Original Article

Randomised Controlled Trial to evaluate the effects of Intravitreal Bevacizumab administration on Visual Outcome in Diabetic Patients with Diabetic Macular Edema who Underwent Cataract Surgery

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Purpose: To evaluate the efficacy of a single intravitreal Bevacizumab injection either immediately after cataract surgery or during cataract surgery for the management of postoperative decrease of vision in patients with DME.

Material and Methods: Randomized, controlled, open-label, parallel group study of 60 eyes of 60 patients, having diabetic macular edema and lens opacity (of more than grade 3). The primary end-point was change in BCVA at 6 weeks compared with that at baseline using the Snellens acuity testing charts.

Results: The mean changes in BCVA at 6 weeks compared with that at baseline were a worsening of visual acuity in the control group (no injection) and an improvement of visual acuity in the Bevacizumab group ($p = 0.01$).

Conclusions: Intravitreal Bevacizumab after cataract surgery appears to be beneficial in preventing post- surgical visual loss in eyes with diabetic retinopathy by reducing the chance of macular thickening.

Many studies have revealed that visual outcome following cataract surgery in diabetic patients depends primarily on the status of macular edema[1,2] or Macular ischemia due to diabetes). Previous reports have described many diabetic patients who developed severe maculopathy, following cataract surgery[3]. 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.

Diabetic macular edema has been shown to worsen after cataract surgery,[4-6] although controversy remains as to the incidence of this worsening[7,8]. It has also been suggested that macular edema tends to show actual worsening in eyes afflicted with DR at the time of cataract surgery[9]. Distinguishing transient edema from substantial progression of maculopathy is important to the timing of treatment for the macular edema, including laser photocoagulation,[10] vitrectomy,[11] and triamcinolone injection[12-14]. H owever, until recently, there had been no quantitative study to examine the progression of diabetic macular edema after cataract surgery. A recent study described by Kim et al[15] showed a short-term increase of macular thickness after cataract surgery. It has been suggested that 22% of diabetic patients develop increases in central retinal thickness after uncomplicated phaco-emulsification. The presence of CSME is a strong risk factor for subsequent macular thickening after surgery[15]. Even if the visual prognosis is improved by cataract surgery, macula edema remains a major risk factor for postoperative visual disturbance in diabetic patients.

Treatment to lessen the risk of postoperative macular thickening in individuals with diabetes, laser photocoagulation remains the standard approach[16]. However, it is sometimes difficult to obtain the sufficient efficacy of laser treatment in the cases with dense cataract. Several other trials using intravitreal or sub-tenon's triamcinolone acetonide[17] and pars plana vitrectomy[11] have been conducted, but no widely accepted technique has yet been established.

Vascular endothelial growth factor (VEGF), is considered a key player in the progress of abnormal angiogenesis including DME[18]. Hypoxia induces VEGF gene transcription, and elevated levels of VEGF have been found in ocular fluid of patients with DME[19].

Bevacizumab is a humanized monoclonal antibody that inhibits all isoforms of VEGF[20]. It has been reported that intravitreal injection of bevacizumab yields promising results in various neovascular eye diseases, including age-related macular degeneration,[21] central retinal vein occlusion,[22] and DME[23]. Similar study was carried out by Lanzagorta et al[24] who have shown improvement in the vision and decrease in the retinal thickening in the Bevacizumab group compared to control group.

MATERIAL AND METHODS

Study Design

This trial was a randomized, controlled, open-label, parallel group study. Patients were recruited from the Al Ibraheem Eye Hospital between July 2008 and July 2009. The trial was conducted in conformance with the tenets of the Declaration of Helsinki. Approval was obtained from the Ethics Committee at the Al Ibraheem Eye Hospital, Karachi and each patient provided signed informed consent before study entry.

Subject Selection

Patients 20 years or older of either gender with type 1 or type 2 diabetes were eligible. All patients in the study underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, funduscopy, applanation tonometry and fluorescein angiography (not more than a week old, other wise it was repeated) before recruitment, (because of the unavailability of optical coherence tomography in our institute we were unable to perform this test on all patients, only on few patients who were able to go to other centers for this test were performed); 60 patients with DME, who had significant lens opacity (more than grade 3 for any type of cataract: cortical, nuclear, or posterior sub capsular) by the Lens Opacities Classification System III were recruited for the study[25]. Other inclusion criteria were that DME had occurred 3 to 18 months earlier, macular edema involved the fovea, and best corrected visual acuity (BCVA) was 20/40 or worse.

Exclusion criteria were a history of ocular surgery, inflammation and poor diabetic control, the presence of other ocular diseases, and intra-operative complications such as posterior capsule rupture and severe iris damage. Eyes with proliferative diabetic retinopathy, mixed maculopathy (ischemic and exudative) and also patients having DME due to Epi-retinal membrane or taut posterior hyaloid were also excluded. No patients had undergone photocoagulation of the treated eye within the previous 12 months, and none did so during follow-up. There was no previous intravitreal injection, including any VEGF inhibitors or steroid.

