Original Article APMC-303

Efficacy of Intra-Vitreal Bevacizumab Combined with Phaco-Emulsification in the Prophylaxis of Macular Edema in Patients with Non-Proliferative Diabetic Retinopathy

Muhammad Ahmed, Muhammad Nawaz, Ejaz Ahmed Javed, Muhammad Sultan

Authors

1. Dr. Mohammad Ahmad
Associate Professor,
Department of Ophthalmology,
Aziz Fatima Medical & Dental College, Faisalabad.

2. Dr. Muhammad Nawaz
Associate Professor,
Department of Ophthalmology,
PMC/Allied Hospital, Faisalabad

3. Dr. Ejaz Ahmad Javed
Assistant Professor,
Department of Ophthalmology,
PMC/Allied Hospital, Faisalabad

4. Prof. Dr. Muhammad Sultan
Professor & Head of
Ophthalmology Department
PMC/Allied Hospital, Faisalabad

Corresponding Author
Dr. Mohammad Ahmed
Associate Professor,
Department of Ophthalmology,
Aziz Fatima Medical & Dental College, Faisalabad.
Contact: +92 300-6621700
Email: 786ahmed2000@gmail.com

Submitted for Publication
15-04-2016
Accepted for Publication
26-04-2016

ABSTRACT

Objective: This study was designed to evaluate the prophylactic efficiency of intra-vitreal Bevacizumab combined with cataract surgery in patients of non-proliferative diabetic retinopathy without macular edema for the prevention of macular edema by assessing the visual outcome. **Methodology:** This was interventional, randomized, open-label and control study of two parallel groups of already diagnosed patients with pre-proliferative diabetic retinopathy without macular edema. 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-vitreal injection of Bevacizumab and the control group (n= 30) did not received intra-vitreal injection of Bevacizumab at the time of standard phaco-emulsification. Main outcome measure was best-corrected visual acuity (BCVA) at the end of two months compared with the baseline visual acuity recorded along with central macular thickness (CMT) measured on optical coherence tomography (OCT) as required. **Results:** The outcome was an improvement of BCVA at the end of 8th week compared with that at baseline in the Bevacizumab group and a worsening of visual acuity in the control group (p = 0.005). **Conclusions:** Prophylactic use of intravitreal Bevacizumab combined with phacoemulsification appears to be beneficial in preventing post-surgical visual loss in eyes with NPDR by preventing the chance of macular edema.

Keywords: Diabetic Macular Edema, Diabetic Retinopathy, Phacoemulsification, Anti –VEGF, Bevacizumab, Intra-Vitreal Injection.

Article Citation: Ahmed M, Nawaz M, Javed EA, Sultan M. Efficacy of Intra-Vitreal Bevacizumab combined with Phaco-Emulsification in the Prophylaxis of Macular Edema in Patients with Non-Proliferative Diabetic Retinopathy. APMC 2016;10(2):58-62.

INTRODUCTION

Diabetic macular edema (DME) is a major cause of central visual loss in diabetic patients.[1] It has been established by many authors that DME after cataract surgery can adversely affect visual outcome [2, 3]. Many studies have revealed that visual outcome following cataract surgery in diabetic patients depends primarily on the status of macular edema,[4,5] or macular ischemia due to diabetes. Previous reports have described that many diabetic patients develop severe maculopathy, following cataract surgery[6]. Since it is important to be able to predict long-term visual effects before cataract surgery is performed, surgeons need to have a better understanding of the natural course of diabetic macular edema in addition to diabetic retinopathy (DR) after cataract surgery.

Shah and Chen[7] suggested that there is no clear evidence that phacoemulsification surgery causes progression of DME, particularly in patients with low-risk or absent diabetic retinopathy or in those with controlled retinal disease.

Distinguishing transient edema from substantial progression of maculopathy is important to the timing of treatment for the macular edema, including laser photocoagulation,[8] vitrectomy,[9] and triamcinolone injection.[10,12]. However, Kim et al[13] found that in 22% of diabetic patients, there was an increase of >30% in central retinal thickness measured by optical coherence tomography (OCT) after uncomplicated phacoemulsification. Treatment to lessen the risk of postoperative macular thickening in individuals with diabetes, laser photocoagulation remains the standard approach.[14] However, it is sometimes difficult to obtain the sufficient efficacy of laser treatment in the cases with dense cataract. Vascular endothelial growth

factor (VEGF) is considered a key player in the progress of abnormal angiogenesis and DME.[15] Hypoxia induces VEGF gene transcription, and elevated levels of VEGF have been found in ocular fluid of patients with DME.[16] Bevacizumab is a humanized monoclonal antibody that inhibits all isoforms of VEGF.[17] Intravitreal injection of bevacizumab have shown promising results in various neovascular eye diseases, including age-related macular degeneration,[18] central retinal vein occlusion,[19] and DME.[20] Lanzagorta et al[21] carried out similar study, which showed improvement in the vision and decrease in the retinal thickening in the Bevacizumab group compared to control group.

