Intravitreal bevacizumab at the time of phacoemulsification may prevent macular edema in diabetic patients with and without preoperative retinopathy.

Khaled W Elsadi*, Ahmed A Dahab, Iman M Eissa, Adel M Fathy, Khaled E El Rakhawy

Department of Ophthalmology, Cairo University, Giza, Egypt

Received: *03-Sep-2019, Manuscript No. AACOVS-19-2041;* ***Editor assigned:*** *06-Sep-2019, PreQC No. AACOVS-19-2041(PQ);* ***Reviewed:*** *20-Sep-2019, QC No. AACOVS-19-2041;* ***Revised:*** *21-Jul-2022, QI No. AACOVS-19-2041 (QI); Manuscript No. AACOVS-19-2041(R);* ***Published:*** *18-Aug-2022, DOI: 10.35841/aacovs.6.3.549-553.*

Abstract

Purpose: To evaluate the effect of intravitreal Bevacizumab at the time of phacoemulsification on the incidence of postoperative Diabetic Macular Edema (DME).

Patients and methods: Twenty eyes of diabetic patients with retinopathy yet without maculopathy, and 20 eyes of diabetic patients without retinopathy were included. Only 10 eyes in each group had 1.25 mg Bevacizumab intravitreal injection at the end of surgery. At two weeks, two months and six months postoperative visits, macular optical coherence tomography and visual acuity assessment were done.

Results: At two weeks, two months and six months after surgery, the incidence of DME in the non injected group was 5%, 20%, 30% as opposed to 0%, 5%, 5% in the Bevacizumab group. No statistically significant difference was found in mean central macular thickness. A statistically significant difference in BCVA postoperatively was found between both groups, especially in cases without retinopathy preoperatively.

Conclusion: Prophylactic Intravitreal injection of Bevacizumab at the time of phacoemulsification is effective in the mid-term prevention of DME in cases with and without preoperative diabetic retinopathy.

Keywords: Bevacizumab, Diabetic macular edema, Phacoemulsification, Non-proliferative diabetic retinopathy.

Introduction

Diabetic Macular Edema (DME) is the most common cause of visual deterioration in diabetic patients [1]. Recent studies have identified that leakage of fluid and plasma components from the damaged vasculature is mediated by the release of soluble vascular and inflammatory mediators, including Vascular Endothelial Growth Factors (VEGF) and pro-inflammatory cytokines [2]. Studies also show that there is increased level of VEGF in both aqueous and vitreous, and suggest that these levels are correlated with the severity of DME. These evidence suggest that VEGF are an important key in the pathogenesis of DME [3-5].

Cataract surgery is important for improving vision and allowing visualization of the retina for better assessment in diabetic patients. Evidence exists that cataract removal will develop or enhance the progression of diabetic retinopathy and DME even after the implementation of new techniques of cataract surgeries [6,7].

Recent retrospective studies showed there is an increased relative risk of new macular edema development in diabetic eyes after surgery despite the absence of preoperative retinopathy (RR, 1.80; 95% CI, 1.36-2.36). The risk was much higher in the presence of any diabetic retinopathy (RR, 6.23; 95% CI, 5.12-7.58) and rose proportionately with increasing severity of DR [8]. The study highlighted the need for prophylactic therapy whether there is retinopathy or not, especially in the high risk groups [8].

Based on this relative risk of developing post operative DME even in patients with no diabetic changes preoperatively, the authors searched but did not find enough studies testing the magnitude of progression of DME in these patients, and whether intraoperative injection of Bevacizumab could help decrease this risk. This prospective study was designed to test the possible prophylactic effect of intravitreal Bevacizumab at the time of phacoemulsification on the development of post operative DME in two groups of diabetic patients; a group with a preoperatively normal fundus (A), and a group with preoperative non proliferative retinopathy (B). Both groups had no evidence of macular edema preoperatively. Despite the presence of studies which have tackled post operative DME, only a few of them if any-included diabetic patients with a preoperatively normal fundus. The authors have included this group of patients, along with patients having Non Proliferative Diabetic Retinopathy (NPDR) with no macular edema.

