Pre-Operative Intravitreal Injection of Bevacizumab In Patients With Diabetic Macular Edema Undergoig Phacoemulsification

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ABSTRACT

Background: Diabetes is a common disease worldwide. The most common cause of decrease vision in diabetics is diabetic macular edema. Cataract develops early in diabetics in comparison to normal population. Phacoemulsification is associated with aggravating macular edema in diabetes. Bevacizumab is anti-VEGF used for the treatment of diabetic macular edema.
Objective: To determine that pre-operative intravitreal injection of bevacizumab prevents increase in diabetic macula edema and help in improvement of macular edema on optical coherence tomography (OCT).
Material and Methods: The study was conducted in Bacha Khan Medical Complex swabi from March 2017 to February 2019.
Results: A total of 120 patients were included in the study with 68 male and 52 female patients with mean age of 58.74 ± 4.82. In all patients there was no futher increase in diabetic macular edema documented on OCT post-operatively after pre-operative intravitreal injection of bevacizumab.
Conclusion: Pre-operative intravitreal anti-VEGF prevents the aggravation of diabetic macular edema and results an improvement in macular thickness on optical coherence tomography.
Keywords: *Intravitreal, Bevacizumab, Diabetic macular edema, Phacoemulsification.*

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INTRODUCTION

Diabetes is a common disease of working population worldwide affecting 200 million people in 2010 and this figure is expected to rise by 62% by the year 2025[1]. Diabetic retinopathy is a major micro vascular complication of diabetes. The most common cause of decrease visual acuity in diabetic patients is diabetic macular edema[2]. Studies have shown the prevalence of diabetic macular edema in type I diabetes is 4.2 to 7.9% and type II diabetes; it ranges from 1.4-12.8%[3]. Diabetes causes micro vascular changes in the retina leading to damage to vascular endothelium which in turn make the vessels leaky and the fluid accumulate in extracellular space resulting in macular edema. Cataract is another complication of diabetes affecting about 20% of diabetic patients needing phacoemulcification[4].

Diabetic macular edema at the time of phacoemulsification is bad prognostic factor for visual recovery and Royal college guidelines suggest that it should be treated before surgical intervention[5]. Studies suggest that there is increased risk of aggravation of diabetic macular edema after phacoemulsification by more than 30% as measured on optical coherence tomography[6,7]. After phacoemulsification and intraocular IOL implantation there are release of various inflammatory factors like cytokines, vascular endothelial growth factors (VEGF), interleukin 1 and epithelial derived growth factors responsible for the increase in diabetic macular edema[8]. Amongst these pro inflammatory factors vascular endothelial growth factors (VEGF) are the most important one making the vessels leaky resulting in increase in diabetic macular edema[9].

Bevacizumab is a monoclonal antibody and is a form of anti-vascular endothelial growth factors which blocks all forms of VEGF-A, resulting in decrease in VEGF in diabetic patients post-operatively and prevents the progression of diabetic macular edema[10]. Studies have shown that pre-operative intravitreal injection of Bevacizumab results in improvement in diabetic macular edema.

The purpose of the study is to determine the stability or improvement of diabetic macular edema after phacoemulsification measured on optical coherence tomography with pre-operative intravitreal injection of 1.25mg of Bevacizumab.

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MATERIALAND METHODS

The study was conducted in the department of ophthalmology Bacha Khan Medical Complex (Gajju Khan Medical College) Swabi from March 2017 to February 2019.

Study Design: Quasi experimental study

Inclusion Criteria:

1. Diabetic patients with diabetic macular edema with cataract were included in the study.
2. Patients in whom diabetic macular edema can be assessed on fundoscopy and optical coherence tomography.

Exclusion criteria:

1. Patients with dense cataracts or vitreous pathology precluding retinal view were excluded from the study as in such patients a good quality OCT scan can not be done and quantitative assessment of macular edema would not be possible.
2. Patients with tractional bands due to diabetic retinopathy were excluded from the study due to the potential aggravation of traction on the retina after injection with bevacizumab.

Data Collection:

Patients were enrolled from the inpatients admitted in Bacha Khan Medical Complex Swabi with diabetes and clinically diabetic macular edema with cataract for phacoemulsification from March 2017 to February 2019. A total of 120 patients were included in the study after taking written informed consent. All patients' were subjected to detailed ocular examination including visual acuity, best corrected visual acuity, slit lamp examination of anterior segment and posterior segment with the help of 78D lens. Patients with cataract and diabetic macular edema were included in the study in which the fundus view permit the visualization of macular edema and OCT can be done. All patients were advised pre-operative OCT (Spectralis Heidelberg Engineering, Germany) to quantitatively assess the amount of macular edema. Patients received intravitreal injection of Bevacizumab 1.25mg in 0.5 ml suspension 4 mm from the limbus one week before phacoemulsification under topical Proxymetacaine hydrochloride (Alcaine) eye drops as anesthetics. Topical tobramycin eye drops were drops were given for 5 days after injection. After one-week Patient's underwent phacoemulsification by an expert ophthalmologist under topical anesthesia (Proxymetacaine hydrochloride) eye drops and a single piece intraocular lens was implanted in the bag. Post operatively patients were given a combination of moxifloxain and dexamethasone eye drops 6 times a day for first week and then in tapering doses till 4 weeks. After 4 weeks post-operatively OCT scan was repeated in all patients to document the changes in macular edema and compared with pre-operative macular OCT. All the data is entered in a proforma and pair t-test was done for comparison.

