



Original research

Role of combined phacoemulsification and intravitreal injection of bevacizumab in prevention of postoperative macular edema in non-proliferative diabetic retinopathy

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Abstract

Purpose: To evaluate the role of combined phacoemulsification and intravitreal injection of bevacizumab in prevention of postoperative diabetic macular edema (DME) in patients with no diabetic retinopathy or non-proliferative diabetic retinopathy (NPDR) and without macular edema.

Methods: In a prospective randomized clinical trial, 71 eyes from 71 diabetic patients with no diabetic retinopathy or mild NPDR and with central macular thickness (CMT) of less than 300 μm were enrolled and were randomized into two groups: combined phacoemulsification and intravitreal bevacizumab injection group and only phacoemulsification group. Our primary outcome measures included best corrected visual acuity (BCVA), CMT, and total macular volume (TMV) before and after (1 month and 3 months) the cataract surgery.

Results: The two groups did not show any significant difference in terms of baseline BCVA, age, CMT, stage of diabetic retinopathy. While the bevacizumab group showed lower CMT one month after the surgery compared to control group (267.3 ± 31.8 and 293.6 ± 53.7 , respectively, $P = 0.019$), this difference did not remain significant 3 months after surgery (264.5 ± 21.9 and 291.4 ± 79.8 , $P = 0.089$). The TMV and BCVA in the two groups showed no significant difference one month or 3 months after surgery. Considering our definition of post-cataract surgery diabetic macular edema (PME) in this study [CMT $>300 \mu\text{m}$ using spectral domain optical coherence tomography (SD-OCT)], there was no significant difference between the incidence of PME at 1 month and at 3 months after surgery.

Conclusions: Although the intravitreal injection of bevacizumab during phacoemulsification would result in decreased macular thickness in patients with no diabetic retinopathy or NPDR and without macular edema in the early postoperative period, this effect would no longer persistent at 3 months. In addition, the BCVA and TMV showed no significant difference between the two groups at any time during follow-up period.

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Keywords: Intravitreal bevacizumab; Phacoemulsification; Postoperative macular edema

Introduction

Phacoemulsification is one of the most common surgical procedures which is being performed in diabetic patients through

the world.¹ It has been shown that even an uncomplicated phacoemulsification may lead to macular edema in non-diabetic patients and those who are not predisposed to this complication.² In diabetic eyes, however, the increased level of vascular endothelial growth factor (VEGF) in aqueous humor has been observed at 1 day after surgery.³ Considering the important role of angiogenic factors such as VEGF in progression of diabetic macular edema (DME), the advent of Anti-VEGF therapies in prophylaxis and treatment of post-cataract surgery diabetic macular edema (PME) has gained much interest.^{4–6}

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Recently, numerous studies have investigated the role of Anti-VEGF therapies combined with phacoemulsification in progression of diabetic retinopathy.^{4,7–9} However, all have included the patients with either preexisting DME or proliferative diabetic retinopathy (PDR) as well. There are only two studies available which have observed the role of Ranibizumab in prevention of PME in diabetic patients without DME.^{10,11} Both have concluded that intravitreal Ranibizumab injection just after phacoemulsification would prevent PME in patients with diabetic retinopathy.

Bevacizumab is a full-length recombinant humanized monoclonal antibody that blocks all isoforms of VEGF and is routinely used as an off-label therapeutic modality in treating DME. Although several studies comparing the efficacy and safety of bevacizumab and Ranibizumab in treating DME have not yielded robust evidence in terms of superiority of each option, it seems that bevacizumab could be a rational option regarding its lower cost and more widespread availability compared to Ranibizumab.^{12–14}

In the present study, we evaluated the efficacy of intravitreal injection of bevacizumab immediately after the phacoemulsification in patients with stable non-proliferative diabetic retinopathy (NPDR) without a present or past history of DME.

Methods

Patients

In a prospective randomized clinical trial, we enrolled 71 eyes from 71 diabetic patients who were referred to Diabetic Retinopathy Clinic, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran, between May 2013 and February 2016. The patients had visually significant cataract which was not too severe to evaluate the posterior segment. At the first visit, all the patients were randomly assigned to one of the two groups by block randomization. While the patients in first group received intravitreal injection of bevacizumab (1.25 mg) immediately at the end of phacoemulsification surgery, the patients in second group (the control group) received only phacoemulsification.

The inclusion criteria were as follows: 1) Patients with diabetes mellitus (DM) and visually significant cataract with best corrected visual acuity (BCVA) under 20/40, as determined by using the Snellen acuity chart; 2) No diabetic retinopathy or mild NPDR as defined by the Early Treatment Diabetic Retinopathy Study.

