Role of combined cataract surgery and intravitreal bevacizumab injection in preventing progression of diabetic retinopathy

Prospective randomized study

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PURPOSE: To evaluate the role of intravitreal bevacizumab, an anti-vascular endothelial growth factor agent, injected at the time of cataract surgery on the postoperative progression of diabetic retinopathy (DR) and diabetic maculopathy.

SETTING: Tertiary-care eye specialty hospital, Dhahran, Kingdom of Saudi Arabia.

METHODS: Patients were randomized to a standardized procedure of phacoemulsification with intraocular lens implantation alone (control group) or to receive 1.25 mg intravitreal bevacizumab at the end of surgery (intervention group). Diabetic retinopathy and maculopathy were assessed at each postoperative visit during a 6-month follow-up.

RESULTS: Sixty-eight eyes (68 patients) with DR and cataract were recruited for this prospective study. Progression of DR occurred in 15 (45.45%) of 33 eyes in the control group and 4 (11.42%) of 35 eyes in the intervention group ($P = .002$) Progression of diabetic maculopathy occurred in 17 eyes (51.51%) in the control group and 2 eyes (5.71%) in the intervention group ($P = .0001$). There was no statistically significant difference in postoperative visual acuity between the 2 groups ($P = .772$). Two eyes in the control group and none in the intervention group progressed to neovascular glaucoma. The mean postoperative central macular thickness and mean macular thickness were not statistically significantly different between the 2 groups ($P = .874$ and .942, respectively).

CONCLUSION: Intravitreal administration of 1.25 mg bevacizumab at the time of cataract surgery was safe and effective in preventing the progression of DR and diabetic maculopathy in patients with cataract and DR.

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Diabetic patients are at higher risk for developing cataract[1] than those without diabetes. It has been estimated that 20% of cataract surgery[2] in the Western world is performed in patients with diabetes mellitus (DM). The prevalence of DM is much higher in the developing world,[3,4] where a large proportion of patients having cataract surgery have DM.

It is well established that after cataract surgery, patients with preexisting diabetic retinopathy (DR) have a significant risk for progression of DR, diabetic maculopathy, and anterior segment neovascularization.[5–7] The risk for progression of retinopathy after cataract surgery is related to the severity at the time of surgery.[8–10] Patients with no retinopathy have an excellent prognosis,[11] while those with retinopathy may have progression of DR and poor visual outcomes after surgery.[12]

The pathogenesis of these complications may be related to the changes and rise in the concentration of angiogenic factors[13] in response to surgical trauma and inflammation. The most relevant angiogenic factor is vascular endothelial growth factor (VEGF).[14] Patel et al.[15] found increased levels of VEGF 165 and other cytokines in aqueous samples of patients with DR having phacoemulsification and intraocular lens (IOL) implantation. They found that the VEGF 165 concentration increased 1 day after surgery from a median baseline of 68 pg/mL to 723 pg/mL at day 1 and decreased to 179 pg/mL at 1 month. An experimental model of diabetic rats[16] also suggests that early blood–retinal barrier (BRB) breakdown in experimental diabetes is VEGF dependent and that VEGF inhibition may provide a useful therapeutic approach in the treatment of early diabetic

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BRB breakdown. Other studies[17] also found that a high VEGF level in the aqueous humor may predict a significant risk for postoperative exacerbation of macular edema after phacoemulsification in patients with nonproliferative DR.

We hypothesized that blockage of the VEGF surge with anti-VEGF therapy at the time of cataract surgery may prevent complications related to progression of DR. We performed a study to assess the safety and efficacy of intravitreal bevacizumab, an anti-VEGF agent, injected at the time of cataract surgery on the progression of DR in patients with cataract and DR.

PATIENTS AND METHODS

Patients

This prospective randomized study included cataract patients with DM and diabetic retinopathy having phacoemulsification and IOL implantation. The patients were recruited between February and December 2007 from the retina clinic at Dhahran Eye Specialist Hospital, a tertiary referral center in the Eastern province of the Kingdom of Saudi Arabia. The patients were randomized to a standardized procedure of phacoemulsification with IOL implantation alone (control group) or to receive 1.25 mg intravitreal bevacizumab (Avastin) at the end of surgery (intervention group). The hospital's institutional review board approved the study, and all patients provided informed consent.