METHODOLOGY

This was a prospective, randomized, control and interventional study. The study included a total of 60 eyes of 60 patients with cataract and some degree of diabetic retinopathy divided randomly in two parallel groups of 30 patients each. Patients were admitted from eye OPD of the teaching hospital of Aziz Fatima Medical & Dental College, Faisalabad. All patients were enrolled from July 2014 to June 2015 and were followed up for 2 months. The study protocol was approved by the Ethical Committee of the college. The study was performed in accordance with the ethical principles laid down in the 1964 Declaration of Helsinki. Patients were provided an information sheet with the study details, and a signed informed consent for inclusion in the study, cataract surgery and intra-vitreal injection was obtained. All patients in the study underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA), slit- lamp biomicroscopy, applanation tonometry, funduscopy. OCT and fundus fluorescein angiography, if required, were performed in Allied Hospital Faisalabad.

Inclusion criteria: Patients over the age of 40 years and able to make decisions, reduced visual acuity secondary to cataractous lens opacities and some degree of diabetic retinopathy without macular involvement were included in the study.

Exclusion criteria: Patients with a history of previous ocular surgery, any kind of complication during the surgery like posterior capsule rupture and severe iris damage, other ocular pathology with macular involvement, DME, uncontrolled hypertension, recent myocardial infarction, and cerebral vascular accident were excluded from the study.

No masking except for those testing the visual acuity, optometrist and statistical analyzers as to treatment assigned to the eyes was done. The operative techniques included phacoemulsification with complete continuous curvilinear capsulorhexis through a 3.5-mm corneo-scleral incision and implantation of a foldable acrylic intraocular lens in the bag. Anti-VEGF group received a single intra-vitreal injection of Bevacizumab at the end of same surgery. Bevacizumab 0.05 ml (1.25 mg) was injected intra-vitrealy using a 30-gauge needle. Eyes in the control group received no intra-vitreal Bevacizumab injection. Postoperative treatment was identical for all the patients and consisted of the topical administration of tobramycin-dexamethasone eye drops and Nepafenac eye drop four times a day for two months.

Outcome Measurements and Follow-up: The main outcome of the trial was a change in BCVA at 8 weeks post-operatively, compared with that at the baseline. BCVA was assessed by Snellen visual acuity chart. Similarly, increase of macular thickness was confirmed by measuring OCT when required.

Follow-up of patients was at day one and then at 4th and 8th weeks post-operatively. Measurement of Visual acuity (BCVA), intraocular pressure (IOP) and slit-lamp biomicroscopic examination and fundus examination was performed at each visit. OCT-Scan performed as required at baseline and 8 weeks postoperatively.

SPSS version 17 was used for statistical analysis. Mean and standard deviations were calculated for quantitative variables and frequency and percentage was calculated for qualitative variables. Chi-square test was used to compare outcome variable between both groups. P-value of ≤ 0.05 was taken as significant.

RESULTS

A total of 60 eyes of 60 patients with no diabetic macular edema were enrolled in the study. Patients were divided in control group and Bevacizumab group in a ratio 1: 1, 30 eyes in each group (Table 2). All patients completed this study at 2 months after surgery. Twenty eight women and 32 men were included (Table 1), being equivalent the proportion of patients of either sex included in both groups.

Table 1: Gender distribution in both groups

	Frequency (%age)
Male	32 (53.33)
Female	28 (46.67)
Total	60 (100)

The mean age of the patients was also similar in the control (55.2±9.66 years) and Bevacizumab groups (56.47±9.13 years) ranging from 40 to 75 years. All the patients had cataract from grade 1 to 3 with mild to moderate non-proliferative diabetic retinopathy without diabetic macular edema. Preoperative visual acuity was similar in both groups (Table 3).

Table 2: Bevacizumab & control group

	Frequency n (%age)
Bevacizumab Group	30 (50)
Control Group	30 (50)
Total	60 (100)

Table 3: Preoperative visual acuity (n=60)

Visual Acuity	Frequency (% age)
6/18	10 (16.7)
6/24	2 (3.3)
6/36	20 (33.3)
6/60	28 (46.7)

Postoperative visual acuity at the end of 8 weeks (Table 4) shows that there has been statistically significant difference of visual acuity gained between the Bevacizumab group and the control group ($p<0.005$).