The exclusion criteria were as follows: 1) HbA1c >7.5; 2) Central macular thickness (CMT) >300 μ m and/or any evidence of cystic spaces as determined by spectral domain optical coherence tomography (SD-OCT) (Spectralis SD-OCT; Heidelberg engineering; Germany); 3) Severe NPDR or PDR; 4) Complicated cataract surgery; 5) DM type 1; 6) Uncontrolled blood hypertension; 7) Previous retinal laser treatment or intraocular surgery.

Patient examination

At the screening visit, all patients underwent comprehensive anterior and posterior segment examination using slit-

lamp and 90 D lens (Volk Optical, Inc, Mentor, OH), intraocular pressure determination using Goldmann applanation tonometry and SD-OCT. Grades of retinopathy were assessed according to the Wisconsin Epidemiology Study of Diabetic Retinopathy.¹⁵ BCVA was converted to logarithm of the minimum angle of resolution (logMAR) visual acuity. After cataract surgery, postoperative complete ophthalmic examinations were performed at 1 day, 7 days, and 1 and 3 months later. SD-OCT was performed at one month and 3 months after surgery.

SD-OCT images were depicted using the 512 \times 128 scan pattern with the center of the 6 \times 6-mm scanning area positioned at the center of the fovea. CMT, namely the average retinal thickness in the central 1-mm subfield of the fovea, was measured. The total macular volume (TMV), namely the volume of the retina summed over all nine subfields of the Early Treatment Diabetic Retinopathy Study—type grid, was also calculated. In the present study, we used the Munk et al. methods to differentiate between the post-cataract surgery cystoid macular edema (CME) and PME.¹⁶ Briefly, when we observed the absence of an epiretinal membrane and solely inner nuclear layer (INL)-cysts, we made the diagnosis of post-cataract surgery CME and excluded the patient from the study. However, when we noticed the absence of subretinal fluid, presence of hard exudates, microaneurysms, and ganglion cell layer and/or retinal nerve fiber layer cysts, we made the diagnosis of PME and included the patient in the study.

Surgical technique

Phacoemulsification was performed under topical anesthesia by a single surgeon (A.KH.). A temporal side clear corneal incision was made using a 3.2 mm keratome. After the anterior chamber was filled with an ophthalmic viscosurgical gel (VISICROM[®]2%, BinaChashm, Tehran, Iran), a continuous curvilinear capsulorhexis was made. Phacoemulsification was done using a phaco-machine (Constellation[®] vision system; Alcon Laboratories). After phacoemulsification, a foldable intraocular lens (Acrysof SN60AT; Alcon Laboratories) was injected in the capsular bag. At the end of cataract surgery in the bevacizumab injection group, 0.1 mL of a solution containing 1.25 mg of bevacizumab (Avastin[®]; Genentech; California; United States) was injected intravitreally through the sclera from 3.5 mm posterior to the limbus. No intraoperative complication including vitreous loss or iris manipulation was noted.

Outcome measures

The bevacizumab injection and control groups were compared in terms of change in BCVA, CMT, and TMV at baseline and after cataract surgery. To better compare our study results with DRCR.net protocols, we defined clinically meaningful postoperative macular edema by CMT >300 μ m using SD-OCT (Spectralis SD-OCT; Heidelberg engineering; Germany).

Compliance with ethical standards

The study was implemented in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the local Ethics Review Committee of Tehran University of Medical Sciences, and all participants provided us with written informed consents prior to inclusion.

Statistical analysis

Statistical analysis was performed using SPSS software (version 18 for windows; SPSS Inc., Chicago, IL, U.S.A.). Variables are expressed as mean \pm standard error of mean. Non-parametric variables were analyzed using Wilcoxon Mann–Whitney test. *P* value of less than 0.05 was considered significant.

Results

We enrolled 78 eyes from 78 patients. Two patients were excluded according to the development of postoperative CME, and five patients were lost to follow-up. Thirty-six eyes were determined as the bevacizumab group, and 35 eyes were determined as the control group using randomization block. All patients had Type 2 DM. Table 1 shows the clinical characteristics of the 71 patients at the initial visit. The two groups did not show any significant difference in terms of baseline BCVA, age, male:female ratio, CMT, stage of diabetic retinopathy, HbA1c, and blood pressure. In the control group, there was significant increase in CMT at both one month ($293.6 \pm 53.7 \mu\text{m}$) and three months ($291.4 \pm 79.8 \mu\text{m}$) after surgery ($P = 0.019$ and $P = 0.005$, respectively). However, the change in CMT was not statistically significant between one month and three months after the procedure ($P = 0.144$). The same scenario was noted in the bevacizumab group: while there was significant increase in CMT at both one month ($267.3 \pm 31.8 \mu\text{m}$) and three months ($264.5 \pm 21.9 \mu\text{m}$) after the surgery ($P = 0.028$ and $P < 0.001$, respectively), this change was not significant between one month and three months ($P = 0.147$). While the bevacizumab group showed lower CMT one month after the

Table 1
Baseline characteristics of bevacizumab group and control group.