Inclusion criteria were sight-limiting cataract in diabetic patients with poor fundus view precluding adequate monitoring and/or laser therapy with (1) the presence of clinically significant macular edema (CSME); (2) mild, moderate, severe, or very severe nonproliferative diabetic retinopathy (NPDR) (any 2 features of NPDR as defined by the 4-2-1 rule) or proliferative diabetic retinopathy (PDR); or (3) a combination of 1 and 2.

Eyes with glaucoma, uveitis, and age-related macular degeneration or a history of trauma or ocular surgery were excluded from the study. Patients with previous focal or grid laser photocoagulation for CSME were eligible, while those with previous panretinal laser photocoagulation for PDR were excluded.

Preoperative Assessment

All patients had a complete preoperative examination including best corrected visual acuity (BCVA) measurement, slitlamp biomicroscopy, and intraocular pressure measurement. A complete retinal assessment with a +90.0 diopter fundus lens was performed to grade the severity of the retinopathy and maculopathy. In cases in which fundus details were obscured by the density of the cataract, retinopathy grading was based on the first postoperative day examination. Grades of retinopathy were defined according to the Wisconsin Epidemiologic Study of Diabetic Retinopathy,[18] and CSME was classified based on the Early Treatment Diabetic Retinopathy Study (ETDRS).[19]

Surgical Technique

All phacoemulsification procedures were performed by the same surgeon (R.A.C.) using sub-Tenon local anesthesia. A superior 3.2 mm corneal tunnel was made, the anterior chamber filled with an ophthalmic viscosurgical device (OVD) (sodium hyaluronate 1%), and a continuous curvilinear capsulorhexis created. After the nucleus was hydrodissected, it was emulsified using a cracking technique and the cortical material was removed. Next, a foldable IOL (AcrySof MA60AC, Alcon Laboratories) was implanted in the capsular bag. A 10-0 monofilament nylon suture was placed to secure the corneal wound. In patients randomized to the intervention group, 1.25 mg in 0.05 mL of bevacizumab was injected with a 27-gauge needle through the pars plana (3.0 to 3.5 mm from the limbus) into the vitreous cavity. The OVD was removed, and a subconjunctival injection of gentamicin was given at the completion of surgery.

All eyes were treated postoperatively with prednisolone acetate 1% (Pred Forte) and ofloxacin drops 4 times daily for the first week followed by prednisolone acetate alone 3 times daily for 3 weeks.

Postoperative Assessment

Postoperative examinations were at 1 day; 1, 2, and 4 weeks; and then at monthly intervals for 6 months. A full ophthalmic examination was performed at each visit. Based on the clinical examination and optical coherence tomography (OCT) assessment, retinal laser photocoagulation was performed according to ETDRS guidelines. Focal or grid laser photocoagulation was performed for CSME and panretinal (scatter) laser photocoagulation, for patients with PDR. Postoperative laser treatment was performed no sooner than 1 week after surgery.

Diabetic retinopathy and maculopathy were assessed at each postoperative visit with clinical examination, digital color fundus photographs (Kowa VX10i, Kowa Co. Ltd.), and OCT. Mapping of the macula with OCT (OCT/SLO-OTI, Ophthalmic Technologies Inc) was also performed. Retinal thickness was measured in a 3.5 mm diameter circle corresponding to 5 zones (central, nasal, temporal, superior, inferior) centered on the fixation point. Mean thickness on the 1.0 mm circle centered on the fovea was considered for statistical analysis of central macular thickness. The thickness of all 5 zones was used to calculate the average macular thickness. Diabetic retinopathy was graded as mild NPDR, moderate NPDR, severe NPDR, very severe NPDR, or PDR. Clinically significant macular edema was classified according to the ETDRS.[19] Progression of DR was based on assessment in a masked fashion by 2 retina specialists (R.A.C., Y.M.A.). In both groups, DR was considered to have progressed when (1) a patient with preexisting DR developed a higher grade of retinopathy, with or without progression within

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the macula (eg, mild NPDR progressed to severe NPDR or higher grade) or (2) a patient with or without maculopathy developed CSME/increase in retinal thickening or hard exudation associated with retinal thickening from baseline levels.

Outcome Measures

The primary outcome measure was progression of postoperative DR and diabetic maculopathy during a 6-month follow-up. Secondary outcome measures were a change in BCVA (Snellen converted to logMAR equivalent), changes in central macular thickness and macular thickness determined by OCT, postoperative laser therapy, and progression to neovascular glaucoma (NVG).