Case Presentation

The study protocol was approved by the local review board of the Ophthalmology department at Cairo University, and followed the tenets of declaration. All patients received a

thorough explanation of the study aim and procedure done, and all signed a written informed consent.

The study included 40 patients (20 with no diabetic retinopathy, group A) and (20 with NPRD, group B). Patients were consecutively recruited from the outpatient clinic of the retina service unit of Kasr Al-Ainy hospital. Within each group (A and B), patients were further allocated (by simple randomization computer software) to two subgroups; a Bevacizumab group (A/Bzb and B/Bzb) who received injections at the end of phacoemulsification, and a control group (A/Ctrl and B/Ctrl) who did not receive injections at the end of surgery. Initially, slightly more than 20 patients were consecutively recruited for each group, to allow for possible follow up drop outs or patients with surgical complications to be excluded. We eventually included 20 patients in each group.

All included patients had diabetes for ± 11 years and had significant nuclear cataract or dense posterior subcapsular cataract. The posterior segment was assessed by slit-lamp biomicroscopy and by macular OCT (RTVue Fourier-Domain OCT, v 6.11.0.12, Optovue Inc., USA) to confirm the absence of DME preoperatively. The Best Corrected Visual Acuity (BCVA) was measured before and after surgery using a Snellen's chart for all patients and converted the reading to logMAR.

All cases underwent surgery when all systemic conditions were controlled (blood sugar and blood pressure). A standard phacoemulsification procedure was done and a foldable hydrophilic acrylic intraocular lens (of the same brand) was implanted in all patients. However, in the Bevacizumab injected (A/Bzb, B/Bzb) group of patients, at the end of surgery intravitreal 1.25 mg Bevacizumab injection (Avastin®, Genentech Inc., San Francisco, CA) was given through 30-gauge needle, introduced 3.5 mm from the limbus supratemporally under the surgical microscope.

Postoperative follow up examinations were scheduled, on the first day and at two weeks, two months and six months postoperatively. All subjects completed their follow up after surgery. All patients were subjected to fundus examination by slit-lamp biomicroscopy and macular mapping by optical coherence tomography (RTVue Fourier-Domain OCT, 6.11.0.12, Optovue Inc., USA) postoperatively.

Statistical analysis was carried out using the statistical package SPSS (Statistical Package for the Social Science; SPSS Inc. Chicago, IL, USA) version 22. Wilcoxon Signed Ranks test was used for data analysis within the groups and Mann-Whitney test for analysis between the Bevacizumab and control subgroups. Chi-squared test was used for the qualitative data. All tests were two-tailed and considered significant at $p \leq 0.05$ and highly significant at $p<0.001$.

Results

Descriptive statistics

Forty eyes of 40 diabetic patients with no DME (as confirmed by OCT) were studied. Twelve of the recruited patients were males (30%) and 28 were females (70%). The mean descriptive statistics for both main groups are shown in Table 1.

Table 1. *Descriptive statistics of diabetic patients in the 2 main groups.*

	Control (A+B)	**Bevacizumab (A+B)**
Total eyes	20	20
Age (mean ± SD)	60.8 ± 6.9	60.5 ± 6.4
Duration of diabetes in years (mean ± SD)	11.4 ± 3.9	11.7 ± 5.3
Diabetic treatment		
Insulin (%)	8 (40)	8 (40)
OAD (%)	12 (60)	12 (60)
Hypertensive (%)	6 (30)	11 (55)
Note: SD: Standard Deviation, OAD: Oral Anti-Diabetic		

Comparative statistics

It is worth mentioning that in comparisons, the authors will at times compare all injected (A/Bzb+B/Bzb) to all non injected (A/Ctrl+B/Ctrl) subjects (regardless of their retinopathy status) and will sometimes compare the normal fundus subjects (group A) to the NPDR subjects (group B).