Table 4: Postoperative visual acuity at the end of 8 weeks

Visual Acuity	Bevacizumab Group	Control Group	p-value
6/6	29 (96.66%)	23 (66.6%)	0.005
6/12	01 (3.33%)	10 (33.3%)	

All of the patients in Bevacizumab group had postoperative visual acuity of 6/6 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).
The one eye in Bevacizumab group (3.33%) after phacoemulsification gained visual acuity of 6/18 at one month and 6/12 at the end of two months.
No local or systemic adverse effects were observed in the Bevacizumab group as well as in control group.

DISCUSSION

Many studies have revealed that intra-vitreal injection of Bevacizumab is useful in the management of DME.[20,23] Surgical insult of cataract surgery increases retinal vascular permeability resulting in retinal and macular edema, due to focal leakage from microaneurysms and dilated capillary segments, has been implicated in some studies[24]. Inner blood– retinal barrier is broken down by many inflammatory mediators like VEGF.[25,26] According to Patel et al,[27] 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. Bevacizumab inhibits VEGF, which is a potent permeability factor implicated in cystoid macular edema (CME).[26]
In our study, as a result of surgical insult only one eye (3.33%) of Bevacizumab group developed decrease of vision while ten (33.3%) eyes of the control group developed decrease of vision (6/12 or less) due to increase in macular thickness at the end of 2 month, which is statistically significant (p-value 0.005). Similar work was carried out by Lanzagorta et al,[21] who have shown improvement in the vision and decrease in the retinal thickness in the Bevacizumab group compared to control group.
Our results showed (33.33%) eyes of control group developed clinically significant macular edema (CSME) as confirmed on OCT at 2 months after phacoemulsification, are little better than the results showed by Patricia et al[28] which were 25.92% of the eyes in the control group due to CSME at 1 and 3 months post-operatively. Our results of control group are also higher than that found by Kim et al,[13] who concluded that 22% of diabetic patients of control group developed increase of the central macular thickness of >30% 4 weeks after uncomplicated phacoemulsification. The main difference between our and latter study is that patients with mild to moderate diabetic retinopathy were included in our study, but Kim et al. included also the patients who did not have diabetic retinopathy.
In our study, decrease in visual acuity due to

increase in macular thickness is in 10 (33.3%) eyes in control group. This value is similar but little higher than that published by many series in diabetic patients after phaco-emulsification.[29,30]

Recently, many studies have shown the clinical effect of intra-vitreal Bevacizumab for pseudophakic CME.[31,33] Mason et al[31] reported on 2 patients with persistent CME who had been effectively treated with Bevacizumab, and both eyes showed noticeable improvement of visual acuity.

In our study, among 30 eyes (100%) only one eye (3.33%) in Bevacizumab group showed decrease of BCVA (6/12) as compared to ten eyes (33.3%) in control group with BCVA (6/12 or less) which is statistically significant.

In our study, the change in BCVA at 8 weeks compared with that at baseline (primary endpoint) in the Bevacizumab group was statistically and significantly better than the change in BCVA in the control group.

CONCLUSION

In conclusion, Bevacizumab is extremely beneficial for the prevention of macular edema in patients having non-proliferative diabetic retinopathy without macular edema who undergo phacoemulsification.

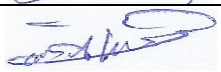
Limitations of our study include the small sample size and short duration of follow-up, which precludes the determination of the long term safety and efficacy of prophylactic use of Bevacizumab combined with phacoemulsification. More number of patients and from different races of the world should be included in the study.

REFERENCES

1. Moss SE, Klein R and Klein BEK. The incidence of vision loss in a diabetic population. Ophthalmology, 1988;95(10):1340-8.
2. Nelson ML and Martidis A. Managing cystoid macular edema after cataract surgery. Curr Opin Ophthalmol. 2003;14(1):39-43.
3. Pollack A, Leiba H, Bukelman A and Oliver M. Cystoid macular oedema following cataract extraction in patients with diabetes. Br. J. Ophthalmol. 1992;76(4):221-4.
4. Joussen AM, Smyth N, Niessen C. Pathophysiology of diabetic macular edema. Dev Ophthalmol. 2007;39:1-12.
5. Zaczek A, Olivestedt G, Zetterstrom C. Visual outcome after phacoemulsification and IOL implantation in diabetic patients. Br J Ophthalmol. 1999;83:1036-41.
6. Benson WE, Brown GC, Tasman W, et al. Extracapsular cataract extraction with placement of a posterior chamber lens in patients with diabetic retinopathy. Ophthalmology. 1993;100: 730-8.
7. Shah S and Chen SH. Cataract surgery and diabetes. Curr Opin Ophthalmol. 2010;21(1):4-9.
8. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol. 1985;103:1796-1806.
9. Tachi N, Ogino N. Vitrectomy for diffuse macular edema in cases of diabetic retinopathy. Am J Ophthalmol. 1996;122:258- 60.
10. Jonas JB, Sofker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. Am J Ophthalmol. 2001;132:425-7.
11. Martidis A, Duker JS, Greenberg PB, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology. 2002;109:920-7.
12. Jonas JB, Kreissig I, Sofker A, et al. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. Arch Ophthalmol. 2003;121:57-61.
13. Kim SJ, Equi R and Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology, 2007;114(5):881-9.
14. Writing Committee for the Diabetic Retinopathy Clinical Research Network. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. Arch Ophthalmol. 2007;125:469-80.
15. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev. 2004;25:581-611.
16. Funatsu H, Yamashita H, Nakamura S, et al. Vitreous levels of pigment epithelium-derived factor and vascular endothelial growth factor are related to diabetic macula edema. Ophthalmology. 2006;113:294-301.
17. Ferrara N, Hillan KJ, Gerber HP, et al. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov. 2004;3:391-400.
18. Avery RL, Pieramici DJ, Rabena MD, et al. Intravitreal bevacizumab (Avastin) for