Statistical Analysis

Statistical analysis was performed with SPSS software (version 13.0.1, Professional Statistics Release, SPSS, Inc.). A 2-sample *t* test was used to compare the means of the parametric data, and the chi-square test was used for categorical data.

RESULTS

Of the 68 eyes (68 patients) recruited into the study, 33 did not receive intravitreal bevacizumab (control group) and 35 received an intravitreal bevacizumab injection (intervention group) at the end of surgery. Table 1 shows the demographics of the patients; there was no statistically significant difference between groups in the number of eyes, age, or sex.

There was no statistically significant difference between the control group and the intervention group in the type of DM ($P = .225$, chi-square test), the mean duration of DM ($P = .663$, *t* test), or the mean duration of systemic hypertension ($P = .920$, *t* test) (Table 1). There was no statistically significant difference in the preoperative BCVA between the 2 groups ($P = .470$, *t* test). Table 2 shows the characteristics of preoperative retinopathy and maculopathy by group; there was no statistically significant difference between groups ($P = .574$, chi-square test). All patients had some degree of preoperative retinopathy; 20 eyes (60.6%) in the control group and 19 eyes (54.2%) in the intervention group had diabetic maculopathy.

Table 3A shows the progression of DR maculopathy after surgery and Table 3B, the change in DR. Diabetic retinopathy progressed in 45.45% of eyes in the control group and 11.42% of eyes in the intervention group; the difference between groups was statistically significant ($P = .002$, chi-square test). Progression of diabetic maculopathy occurred in 51.51% of eyes in the control group and 5.71% of eyes in the intervention group; the difference between groups was statistically significant ($P = .0001$, chi-square test). Figure 1 shows color fundus photographs and OCT analysis of the progression of DR and diabetic maculopathy in an eye in the control group.

Table 1. Clinical characteristics of patients at 6 months.

Characteristic	Group: Control (No IVB)	Group: Intervention (IVB)	*P* Value
Patients, n	33	35	
Age, y			.468
Mean	64.5	66.14	
Range	41 to 88	48 to 87	
CI	61.2-67.9	63.1-69.1	
Sex			.947
Male	21	22	
Female	12	13	
Eye			.016
Right	12	23	
Left	21	12	
Type of DM			.225
IDDM	19	23	
NIDDM	14	12	
Duration of DM, y			.663
Mean	17.7	15.3	
Range	5 to 25	3 to 25	
95% CI	12.5-16.8	13.4-17.2	
Duration of hypertension, y			
Mean	5.30	5.17	.920
Range	0 to 20	0 to 15	
95% CI	3.05-7.56	3.71-6.63	

CI = confidence interval; DM = diabetes mellitus; IDDM = insulin-dependent diabetes mellitus; IVB = intravitreal bevacizumab; NIDDM = non-insulin-dependent diabetes mellitus

Table 2. Preoperative DR and visual acuity.

Characteristic	Group: Control	Group: Intervention	*P* Value
Retinopathy			—
Mild NPDR	6	2	
Moderate NPD	12	4	
Severe NPDR	11	17	
Very severe NPDR	3	10	
PDR	1	2	
Maculopathy/CSME			.574
Not present	13	16	
Present	20	19	
Visual acuity (logMAR)			.470
Mean ± SD	1.137 ± 0.728	1.256 ± 0.672	
Range	0.1 to 3.0	0.1 to 3.0	
95% CI	0.878-1.395	1.040-1.472	

CI = confidence interval; CSME = clinically significant macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

Table 3A. Postoperative progression of DR and diabetic maculopathy.

Progression	Group		*P* Value
	Control	Intervention	
DR			.002
No progression	18	31	
Progression	15	4	
Maculopathy			.0001
No progression	16	33	
Progression	17	2	

Table 4 shows the mean postoperative BCVA over the 6-month follow-up. There was no statistically significant difference in postoperative visual acuity at any time point.

Table 5 shows the changes in central macular thickness and average macular thickness over the 6-month follow-up. There was no statistically significant difference between groups at any time point.

Table 6 compares the secondary outcomes between control group and intervention group at 6 months. Laser photocoagulation was performed in 48.48% of eyes in the control group and 57.14% eyes in the intervention group; the difference was not statistically significant ($P = .475$, chi-square test). Postoperative progression to NVG occurred in 2 eyes in the control group and in no eye in the intervention group. There was no statistically significant difference between groups in central macular thickness or average macular thickness at any postoperative time point.