Firstly, upon comparing all injected individuals in the two main groups (A/Bzb+B/Bzb) to all control ones in both groups (A/Ctrl+B/Ctrl) the authors found that:

Collectively, the incidence of DME at 2 months post operatively was 4 eyes (20%) in all control subjects altogether, *versus* only one eye (5%) in all injected subjects altogether. At 6 months postoperatively the incidence of developing DME was 6 eyes (30%) within all control subjects and one eye (5%) within all injected subjects (p-value=0.04) (Table 2). The difference at 6 months was statistically significant.

Table 2. Collective incidence of postoperative DME in all (controls and Bevacizumab injected) subjects.

	Control (A+B)	Bevacizumab (A+B)	P* value
DME at 2 weeks (%)	1 (5%)	0 (0%)	N/A
DME at 2 months (%)	4 (20%)	1 (5%)	0.15
DME at 6 months (%)	6 (30%)	1 (5%)	0.04

Note: * Chi-Squared test (p value<0.05 is considered statistically significant); DME: Diabetic Macular Edema. N/A: Not Applicable

We also compared the Central Macular Thickness (CMT) in microns between both types of subjects (all injected subjects *versus* all controls) postoperatively by OCT. Table 3 shows there was no statistically significant difference between these two collective groups in the mean CMT at 2nd week, 2nd months and 6th months after surgery (p>0.05).

Table 3. *CMT at baseline compared to 2 weeks, 2 months and 6 months after phacoemulsification in all injected versus all control subjects.*

	Control (A+B)	Bevacizumab (A+B)	P* value
	(mean ± SD)	(mean ± SD)	
Baseline (µm)	229.4 ± 26.8	230.8 ± 26.7	
2nd week (µm)	254.3 ± 34.3	238.9 ± 19.6	0.78
2nd month (µm)	274.4 ± 60.8	250.6 ± 23	0.86
6th month (µm)	278.3 ± 52.3	254.7 ± 26.2	0.11

Note: *Mann-Whitney test (p-value<0.05 is considered statistically significant); CMT: Central-Macular Thickness, SD: Standard Deviation

However, a statistically significant difference in CMT was found when comparing baseline CMT to the last follow-up visit between both groups, with higher increase in CMT lying in (all) control subjects (p<0.001) versus (all) injected ones (p>0.02) denoting a potential protective role for Bevacizumab against DME (Table 4).

Table 4. *Comparison between CMT at baseline and at 6 months follow-up in all subgroups.*

Group	Baseline (µm)	6 months (µm)	P* value
	(mean ± SD)	(mean ± SD)	
Control (A+B)	229.4 ± 26.8	278.3 ± 52.3	<0.001
Bevacizumab (A+B)	230.8 ± 26.7	254.7 ± 26.2	0.002
A/Ctrl	230.4 ± 23.2	272.8 ± 36.2	0.007
B/Ctrl	228.4 ± 31.2	283.8 ± 66.3	0.005
A/Bzb	236.8 ± 28.5	254.9 ± 30.9	0.074
B/Bzb	224.7 ± 24.8	252.5 ± 21.8	0.012

Note:* Wilcoxon Signed Ranks test (p value<0.05 is considered statistically significant); A/Ctrl: Normal fundus controls; B/Ctrl: NPDR fundus controls; A/Bzb: Normal fundus injected with Bevacizumab; B/Bzb: NPDR fundus injected with Bevacizumab; SD: Standard Deviation; CMT: Central Macular Thickness

The BCVA was assessed by Snellen chart and then converted to LogMAR reading. The mean BCVA was improved in controls (A+B) as well as Bevacizumab (A+B) subjects of both groups, with higher achieved BCVA in injected subjects (A/Bzb+B/Bzb) than non-injected ones (A/Ctrl+B/Ctrl) at 2 weeks (p<0.012), 2 months (p<0.007) and 6 months (p<0.008)

respectively. Table 5 describes the results of comparing baseline BCVA with that of the last follow-up visit in all six subgroups (injected *versus* controls, as well as normal fundus subgroups *versus* NPDR subgroups).