Randomization and Masking

Eyes were allocated to one of two groups (Bevacizumab or control). Neither subjects nor investigators were masked, but those who tested visual acuity, optometrists and statistical analyzers were masked as to treatment assignment of the eyes.

Study Treatment

The operative techniques included complete continuous curvilinear capsulorhexis and phacoemulsification through a 3.5-mm corneoscleral incision with intracapsular implantation of a foldable acrylic intraocular lens followed by a single intravitreal injection of bevacizumab. Bevacizumab was prepared by the institutional pharmacy as sterile filled and packed tuberculin syringes containing 0.05 ml (1.25 mg) bevacizumab, which was injected intra-vitrealy using a 30-gauge needle. Postoperatively, all patients received similar routine medication, including topical application of diclofenac sodium, an antibacterial agent, and 0.1% prednisolone 3 times daily for 3 months after surgery. Eyes in the control group received no injections.

Outcome Measurements and Follow-up

The primary end-point of the trial was a change in BCVA at 6 weeks follow-up, compared with that at baseline. BCVA was assessed by Snellen visual acuity chart. Similarly, resolution in macular edema in fluorescein angiography compared to baseline.

Patients were evaluated at baseline and at 1, 3 and 6 weeks. BCVA, intraocular pressure (IOP), slit-lamp assessment and indirect ophthalmoscopic examination performed at each visit; fluorescein angiography was performed at baseline and 6 weeks follow-up.

Sample Size

30 eyes (assuming a few dropouts) in each group were required to achieve a power of 80% based on an unpaired Student t test with a two-sided significance level of 0.05.

Statistical Analysis

Values are expressed as mean (SD). The significance of the differences between the intervention group and the control group data was assessed by the unpaired Student t test, and that between the pretreatment and post-treatment data within the same group was assessed by the paired Student t test. All statistical analyses were performed SPSS 17.0. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

The study was performed at Al Ibrahim Eye Hospital, Karachi. During the study period, total 60 eyes of 60 patients were examined. All the patients fulfilled the inclusion and exclusion criteria.

Out of 60 patients 32 (53.3%) were males and 28 (46.7%) were females (Table 1).

Age range of patients was 45-83 years. Mean age of the patients was 58.3 years with standard deviation=7.35.

Table 2 shows the distribution of Bevacizumab and control group. There were no significant differences between the groups (Bevacizumab and control) in age, gender and duration of DM, indicating that the baseline characteristics were well balanced. Also, there were no statistically significant differences in BCVA at the baseline. To evaluate postoperative changes we measured it at 1 day before and 1 and 6 weeks after cataract surgery.

Preoperative visual acuity is shown in (Table 3).

Postoperative visual acuity shows that there has been statistically significant difference between the Bevacizumab and control group ($p<0.005$). Most of the patients in Bevacizumab group had postoperative visual acuities above 6/18 with 27 out of 30 having either 6/12 or better compared to only 6 out of 30 in control group having 6/12 or better visual acuity. On the other hand none of the patients in Bevacizumab group had visual acuity lesser than 6/18 while control group has 11 patients having visual acuity lesser than 6/18 (Table 4, 5). Changes in DME between the two groups (on the basis of fluorescein angiography) is shown in figure 1.

Table 1: Gender distribution

	Frequency n (%)
Male	32 (53.3)
Female	28 (46.7)
Total	60 (100)

Table 2: Control or bevacizumab group

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

Table 3: Preoperative vision

	Frequency n (%)
6/24	2 (3.3)
6/36	21 (35)
6/60	28 (46.7)
Fc	8 (13.3)
Hm	1 (1.7)
Total	60 (100)

Table 4: Post operative vision

	Frequency n (%)
6/6	20 (33.3)
6/9	13 (21.7)
6/12	8 (13.3)
6/18	8 (13.3)
6/24	5 (8.3)
6/36	2 (3.3)
6/60	4 (6.7)
Total	60 (100)

Table 5: Post operative vision in control group vs bevacizumab group

Visual acuity	Bevacizumab Group (No. of patients)	Control Group (No of patients)	Total
6/6	18	2	20
6/9	9	4	13
6/12	2	6	8
6/18	1	7	8
6/24	--	5	5
6/36	--	2	2
6/60	--	4	4
Total	30	30	60

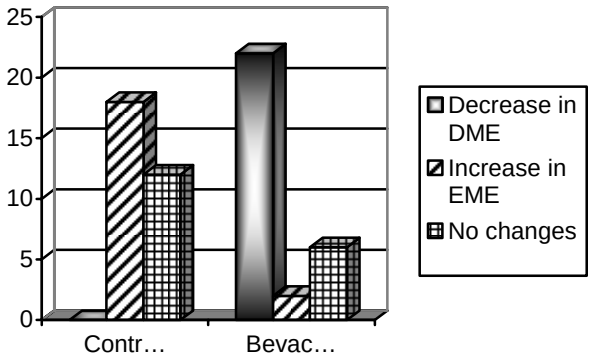

Fig. 1: (Changes in DME in both groups)