	Bevacizumab group	Control group	<i>P</i> -value
Age, years	61.7 \pm 6.4	66.3 \pm 10.8	0.090
Male/Female	8/28	13/22	0.184
No DR/Mild NPDR	24/12	18/17	0.214
HbA1C, %	6.7 \pm 0.4	6.9 \pm 0.3	0.129
Sys BP	129.1 \pm 16.8	131.9 \pm 15.5	0.504
Dias BP	78.1 \pm 13.8	82.2 \pm 14.8	0.248
BCVA before surgery, logMAR	0.54 \pm 0.21	0.46 \pm 0.16	0.137
CMT, μm	261 \pm 24.3	267.5 \pm 27.4	0.303

DR: Diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; Sys: Systolic; Dias: Diastolic; logMAR: Logarithm of the minimum angle of resolution; SD: Standard deviation; CMT: Central macular thickness; BCVA: Best corrected visual acuity; BP: Blood pressure.

Table 2

Central macular thickness (CMT) and total macular volume (TMV) before and at 1 month and 3 months after cataract surgery, and the incidence of postoperative macular edema (PME).

	Bevacizumab group	Control group	<i>P</i> -value
CMT, preop, μm	261.4 \pm 24.3	267.5 \pm 27.4	0.303
CMT, 1 month postop, μm	267.3 \pm 31.8	293.6 \pm 53.7	0.019
CMT, 3 months postop, μm	264.5 \pm 21.9	291.4 \pm 79.8	0.089
TMV, Preop	8.39 \pm 0.54	8.40 \pm 0.51	0.937
TMV, 1 month postop	8.40 \pm 0.62	8.63 \pm 0.70	0.147
TMV, 3 months, postop	8.49 \pm 0.50	8.71 \pm 0.71	0.140
BCVA, Preop, logMAR	0.54 \pm 0.21	0.46 \pm 0.16	0.137
BCVA, 1 month postop	0.07 \pm 0.06	0.10 \pm 0.09	0.226
BCVA, 3 months postop	0.06 \pm 0.04	0.06 \pm 0.06	0.622
PME, 1 month postop, n, %	2 (5.5)	5 (14.7)	0.244
PME, 3 months postop, n, %	3 (8.33)	8 (22.8)	0.076

CMT: Central macular thickness; TMV: Total macular Volume; BCVA: Best corrected visual acuity; PME: Postoperative macular edema.

surgery compared to the control group (267.3 ± 31.8 and 293.6 ± 53.7 , respectively, $P = 0.019$), this difference did not remain significant 3 months after surgery (264.5 ± 21.9 and 291.4 ± 79.8 , $P = 0.089$). The TMV and BCVA in the two groups showed no significant difference at one month or at 3 months after surgery (Table 2). When we calculated the amount of CMT change in each follow-up visit compared to preoperative value, no significant differences were noted at one month and three months after surgery ($P = 0.381$ and $P = 0.253$, respectively). Considering our definition of PME in this study according to DRCR.net protocols (CMT $>300 \mu\text{m}$ using SD-OCT), two (5.5%) patients in the bevacizumab group and five (14.7%) patients in the control group developed PME one month after surgery. Three months thereafter, three (8.33%) patients in the bevacizumab group and eight (22.8%) patients in the control group developed PME. Although the incidence of PME was slightly higher in the control group, this difference was not statistically significant neither at 1 month nor at 3 months after surgery ($P = 0.244$ and $P = 0.076$, respectively). Of 11 patients who developed PME, 3 patients had mild NPDR, and 8 patients had no DR. There was no significant association between the presence of mild NPDR and development of PME after surgery (Fisher's exact test, $P = 0.321$).

After analyzing our data in the subset of patients who had mild NPDR, not only did we find no significant difference between our two groups regarding all our measures, but the significant effect of intravitreal bevacizumab at 1 month even disappeared.