RESULTS

A total of 120 patients were included in the study with mean age of 58.74 $\pm$ 4.82 years (Age range 47 years to 72 years). 68 (56.66%) were male and 52 were female (43.33%). Most of the patients visual acuity were in the range of 6/24 (20.83%) and 6/36 (22.50%). Majority of the patients with diabetic macular edema were in the stages of moderate to severe NPDR and PDR. Four weeks post-operative OCT showed not only stabilization of macular edema but also a decrease in central macular thickness in all patients. Severe pre-operative macular edema was found in proliferative diabetic retinopathy stage (327.28 + 22.69 microns) than earlier stages of retinopathy. One month post-operatively there is significant improvement in macular edema in Non-proliferative stages of diabetic retinopathy but no obvious improvement in proliferative stage, though there was no further deterioration than pre-operative thickness in proliferative diabetic retinopathy (327.28 $\pm$ 22.69 microns pre-operatively vs 316.52 $\pm$ 32.72 microns post-operatively).

By comparing the macular thickness OCT in pre-operative and 4 weeks post-operatively it was evident that there was not a significant difference in improvement of macular thickness in mild non-proliferative diabetic retinopathy and proliferative diabetic retinopathy though it remained stabilized (p-value >0.05). In moderate and severe non-proliferative diabetic retinopathy there was a significant improvement in macular edema on OCT after 4 weeks of intravitreal injection of bevacizumab (p-value <0.05).

Table No I. Patients distribution according to visual acuity

Visual Acuity	Number of patients	Percentage
6/12	12	10.00%
6/18	17	14.16%
6/24	25	20.83%
6/36	27	22.50%
6/60	18	15.00%
Counting figures	21	17.50%

Table No II . Stages of Diabetic Retinopathy with macular edema on pre - operatively

Stage of DR	Number of patients	Average macular thickness on OCT (microns)	Percentage
Mild NPDR	12	285.43 ± 18.62	10.00%
Moderate NPDR	38	304.20 ± 21.35	31.66%
Severe NPDR	39	302.72 ± 24.58	32.50%
PDR	31	327.28 ± 22.69	25.83%
Total	120		100%

NPDR= Non -Proliferative Diabetic Retinopathy, PDR= Proliferative Diabetic Retinopathy

Table No III . One month Post -operative changes in macular thickness on OCT (Microns)

Stage of DR	Number of patients	Average macular thickness of OCT (Microns)	Percentage
Mild NPDR	16	274.38 ± 21.46	13.33%
Moderate NPDR	45	286.74 ± 23.38	37.50%
Severe NPDR	35	292.65 ± 26.43	29.10%
PDR	26	316.52 ± 32.72	21.66%
Total	**120**		**100%**

NPDR= Non -Proliferative Diabetic Retinopathy, PDR= Proliferative Diabetic Retinopathy, OCT= Optical Coherence Tomography

Table IV. Comparison of mean change in macular thickness on OCT (microns) before and after phacoemulsification

Stage of DR	Pre-operative average macular thickness on OCT (Microns)	Post-operative average macular thickness on OCT (Microns)	p-value
Mild NPDR	285.43 ± 18.62	274.38 ± 21.46	0.11
Moderate NPDR	304.20 ± 21.35	286.74 ± 23.78	0.04
Severe NPDR	302.72 ± 24.58	292.65 ±26.43	0.05
PDR	327.28 ± 22.69	316.52 ± 32.72	0.05

NPDR= Non -Proliferative Diabetic Retinopathy, PDR= Proliferative Diabetic Retinopathy, OCT = Optical Coherence Tomography

DISCUSSION

Anti-VEGF is recommended treatment for diabetic macular edema worldwide[11]. In diabetic macular edema there is release of vascular endothelial growth factors resulting in thickening of endothelial basement membrane and loss of pericyte[12]. As a consequence there is exudation of fluid to the extracellular spaces resulting in diabetic macular edema. Phacoemulsification is associated with an increase in macular edema due to the release of certain inflammatory

mediators like interleukins and cytokines along with vascular endothelial growth factors. For this reason some surgeon prefer intravitreal triamcinolone but it is associated with well-known complication of raised intraocular pressure post-operatively[13]. Our study showed that pre-operative intravitreal injection of Bevacizumab is associated with significant reduction in central macular thickness due to its anti-VEGF effect. Chen et al obtained similar results and used to give peri-operative intravitreal injections of Bevacizumab to patients with diabetic macular edema at the end of phacoemulsification[14]. Patel et al proposed that post operatively there is release of increase amount of VEGF leading to aggravation of diabetic macular edema[15]. Luminex technology was used by Muether et al to measure the amount of VEGF in aqueous humor and concluded that the concentration of VEGF falls to base line after 33 days post-operatively[16]. Our study results were almost similar to the study carried out by Takamura et al who proposed that 1.25 mg of intravitreal Bevacizumab not only prevent the progression of diabetic macular edema after phacoemulsification but was also associated with a decrease in macular edema[17]. Some authors suggest administration of intravitreal anti-VEGF at the conclusion of surgery where as some propose pre-operative administration of these injections[18].

In patients with proliferative diabetic retinopathy with macular edema the ideal treatment is Anti-VEGF and Pan retinal photocoagulation but in the presence of cataract laser treatment is not possible due to poor fundus view. So Intravitreal Bevacizumab is a better option in such patients to prevent the aggravation of post-operative diabetic macular edema.

CONCLUSION

Patients with diabetic macular edema, phacoemulsification is a risk factor for aggravating macular edema. Pre-operative intravitreal injection of bevacizumb is associated with decrease in the progression and improvement of diabetic macular edema post-operatively.

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