DISCUSSION

Recent studies[20–22] have established a strong link between alterations in angiogenic growth factors and pathogenesis of DR. Angiogenic growth factors, such as VEGF, induce subclinical and clinical worsening of DR[15,17] and are biochemical mediators of progression of DR and maculopathy after uneventful cataract surgery. Vascular endothelial growth factor is a potent endothelial cell mitogen angiogenic factor and a powerful mediator of vascular permeability. It leads to breakdown of the BRB, resulting in leakage of intravascular fluid from abnormal retinal capillaries.[23] However, to our knowledge, there is no published clinical study evaluating the benefits of recently available specific anti-VEGF agents (eg, bevacizumab) in cataract surgery.

In the present study, progression of DR during a follow-up period of 6 months occurred in 45.45% of eyes that did not receive intravitreal bevacizumab (control group) and 11.42% of eyes that did receive intravitreal bevacizumab (intervention group) after cataract surgery with IOL implantation. The reported rate of progression of DR after cataract surgery varies widely between studies. This may represent influence of numerous variables such as poor systemic control of diabetes,[24] high levels of HbA1c glycolated hemoglobin, duration of DM,[25] poor renal function,[26] hypertension, race,[27] insulin treatment,[28] surgeon inexperience,[29] postoperative inflammation, and severity of retinopathy at the time of cataract surgery. Jaffe et al.[9] report a rate of DR progression of more than 70% after extracapsular cataract surgery, while Squirrell et al.[28] report a rate of 20% after phacoemulsification surgery. In

Table 3B. Change in DR after cataract surgery.

Group	Number		
	Eyes	No Change	Progression
Control (n = 33)			
Preop retinopathy			
Mild NPDR	6	4	2
Moderate NPD	12	8	4
Severe NPDR	11	4	7
Very severe NPDR	3	1	2
PDR	1	1	0
Intervention (n = 35)			
Preop retinopathy			
Mild NPDR	2	2	0
Moderate NPD	4	4	0
Severe NPDR	17	14	3
Very severe NPDR	10	9	1
PDR	2	2	0

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

Table 4. Postoperative visual acuity.

Postop Exam	BCVA (LogMAR)		*P* Value
	Control Group	Intervention Group	
1 month			.539
Mean ± SD	0.482 ± 0.475	0.552 ± 0.460	
Range	0.0 to 2.0	0.0 to 2.0	
95% CI	0.313-0.651	0.394-0.710	
3 months			.582
Mean ± SD	0.477 ± 0.387	0.534 ± 0.476	
Range	0.0 to 1.3	0.0 to 2.0	
95% CI	0.339-0.614	0.371-0.690	
6 months			.772
Mean ± SD	0.556 ± 0.482	0.574 ± 0.470	
Range	0.0 to 2.0	0.0 to 2.0	
95% CI	0.385-0.727	0.412-0.736	

BCVA = best corrected visual acuity; CI = confidence interval

contrast, Wagner et al.[30] report that the worsening of DR seems to be correlated not with the cataract surgery but with the natural course of the diabetic vascular disease. Although patients in our study had sight-limiting cataract, every effort was made to perform laser therapy before cataract surgery as it is well known that diabetic macular edema can progress after such surgery. Our patients were from the Arabian Gulf, an area where DM is common and usually poorly controlled. Because most patients were referred from other hospitals, accurate data on previous laser treatments, the duration of CSME, and systemic control of diabetes were not available and thus could not be included in the statistical analysis. In our study, the rate of progression of DR in the control group was 45.45%, which is similar to that reported by Chatterjee et al.[27] in British Afro-Caribbean diabetic patients having phacoemulsification. Although direct comparison between studies is difficult, our study found a significant reduction in the rate of progression of DR in eyes that received an intravitreal injection of bevacizumab.

In our study, progression of diabetic maculopathy occurred in 51.51% of eyes in the control group and 5.71% in the intervention group; the difference between groups was highly statistically significant. Romero-Aroca et al.[25] report diabetic macular edema in 6.6% of eyes with nonproliferative DR after phacoemulsification and Dowler et al.[31] in 44% of eyes 6