DISCUSSION

Many studies have revealed that intravitreal injection of bevacizumab is useful in the management of DME[23,26]. Similarly studies have shown that cataract surgery leads to noticeable thickening of retina, implying that operative invasion enhances retinal vascular permeability, because localized retinal edema is caused by focal leakage from microaneurysms and dilated capillary segments[27]. Many inflammatory mediators such as VEGF cause breakdown of the blood– retinal barrier[28,29]. Patel et al[30] reported that VEGF levels in aqueous sample obtained from DM patients 1 day after surgery were approximately 10-fold higher than those of controls. Bevacizumab inhibits VEGF, which is a potent permeability factor implicated in cystoid macular edema (CME)[29]. Thus, we hypothesized that anti-VEGF therapy would help to prevent the development of macular edema after cataract surgery in DM patients. Similar work was carried out by Lanzagorta et al,[24] who have shown improvement in the vision and decrease in the retinal thickening in the Bevacizumab group compared to control group.

Recently, many studies have shown the clinical effect of intravitreal 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 VA. Similarly, another study, 25 cases of pseudophakic CME after cataract Surgery were investigated, and found a significant improvement in vision and a decrease in macular thickness[32]. However, unlike these studies, Spitzer et al[33] reported that although 81% of patients showed significant improvement in central retinal thickening, visual outcome was not evidently improved. Therefore, the clinical effectiveness of intravitreal bevacizumab for pseudophakic CME remains controversial. These case series excluded diabetic patients, and there were several weeks (approximately 13 weeks) between the day of cataract surgery and intravitreal bevacizumab therapy. In contrast, we injected bevacizumab into the vitreous cavity on the same day as the cataract surgery, immediately after intraocular lens implantation. Our data suggested that the intravitreal injection of bevacizumab was effective in improving vision after cataract surgery in patients having diabetic macular edema.

Based on our results, intravitreal injection of bevacizumab improved BCVA more effectively. The natural course of macular edema after cataract surgery can be self-limiting in some diabetic patients[34]. In fact, the increased retinal thickening at first month tended to show a decrease at third month. This incidence was consistent with the results of intravitreal triamcinolone for DME[35,36]. Among the new treatments, such as corticosteroid and anti-VEGF, drugs, laser photocoagulation remains the standard and the only treatment with proven efficacy in a large clinical trial[10, 16]. Even though we report the effectiveness of bevacizumab, the application of photocoagulation should be considered for the treatment of DME in most of cases with the exception of the dense cataract.

The dose of bevacizumab evaluated in this study was 1.25 mg, which is that used most commonly in clinical practice[21–26]. However, because no dose-ranging studies were done, the ideal intravitreal concentration remains to be determined. Recurrence of

CME is a possibility and may require additional multiple injections of bevacizumab. Although there was no case of recurrent CME in our series, the long-term efficacy is also currently unknown.

In the present study, the change in BCVA at 6 weeks compared with that at baseline (primary end-point) in the Bevacizumab group was statistically significantly less than that in the control group.

One of the limitations of the study described herein is the use of an observation arm as control, rather than a sham injection, thereby making it impossible to ensure that the patient and investigators were masked with regard to treatment. However, this limitation was mitigated by ensuring that the technicians who performed the visual-acuity were masked. Other limitations of this study are that it was performed at a single centre, and that it involved individuals of only one race, factors that limit its generalizability. Although further investigation with a longer follow-up and a larger series of patients may be needed, anti-VEGF therapy may be a potent tool for the treatment of DME after cataract surgery. Bevacizumab contributed to the significant improvement of VA after cataract surgery at 6 weeks. Although a longer follow-up is needed, it is possible that intravitreal bevacizumab has the potential not only to prevent the progression of DME after cataract surgery, but also to improve its severity. Several reports have indicated that intravitreal or posterior sub-Tenon triamcinolone acetonide, or corticosteroid treatment, is also effective for reducing macula thickness in DME[37–40]. Shimura et al[41] compared the effect of an intravitreal injection of bevacizumab with triamcinolone acetonide for DME, and found that the triamcinolone treatment yielded better results in terms of macular thickness reduction and improvement of VA[41]. However, they also found a significant postoperative increase of IOP in the triamcinolone injected eyes, whereas the bevacizumab-treated eyes showed no significant change. Because one of the most important side effects of triamcinolone treatment is elevation of the IOP, bevacizumab may be beneficial for patients who are known steroid responders and who are unresponsive to non-steroidal anti-inflammatory drugs. In our small case series, there was not significant increase of IOP postoperatively, and no eyes showed infection and other severe ocular complications. However, a larger number of cases are needed to verify the safety of bevacizumab treatment.

In summary intravitreal bevacizumab immediately after phacoemulsification or during the cataract surgery prevents exacerbation of the macular edema seen in many diabetic patients undergoing cataract surgery. Results of our study show that patients who have diabetic macular edema before undergoing the cataract surgery, should receive an intravitreal injection of bevacizumab either during the cataract surgery or immediately after it, to improve visual outcome after cataract surgery and to prevent decrease in vision due to increase in macular edema after cataract surgery.

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