BCVA significantly improved over baseline at 6 months follow up in all subgroups ($p<0.001$, p 0.005) respectively.

Table 5. *Comparison between CMT at baseline and at 6 months follow-up in all subgroups.*

Group	Baseline (LogMAR) (mean ± SD)	6 months (LogMAR) (mean ± SD)	P* value
Control (A+B)	0.79 ± 0.24	0.28 ± 0.09	<0.001
Bevacizumab (A+B)	0.69 ± 0.26	0.19 ± 0.07	<0.001
A/Ctrl	0.78 ± 0.23	0.28 ± 0.07	0.005
B/Ctrl	0.82 ± 0.27	0.28 ± 0.11	0.005
A/Bzb	0.62 ± 0.19	0.19 ± 0.08	0.005
B/Bzb	0.77 ± 0.30	0.19 ± 0.07	0.005

Note: * Wilcoxon Signed Ranks test (p value< 0.05 is considered statistically significant); A/Ctrl: Normal fundus controls; B/Ctrl: NPDR fundus controls; A/Bzb: Normal fundus injected with Bevacizumab B/Bzb: NPDR fundus injected with Bevacizumab; SD: Standard Deviation; BCV A: Best Corrected Visual Acuity.

Further statistical analysis was done to highlight the difference between group A (previously normal fundus) and group B (NPDR fundus). This was done to assess if there was any statistical difference between a preoperative pathological retina and a morphologically free retina.

The difference in CMT was not found to be statistically significant in each follow-up visit when comparing group A to group B controls, or group A to group B injected subjects (Table 6).

Table 6. *Comparison between CMT at baseline and at 6 months follow-up in all subgroups.*

	Group A/Ctrl (mean ± SD)	Group B/Ctrl (mean ± SD)	P* value	Group A/Bzb (mean ± SD)	Group B/Bzb (mean ± SD)	P* value
Baseline (µm)	230.4 ± 23.2	236.8 ± 28.5		228.4 ± 31.2	224.7 ± 24.8	
2nd week (µm)	250.9 ± 27.8	242.2 ± 17.5	0.44	257.6 ± 41.1	235.6 ± 21.9	0.11
2nd month (µm)	266.3 ± 31.6	254.7 ± 27.2	0.53	282.5 ± 81.7	246.4 ± 18.5	0.11
6th month (µm)	272.8 ± 36.2	254.9 ± 30.9	0.44	283.8 ± 66.3	252.5 ± 21.8	0.19

Note: * Mann-Whitney test (p value<0.05 is considered statistically significant). A/Ctrl: Normal fundus controls. B/Ctrl: NPDR fundus controls. A/Bzb: Normal fundus injected with Bevacizumab. B/Bzb: NPDR fundus injected with Bevacizumab; SD: Standard Deviation; CMT: Central-Macular Thickness.

While comparing CMT between preoperative and last follow-up visit, there was a statistically significant difference in thickness in all subgroups (denoting progression of DME) except subjects of the normal fundus group who received Bevacizumab; A/Bzb ($p<0.074$).

This statistical finding highlights that the least progression in macular thickness postoperatively was achieved in the subgroup with a normal fundus preoperatively who also received prophylactic intraoperative Bevacizumab (A/Bzb).

The same analysis was also done for BCVA, and revealed a statistically significant higher improvement in BCVA in normal fundus subjects who received Bevacizumab (A/Bzb) than controls within the same group (A/Ctrl) at all stages of follow up ($p<0.05$). Meanwhile, there was no statistically significant difference in BCVA between injected (B/Bzb) and non-injected subjects (B/Ctrl) in the NPDR group (p value>0.05) (Table 7).