Discussion

DME is the most common reason of poor visual outcomes in diabetic patients after cataract surgery. It has been shown that level of aqueous VEGF was significantly positively correlated with a clinically meaningful change in CMT in diabetic patients 1 month following cataract surgery. Of note, the disease severity is also correlated with VEGF level

preoperatively.¹⁷ Therefore, it could be postulated that controlling this VEGF increase would fruitfully play an important role in preventing postoperative increase in CMT and thereby in improving the vision outcome of the patients after cataract surgery. The present study showed that intravitreal bevacizumab injection at the time of cataract surgery caused an insignificant decrease in macular thickness in patients with no or mild diabetic retinopathy.

According to DRCR network (Protocol Q), the probability of developing central involved PME after cataract surgery in patients without preoperative DME is extremely low. However, presence of non-central DME immediately prior to cataract surgery or history of DME treatment may significantly increase the chance of developing PME in these patients.¹⁸ Takamura et al. in their study evaluated the effect of intravitreal bevacizumab injected in adjunction with phacoemulsification in diabetic patients with preexisting macular edema. While at the first and third month after surgery, the CMT significantly decreased in bevacizumab group, it significantly increased in the control group. Although at the third month after surgery, BCVA significantly improved in both groups, BCVA was significantly higher in the bevacizumab group than in the control group.⁵ There are numerous studies concluding the beneficial effect of intravitreal bevacizumab during phacoemulsification in terms of improving BCVA and decreasing macular thickness in patients with preexisting macular edema.^{8,19} However, it seems that this interesting effect would be evanescent when considering in patients without preexisting macular edema. To understand the role of Anti-VEGF therapy combined with phacoemulsification in diabetic patients without preexisting macular edema, Chae et al. conducted a randomized clinical trial in eighty diabetic patients, 46 of which received panretinal laser photocoagulation at least 3 months before the surgery.¹¹ The Ranibizumab group and control group did not show clinically significant differences in terms of the change of BCVA from baseline at the one week and one- and three-month follow-up visits. However, at the 6-month follow-up visit, the Ranibizumab group showed greater BCVA improvement relative to baseline than the control group. In line with our study, although the two groups differed significantly in terms of the mean CMT changes at 1 month, there were no clinically significant differences at the 3- and 6-month follow-up visits. TMV increased after cataract surgery in both groups. However, in contrast to our results, the Ranibizumab group exhibited a significantly smaller change in TMV than the control group at all follow-up visits. Therefore, considering the hypothesis that TMV would better reflect the changes in macular situation compared to CMT, we evaluated both CMT and TMV in our two groups to observe any subtle change with the use of intravitreal bevacizumab in our patients. Although in their study, the Ranibizumab group had a significantly lower PME incidence rate than the control group 1 month after the cataract surgery, similar to our results, the differences between the two groups at 3 and 6 months were not significant. Of note was that they defined PME as a CMT increase of ≥ 60 μm relative to

the preoperative baseline. Interestingly, the two groups only differed in CMT changes until 1 month after surgery, whereas they differed at all time points in terms of TMV changes. The authors hypothesized that the ability of Ranibizumab injection to prevent macular edema in the early period after surgery (1 month) may be responsible, at least in part, for the persistently smaller increase in TMV as well as the better improvement in BCVA at the 6-month follow-up visit. Fard et al. in their study, evaluating the effect of intravitreal bevacizumab in patients with CMT of less than 200 μm , found a significant increase one month after surgery in the control group, whereas the bevacizumab group did not show the same. However, in line with our study, after 6 months, there was no significant difference in macular thickness and postoperative visual acuity between the two groups. They concluded that intravitreal administration of 1.25 mg bevacizumab at the time of cataract surgery is effective only in the short-term, and 6-month results are the same as the control group.²⁰

It seems that patients with moderate to severe NPDR and/or macular edema prior to phacoemulsification are more likely to develop subsequent persistent macular edema or progression of diabetic retinopathy following surgery compared to patients with no or mild NPDR initially.⁴ We believe that although combined intravitreal Anti-VEGF and phacoemulsification in patients with mild diabetic retinopathy and without macular edema would lead to a decrease in CMT in the early (one month) postoperative period, this effect would diminish after 3 months. Therefore, this combined procedure seems to be beneficial mostly in patients with at least moderate NPDR and/or preexisting macular edema.

Our study has some limitations. First, our sample size in each group is small and probably not large enough to elucidate the subtle differences especially in PME incidence between the two groups. Second, our follow-up period is small. Some dramatic change might occur during further visits. Third, we defined PME by CMT >300 μm using SD-OCT. Considering the definition of PME as an increase of ≥ 60 μm might result in another comparable conclusion.

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