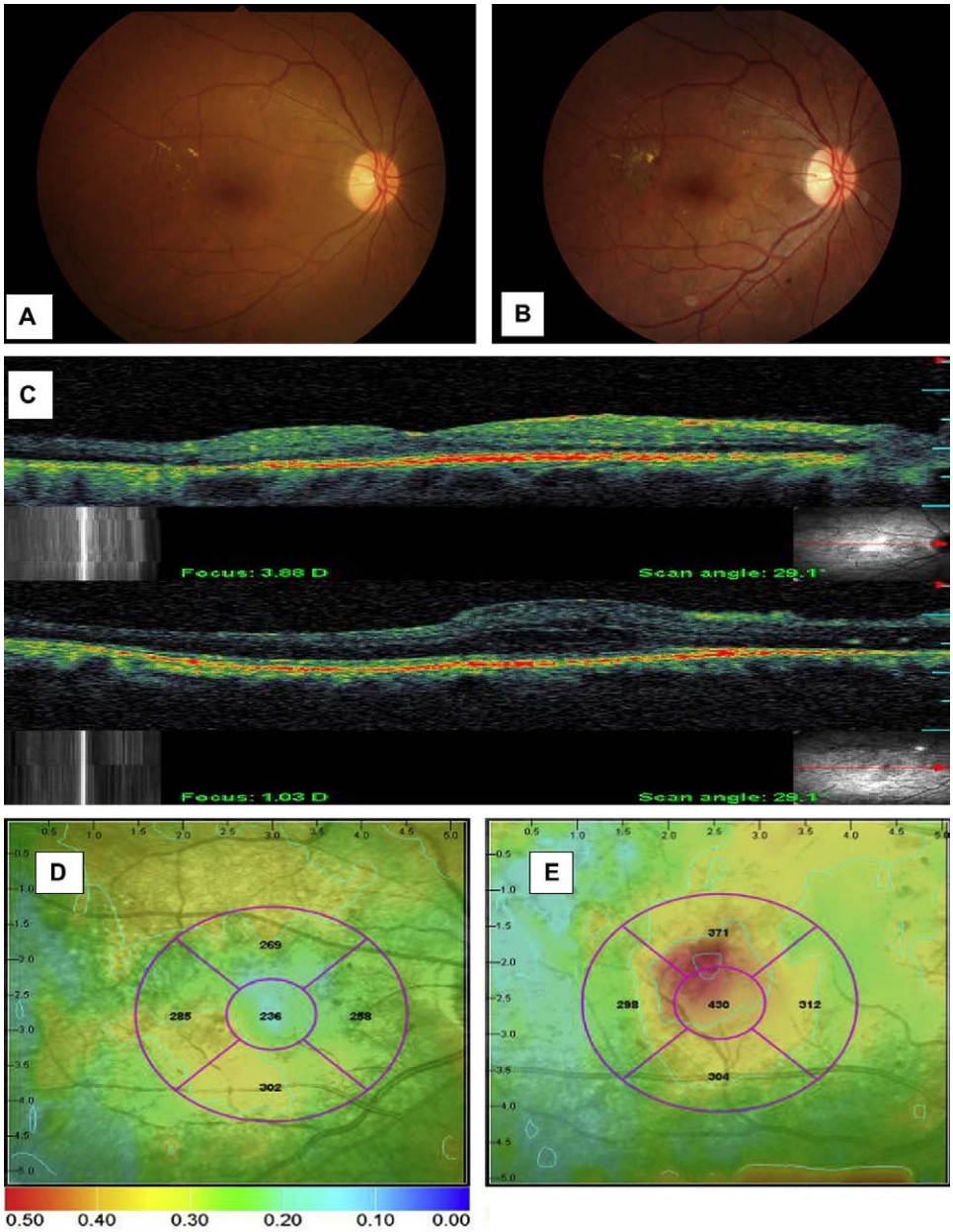

Figure 1. Color fundus photographs and OCT analysis showing the progression of DR and diabetic maculopathy in a control group eye. *A*: Preoperative color fundus photograph. *B*: Postoperative fundus photograph 2 months after surgery shows progression to severe NPDR and CSME. *C*: Preoperative and 2-month postoperative OCT months shows progression of retinal thickening and macular edema. *D* and *E*: Preoperative and postoperative OCT shows retinal thickness in 5 zones at macula. Central macular thickness progressed from 236 μm to 430 μm 2 months after surgery due to progression of macular edema.

Table 5. Postoperative macular thickness determined by OCT.

