ABSTRACT

AIMS: To evaluate the efficacy of a single intravitreal Bevacizumab injection before cataract surgery in patients with diabetic macular edema. METHODS: Randomised, controlled, open-label, parallel group study of 90 eyes of 90, having diabetic macular edema and lens opacity (of more than grade 3). Change in BCVA at 6 weeks compared with that at baseline. Central macular thickness was compared in both groups pre and post operatively. RESULTS: In Bevacizumab group, 86.7% had BCVA of 6/18 or better and decrease in macular thickness (mean 97 microns), while in control group, only 46.7% had BCVA of 6/18 or better and increased macular thickness (mean 30 microns) was observed. CONCLUSIONS: Intravitreal Bevacizumab before cataract surgery appears to be beneficial in preventing post- surgical visual loss in eyes with diabetic retinopathy by reducing the chance of macular thickening. KEYWORDS: BCVA: best corrected visual acuity, DME: diabetic macular edema.

INTRODUCTION
Many studies have revealed that visual outcome following cataract surgery in diabetic patients depends primarily on the status of macular oedema. Previous reports have described many diabetic patients who developed severe maculopathy, following cataract surgery. Because 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, although controversy remains as to the incidence of this worsening. It has also been suggested that macular edema tends to show actual worsening in eyes afflicted with DR at the time of cataract surgery. Distinguishing transient edema from substantial progression of maculopathy is important to the timing of treatment for the macular edema, including laser photocoagulation, vitrectomy, and triamcinolone injection. However, 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 showed a short-term increase of macular thickness after cataract surgery. It has suggested that 22% of diabetic patients develop increases in central retinal thickness after uncomplicated phacoemulsification. The presence of CSME is a strong risk factor for subsequent macular thickening after surgery. 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 may recover visual outcomes in similar individuals with diabetes. Laser photocoagulation remains today the standard approach for treating DME. However, it is sometimes difficult to obtain the sufficient efficacy of laser treatment in the cases of dense cataract. Several other trials using intravitreal or sub-Tenon triamcinolone acetonide, and pars plana vitrectomy 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. Hypoxia induces VEGF gene transcription, and elevated levels of VEGF have been found in ocular fluid of patients with DME.

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

In this study, Bevacizumab is injected into the vitreous cavity immediately after phacoemulsification and intraocular lens implantation is performed in diabetic patients with CSME, and progression of DME was assessed by clinical examination and visual acuity testing.

METHODS

This trial was a randomized, controlled, open-label, parallel group study. Patients were recruited from the Al Ibrahim Eye Hospital between July 2008 and July 2010. The trial was conducted in conformance with the tenets of the Declaration of Helsinki. Approval was obtained from the Ethical Committee at the Al Ibrahim Eye Hospital, Karachi and each patient provided signed informed consent before study entry. 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, optical coherence tomography and fluorescein angiography before recruitment; 90 patients with DME who had significant lens opacity (more than grade 3 for any type of cataract: cortical, nuclear, or posterior subcapsular) by the Lens Opacities Classification System III was used to grade the cataract. Other inclusion criteria included DME and macular edema involving the fovea. Exclusion criteria included any history of ocular surgery and inflammation, the presence of other ocular diseases, and intraoperative complications such as posterior capsule rupture and severe iris damage. Also, eyes with proliferative diabetic retinopathy were excluded. No patients had undergone photoacoagulation 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. Systematic randomized sampling was done by allocating every alternate eye into the control group or either bevacizumab group (i.e. 1st eye was included in the bevacizumab group while the 2nd in control, similarly 3rd eye into bavacezumab again). Neither subjects nor investigators were masked, but those who tested visual acuity, technicians who performed OCT, optometrists and statistical analyzers were masked as to treatment assignment of the eyes.

A single intravitreal Bevacizumab injection or sham injection was given to Bevacizumab group or control group respectively, 2 days before the cataract extraction surgery was planned. Bevacizumab was prepared by the institutional pharmacy as sterile fluid and packed tuberculin syringes containing 0.05 ml (1.25 mg) bevacizumab, which was injected intravitreally using a 30-gauge needle. 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. 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.

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. OCT was performed at baseline that is before injection was given and after 6 weeks of cataract surgery. Patients were evaluated at baseline and at 1, 3 and 6 weeks. BCVA, intraocular pressure (IOP), slit-lamp assessment and indirect ophthalmological measurements performed at each visit; fluorescein angiography was performed at baseline and 6 weeks follow-up. 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 analysis were performed on 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 90 eyes of 90 patients were examined. All the patients fulfill the inclusion and exclusion criteria. Out of 90 patients 41 (45.6%) were males and 49 (54.4%) were females.

Age range of patients was 45-83 years. Mean age of the patients was 58.1 years with standard deviation=.
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.

Postoperative visual acuity shows that there has been an statistically significant difference between the Bevacizumab and control group (p<0.005). Most of the patients in Bevacizumab group has postoperative visual acuities above 6/18 with 39 out of 45 (86.7%) having either 6/12 or better compared to only 21 out of 4 (46.7%) in control group having 6/12 or better visual acuity. On the other hand none of the patients in Bevacizumab group has visual acuity lesser than 6/18 while control group has 13 patients have visual acuity lesser than 6/18.

Comparison of pre and postoperative changes in visual acuity in both groups are shown in Figure 1 and 2.

Optical coherence tomography showed that mean central macular thickness increased from 290 microns to 320 microns in the control group, while the mean central macular thickness decreased 302 microns to 205 microns in the Bevacizumab group.

Only 11 eyes out of 90 developed subconjunctival hemorrhage as a complication of this injection. Raised intraocular pressure was noted in only 2 eyes in Bevacizumab group. No other complications noted during the study. Comparison of preoperative and postoperative central macular thickness in both groups is seen in figure-3.

**DISCUSSION**

Many studies have revealed that intravitreal injection of bevacizumab is useful in the management of DME. 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. Many inflammatory mediators such as VEGF causes breakdown of the blood–retinal barrier. 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, who have shown improvement in the vision and decrease in the retinal thickening in the Bevacizumab group compared to control group. 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 2 days before the cataract surgery. 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, also resulted in much decrease in central macular thickness. Among the new treatments, such as corticosteroid and anti-VEGF, drugs clinically available for DME, laser photocoagulation remains the standard and the only treatment with proven efficacy in a large clinical trial.\textsuperscript{10,11} The dose of bevacizumab evaluated in this study was 1.25 mg, which is that used most commonly in clinical practice.\textsuperscript{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.

One of the 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 before 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 decreases DME. 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.

CONCLUSION

In conclusion, Intravitreal bevacizumab injection before phacoemulsification not only prevents exacerbation of the macular edema in patients with diabetic macular edema but it reduces macular edema as well. Thus improving post operative vision significantly.

REFERENCES