Table 7. *Comparison between CMT at baseline and at 6 months follow-up in all subgroups.*

BCVA	Group A/Ctrl	Group A/Bzb	P* value	Group B/Ctrl	Group B/Bzb	P* value
(LogMAR)	(mean ± SD)	(mean ± SD)		(mean ± SD)	(mean ± SD)	
Preoperative	0.78 ± 0.23	0.62 ± 0.19		0.82 ± 0.27	0.77 ± 0.30	
1st day	0.47 ± 0.15	0.29 ± 0.13	0.019	0.43 ± 0.17	0.33 ± 0.15	0.143
2nd week	0.38 ± 0.11	0.25 ± 0.09	0.029	0.36 ± 0.15	0.26 ± 0.10	0.218
2nd month	0.29 ± 0.08	0.19 ± 0.08	0.035	0.28 ± 0.11	0.19 ± 0.07	0.123
6th month	0.28 ± 0.07	0.19 ± 0.08	0.043	0.28 ± 0.11	0.19 ± 0.07	0.123

Note: * Mann-Whitney test (p value<0.05 is considered significant). A/Ctrl: Normal fundus controls; A/Bzb: Normal fundus injected with Bevacizumab; B/Ctrl: NPDR fundus controls; B/Bzb: NPDR fundus injected with Bevacizumab; SD: Standard Deviation; BCV A: Best Corrected Visual Acuity

While comparing BCVA at baseline to the last follow-up in all subgroups, revealed a statistically highly significant difference ($p<0.005$) with improvement noted in all 4 subgroups.

Finally, there was no development of retinopathy in any of the normal fundus patients (group A), nor there was progression of retinopathy in the NPDR group (group B) during the six months follow up.

Discussion

Cataract surgery is evolving to be a safer procedure with shorter recovery time and higher visual outcome. However, DME is still a major challenge as it commonly follows uneventful phacoemulsification in diabetics [7]. DME results from biochemical and cellular changes such as increased VEGF, increased retinal vascular permeability and impaired blood retinal barrier which lead to leakage and exudation [8-10].

A ten time increase in the level of VEGF is found in the aqueous of diabetic patients *versus* non-diabetic patients first day postoperatively [11]. Bevacizumab is a commonly used anti-VEGF in DME. Studies claimed that intravitreal Bevacizumab in earlier DME stages will give better visual acuity outcomes [12].

Our study found that the incidence of DME was 30% in controls of both groups (A/Ctrl+B/Ctrl) and 5% in all Bevacizumab injected subjects of both groups (A/Bzb+B/Bzb) (p value 0.04) which is comparable with the results of a study done where the incidence of DME was 33% in the control group and 3% in the bevacizumab group. Their study examined the effect of intravitreal Bevacizumab combined with phacoemulsification in diabetic patients with a follow up of two months. Our study offered a longer follow up period, as well as further subgrouping of patients. Our study found a statistically significant difference between the main groups in BCVA ($p>0.007$), which is comparable to their study (p value>0.005) [13].

On the other hand, a study on 54 patients divided into control and Ranibizumab groups with a follow up of three months. They recorded an incidence of 26% in the control group and 4% in the Ranibizumab group which is comparable with our results despite using a different type of anti-VEGF agent [14].

In our study, the incidence of DME in patients in group B (NPDR group) was 30%. This incidence is higher found (22%). They assessed the incidence of DME in 50 diabetic patients (some with no retinopathy, some with NPDR and some with PDR) after cataract surgery and followed them up for 3 months. We postulate that we reported higher incidence probably due to our longer follow up period [15].

Our study found no statistically significant difference between the two main study groups and subgroups in central macular thickness over the follow up period. Their study (61 patients with NPDR with no DME and divided into a control and a Bevacizumab groups), which followed patients up for 6 months, found no statistically significant differences between the two studied groups in central macular thickness at six months [16]. They also reported no statistically significant difference between the two study groups in BCVA at six months posoperatively, a finding which did not agree with our results, as we found a statistically significant improvement in BCVA especially in patients with a preoperatively normal fundus.

Conclusion

Our study highlighted the better visual outcome as well as better baseline to follow up progression of macular edema in a newly studied subgroup of patients; the diabetic patients without retinopathy. Whether routine intravitreal Bevacizumab should be given to diabetic patients-regardless of the presence or absence of retinopathy at the time of phacoemulsification is our proposed recommendation. This may however, need further studies from other authors at different areas of the world to confirm that our results are reproducible.