Postop Exam	Group		*P* Value
	Control	Intervention	
1 month			.882
Central macular thickness (μm)			
Mean ± SD	314.5 ± 208.2	315.08 ± 221.5	
95% CI	216.0-410.8	221.5-408.6	
Average macular thickness (μm)			.883
Mean ± SD	374.5 ± 186.1	374.2 ± 189.6	
95% CI	287.3-461.5	294.1-454.2	
3 months			.846
Central macular thickness (μm)			
Mean ± SD	319.1 ± 204.0	332.2 ± 232.7	
95% CI	223.6-416.6	233.9-430.5	
Average macular thickness (μm)			.916
Mean ± SD	379.95 ± 185.4	382.7 ± 195.2	
95% CI	293.1-466.7	300.3-465.2	
6 months			
Central macular thickness (μm)			.874
Mean ± SD	359.6 ± 250.2	347.3 ± 261.2	
95% CI	231.1-466.8	CI: 237.0-457.6	
Average macular thickness (μm)			.942
Mean ± SD	411.0 ± 207.6	406.8 ± 212.6	
95% CI	305.4-501.9	CI: 316.9-496.5	

CI = confidence interval

Table 6. Between-group comparison of secondary postoperative outcomes.

Outcome	Group		*P* Value
	Control	Intervention	
BCVA (logMAR)			.772
Mean ± SD	0.556 ± 0.482	0.574 ± 0.470	
Range	0.0 to 2.0	0.0 to 2.0	
95% CI	0.385-0.727	0.412-0.736	
Postop progression to NVG (n)			.139
No progression	31	35	
Progression	2	0	
Postop laser therapy (n)			.475
Not performed	17	15	
Performed	16	20	
Mean central macular thickness (μm) ± SD	359.6 ± 250.2	347.3 ± 261.2	.874
Mean average macular thickness (μm) ± SD	411 ± 207.6	406.79 ± 212.6	.942

BCVA = best corrected visual acuity; CI = confidence interval

months after cataract surgery. However, the progression rate of maculopathy was significantly lower in the intervention group than in the control group in our study over the 6-month follow-up.

Distinguishing between diabetic macular edema and cystoid macular edema (CME) after cataract surgery in diabetic patients can be difficult, especially in the early postoperative period. However, CME tends to resolve when caused by Irvine-Gass syndrome[32] and progress when caused by diabetes.[19] The predictive value of fluorescein angiography[31] in clearly differentiating between the 2 forms is uncertain, and clinical examination may provide valuable clues. We performed serial OCT examinations rather than fluorescein angiography after surgery because OCT is a more sensitive means of detecting macular topography changes.[33] Although patients in the intervention group had a significantly lower incidence of progression of maculopathy, the central macular thickness and average macular thickness were not statistically significantly different between groups at any postoperative time point. This was reflected in the finding that there was no difference between groups in mean visual acuity during the follow-up period.

Laser photocoagulation for CSME and PDR was performed in both groups during the study period based on ETDRS criterion. Although progression of postoperative DR and maculopathy occurred more frequently in the control group, there was no statistical difference in the rate of laser therapy between groups. This was a reflection of the presence of untreated preoperative retinopathy and maculopathy in both groups in the early postoperative assessment rather than of a progression of diabetic changes. Two eyes in the control group progressed to NVG during the follow-up; no eye in the intervention group progressed to NVG. Laser therapy was performed promptly, especially for CSME, which may explain why both groups had similar visual acuity and CMT during the 6-month follow-up period. However, it has also been observed that after laser photocoagulation for CSME, visual acuity may not improve for a considerable time and OCT may not show any significant change in macular thickness values.[34]

Various case reports[35] and studies[36,37] show the effectiveness of anti-VEGF therapy on retinal neovascularization in patients with DM. Some studies[38,39] document the usefulness of nonspecific antiangiogenic therapy, such as triamcinolone acetonide, injected into the vitreous at the completion of cataract surgery in cases of diabetic maculopathy. Other studies[40–45] report beneficial effects of bevacizumab as an adjuvant or a primary treatment in cases of DR and maculopathy.

Combining the 2 procedures of cataract surgery and intravitreal injection of bevacizumab reduces the potential risk for 2 intraocular episodes to a single episode.

In conclusion, this randomized study suggests that intravitreal administration of 1.25 mg bevacizumab at the time of cataract surgery is safe and effective in preventing the progression of DR and maculopathy in patients with cataract and DR. Progression of DR occurred in 45.45% of eyes in the control group and 11.42% of eyes in the intervention group, and progression of diabetic maculopathy occurred in 51.51% and 5.71%, respectively. Further long-term studies are recommended to realize the full potential of this therapy in diabetic patients having cataract surgery.

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