *Curr Opin Ophthalmol.* 2017;28(1): 23-8.
15. Kwon SI, Hwang DJ, Seo JY, Park IW. Evaluation of changes of macular thickness in diabetic retinopathy after cataract surgery. *Korean J Ophthalmol.* 2011;25 (4): 238-42.
16. Barber AJ, Gardner TW, Abcouwer SF. The significance of vascular and neural apoptosis to the pathology of diabetic retinopathy. *Invest Ophthalmol Visual Sci.* 2011;52(2): 1156-63.
17. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. *Ophthalmol* 2007;114(8): 881-9.
18. Chu CJ, Johnston RL, Buscombe C, Sallam AB, Mohamed Q, Yang YC. United Kingdom pseudophakic macular edema study group. risk factors and incidence of macular edema after cataract surgery: a database study of 81984 eyes. *Ophthalmol.* 2016; 123(2):316-23.
19. Dugel PU, Campbell JH, Kiss S, Loewenstein A, Shih V, Xu X, Holekamp NM. Association between early anatomic response to anti-vascular endothelial growth factor therapy and long-term outcome in diabetic macular edema: an independent analysis of protocol i study data. *Retina.* 2019;39(1):88-92.
20. Ahmed M, Nawaz M, Javed EA, Sultan M. Efficacy of intra-vitreal bevacizumab combined with phacoemulsification in the prophylaxis of macular edema in patients with non-proliferative diabetic retinopathy. *Ann Punjab Med Coll.* 2016;10(2):58-62.
21. Cheema HR, Al Habash A, Al-Askar E. Improvement of visual acuity based on optical coherence tomography patterns following intravitreal bevacizumab treatment in patients with diabetic macular edema. *Int J Ophthalmol.* 2014;7(2):251-255.
22. Jabeen S, Khan R, Raza A. Prophylaxis of macular edema with preoperative intravitreal bevacizumab in diabetic retinopathy patients undergoing phacoemulsification. *Pak J Ophthalmol.* 2019;35(1):1-7.