There are limitations to our study. First, the relatively small number of patients in each subgroup, which despite shedding light on the fact that patients with no diabetic changes before surgery were the subgroup with best prognosis postoperatively, still need to be further confirmed with larger patient numbers in further studies. Second, the six month follow up period,

which despite being longer than most other studies, could be prolonged further to one year or more after surgery.

In conclusion, the incidence of DME is high after phacoemulsification. The use of intravitreal Bevacizumab at time of phacoemulsification could offer a safe and effective prophylactic modality in the short-term prevention of postoperative DME for cases with and without preoperative retinopathy.

Declaration of Interest

The authors report no financial interest to any of the material or instruments used in this study.

Funding Statement

No funding or grants were received for this study.

References

1. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabet Care. 2012;35:556-64.
2. Semeraro F, Cancarini A, Rezzola S, et al. Diabetic retinopathy: Vascular and inflammatory disease. J Diabetes Res. 2015.
3. Funatsu H, Yamashita H, Nakamura S, et al. Vitreous levels of pigment epithelium–derived factor and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology. 2006;113:294-301.
4. Roh MI, Kim HS, Song JH, et al. Effect of intravitreal bevacizumab injection on aqueous humor cytokine levels in clinically significant macular edema. Ophthalmology. 2009;116:80-6.
5. Matsuyama K, Ogata N, Jo N, et al. Levels of vascular endothelial growth factor and pigment epithelium-derived factor in eyes before and after intravitreal injection of bevacizumab. Jpn J Ophthalmol. 2009;53:243-48.
6. Krepler K, Biowski R, Schrey S, et al. Cataract surgery in patients with diabetic retinopathy: Visual outcome, progression of diabetic retinopathy, and incidence of diabetic macular oedema. Graefes Arch Clin Exp Ophthalmol. 2002;240:735-38.
7. Baker CW, Almukhtar T, Bressler NM, et al. Macular edema after cataract surgery in eyes without preoperative central-involved diabetic macular edema. JAMA Ophthalmol. 2013;131:870-79.
8. Chu CJ, Johnston RL, Buscombe C, et al. Risk factors and incidence of macular edema after cataract surgery: A database study of 81984 eyes. Ophthalmology. 2016;123:316-23.
9. Witmer AN, Vrensen GF, Van Noorden CJ, et al. Vascular endothelial growth factors and angiogenesis in eye disease. Prog Retin Eye Res. 2003;22:1-29.
10. Penn JS, Madan A, Caldwell RB, et al. Vascular endothelial growth factor in eye disease. Prog Retin Eye Res. 2008;27:331-71.
11. 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.
12. Kook D, Wolf A, Kreutzer T, et al. Long-term effect of intravitreal bevacizumab (avastin) in patients with chronic diffuse diabetic macular edema. Retina. 2008;28:1053-60.
13. Ahmad M, Nawaz M, Javed EA, et al. Efficacy of intravitreal bevacizumab combined with phaco-emulsification in the prophylaxis of macular edema in patients with non-proliferative diabetic retinopathy. Ann Punjab Med Coll. 2016;10:58-62.
14. Udaondo P, Garcia-Pous M, Garcia-Delpech S, et al. Prophylaxis of macular edema with intravitreal ranibizumab in patients with diabetic retinopathy after cataract surgery: A pilot study. J Ophthalmol. 2011.
15. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology. 2007;114:881-9.
16. Fard MA, Abyane AY, Malihi M. Prophylactic intravitreal bevacizumab for diabetic macular edema (thickening) after cataract surgery: Prospective randomized study. Eur J Ophthalmol. 2011;21:276-81.

*Correspondence to

Dr. Khaled W Elsadi

Department of Ophthalmology

Cairo University

Giza

Egypt

E-mail: khaled.elsadi@kasralainy.edu.eg