neovascular age-related macular degeneration. Ophthalmology. 2006;113:363-72.
19. Iturralde D, Spaide RF, Meyerle CB, et al. Intravitreal bevacizumab (Avastin) treatment of macular edema in central retinal vein occlusion: a short-term study. Retina. 2006;26:279-84.
20. Arevalo JF, Fromow-Guerra J, Quiroz-Mercado H, et al. Pan American Collaborative Retina Study Group. Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. Ophthalmology. 2007;114:743-50.
21. Lanzagorta-aresti A, Palacios-Pozo E, Menezo Rozalen JL, et al. Prevention of vision loss after cataract surgery in diabetic macular edema with intravitreal bevacizumab: a pilot study. Retina. 2009;29:530-5.
22. Chylack LT Jr, Wolfe JK, Singer DM, et al. Longitudinal Study of Cataract Study Group. The Lens Opacities Classification System III. Arch Ophthalmol. 1993;111:831-6.
23. Diabetic Retinopathy Clinical Research Network. A phase II randomized clinical trial of intravitreal bevacizumab for diabetic macular edema. Ophthalmology. 2007;114:1860-7.
24. Cunha-Vaz JG. Studies on the pathophysiology of diabetic retinopathy: the blood-retinal barrier in diabetes. Diabetes. 1983;32:20-7.
25. Stern AL, Taylor DM, Dalburg LA, et al. Pseudophakic cystoid maculopathy: a study of 50 cases. Ophthalmology. 1981;88:942-6.
26. Qaum T, Xu Q, Joussen AM, et al. VEGF-initiated bloodretinal barrier breakdown in early diabetes. Invest Ophthalmol Vis Sci. 2001;42: 2408-13.
27. Patel JI, Hykin PG, Cree IA. Diabetic cataract removal: postoperative progression of maculopathy-growth factor and clinical analysis. Br J Ophthalmol. 2006;90:697-701.
28. Udaondo P, Garcia-Pous M, Garcia-Delpech S, Salom D and Diaz-Llopis M. Prophylaxis of Macular Edema with Intravitreal Ranibizumab in Patients with Diabetic Retinopathy after Cataract Surgery: A Pilot Study Journal of Ophthalmology. 2011;4:112-6.
29. Akinci A, Batman C, Ozkilic E and Altinsoy A. Phacoemulsification with intravitreal bevacizumab injection in diabetic patients with macular edema and cataract. Retina, 2009;29(10):1432-5.
30. Chen CH, Liu YAC and. Wu PC. The combination of intravitreal bevacizumab and phacoemulsification surgery in patients with cataract and coexisting diabetic macular edema. J Ocul Pharmacol. 2009;25(1):83-9.
31. Mason JO, Albert MA, Vail R. Intravitreal bevacizumab (Avastin) for refractory pseudophakic cystoid macular edema. Retina. 2006;26:356–7.
32. Arevalo JF, Garcia-Amaris RA, Roca JA, et al. Pan-American Collaborative Retina Study Group. Primary intravitreal bevacizumab for the management of pseudophakic cystoids macular edema: pilot study of the Pan-American Collaborative Retina Study Group. J Cataract Refract Surg. 2007;33:2098-105.
33. Spitzer MS, Ziemssen F, Yoeruek E, et al. Efficacy of intravitreal bevacizumab in treating postoperative pseudophakic cystoid macular edema. J Cataract Refract Surg. 2008;34:70-5.

AUTHORSHIP AND CONTRIBUTION DECLARATION

Name of Author	Contribution to the paper	Author's Signatures
Dr. Muhammad Ahmed	Patient selection, Surgery, Follow-up, Data collection	
Dr. Muhammad Nawaz	Literature review	
Dr. Ejaz Ahmed Javed	Statical analysis	
Prof. Dr. Muhammad Sultan	Supervision