Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Analyzing the Effect of Single Intraoperative Intravitreal Bevacizumab on Central Macular Thickness in Diabetes Mellitus Patients Undergoing Phacoemulsification Under Local Anesthesia

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Abstract

Aim: The aim of the study was to assess the effect of combined phacoemulsification and single intraoperative intravitreal injection of bevacizumab on the central macular thickness (CMT) in diabetic patients.

Materials and Methods: A prospective observational study was conducted on 30 eyes with diabetic retinopathy from February 2018 to February 2019. All patients underwent thorough ophthalmic evaluation. Phacoemulsification performed by a single surgeon using either 0.5% topical proparacaine eye drops or sub-tenon local anesthesia as per the preference of the surgeon in individual case. Bevacizumab 0.05 ml (1.25 mg) was injected intravitreal using a 30-gauge needle through the pars plana into the vitreous cavity after intraocular lens implantation. Patients were followed postoperatively at day 1 then at 1 week and 1 month, respectively, for recording the CMT and best corrected visual acuity at 1 month postoperatively.

Results: The mean CMT for all the patients at post-operative day 1 and month 1 was 277.96 ± 142.40 μm and 289.50 ± 155.74 μm, respectively. Patients with <10 years of diabetes had mean CMT of 329.09 μm and 318.90 μm, at post-operative day 1 and at 1 month, respectively, while those with diabetes more than 10 years had mean CMT of 248.36 μm and 272.47 μm, respectively. In mild non-proliferative diabetic retinopathy (NPDR) and stable proliferative diabetic retinopathy group no significant worsening occurred in CMT thickness, while in moderate NPDR, four out of 13 cases showed significant increase in CMT (>10%) at 1 month. In severe NPDR, out of 4 cases 1 case showed significant increase in CMT while other three cases showed modest reduction of CMT.

Conclusion: Intravitreal administration of 1.25 mg bevacizumab at the time of cataract surgery is a safe and effective way in avoiding new onset maculopathy in diabetic retinopathy patients. It is also effective to treat pre-existing clinically significant macular edema and prevent its progression to some extent in few cases.

Key words: Anti-VEGF, Central retinal thickness, Diabetic maculopathy, Intravitreal bevacizumab, Optical coherence tomography, Phacoemulsification

INTRODUCTION

Phacoemulsification is one of the most common surgical procedures for cataract.[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] Diabetes mellitus has been linked to increased risk of postoperative macular edema.[3]

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www.ijss-sn.com

Month of Submission : 03-2020
Month of Peer Review : 04-2020
Month of Acceptance : 05-2020
Month of Publishing : 05-2020

The pathogenesis of these complications may be related to the changes and rise in the concentration of angiogenic factors in response to surgical trauma and inflammation.[4] The most relevant angiogenic factor is vascular endothelial growth factor (VEGF).[5] According to Patel *et al.*[6] raised VEGF levels in aqueous sample obtained from diabetic

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patients 1 day after surgery approximately was noted to be 10 times higher than those of controls.

There is an important role of angiogenic factors such as VEGF in progression of diabetic macular edema (DME). Hence, the advent of anti-VEGF therapies in prophylaxis and treatment of post-cataract surgery DME has gained much interest.

Cataract surgery provides the ideal setting for administration of intravitreal medications in a sterile surgical field. Intravitreal injections of bevacizumab (Avastin) have been employed for the treatment of neovascular and exudative ocular diseases since 2005.[7]

Bevacizumab (Avastin) is a recombinant full-length humanized monoclonal antibody (149 kDa), which binds to the receptor binding domain of all isoforms of VEGF-A. The recommended dose is 1.25 mg intravitreally every 4 weeks. Bevacizumab can penetrate all layers of the retina. After intravitreal injection, its vitreous half-life is 9.8 days, and plasma half-life is 17–21 days.[8]

Optical coherence tomography (OCT) has been shown to be highly reproducible in measuring macular thickness in normal individuals and diabetic patients. It is an objective, non-contact, non-invasive, well tolerated, and highly reproducible method for quantitative retinal thickness measurements, with good reproducibility, and with approximately 10 μm resolution. OCT is a well-established method of analyzing the *in vivo* retinal architecture. OCT is the single most important diagnostic and prognostic tool in the management of DME.[9]

There is growing evidence in support of a more interventional approach. A shift in attitude toward earlier cataract extraction in diabetes mellitus has contributed to an improved visual outcome. In the present study, we evaluated the efficacy of intravitreal injection of bevacizumab after the phacoemulsification in patients with stable diabetic retinopathy without a present or history of DME.

MATERIALS AND METHODS

A prospective observational study, conducted from February 2018 to February 2019. The estimated minimum sample size given by statistician was 30 cases.

Inclusion Criteria

The following criteria were included in the study:

- Sight-limiting cataract in diabetic patients with poor fundus view precluding adequate monitoring and/or laser therapy.
- Diabetic patients with non-proliferative diabetic retinopathy (NPDR) and stable proliferative diabetic retinopathy (PDR) according to the established criteria by the Early Treatment Diabetic Retinopathy Study (ETDRS).
- Adequate metabolic control for at least 2 months before the procedure considered as having glycosylated hemoglobin (HbA1c) with figures equal to or below 7.
- Arterial blood pressure control was defined as below 140/90 mmHg during at least three visits before the operation.

Exclusion Criteria

The following criteria were excluded from the study:

- Diabetic patients who have previously received grid/focal laser, steroid implants, anti-VEGF, etc., for diabetic retinopathy in past 3 months.
- Diabetic patients with tractional retinal detachment involving macula, active PDR, vitreous hemorrhage, etc.
- Other macular pathologies affecting vision such as age-related macular degeneration (wet ARMD), choroidal neovascular membrane, and macular edema secondary to vascular occlusion.
- Patients with inadequate metabolic control, kidney failure, uncontrolled high arterial blood pressure, recent myocardial infarction, and cerebral vascular accident.
- Cases with optic nerve diseases, glaucoma, and ocular hypertension and uveitic patients.
- Cases complicated with posterior capsular tear and vitreous loss during cataract surgery.

Methodology

All the patients with known diabetes and visually significant cataract were selected based on the inclusion criteria. A detailed history, the fasting and postprandial blood sugar levels, HbA1c level, and blood pressure were recorded for all the patients.

Patients underwent a detailed ophthalmic evaluation including Snellen best corrected visual acuity and slit lamp evaluation of the anterior segment was done to know the lenticular status of the eye and to rule out the presence of any rubeosis. Other details regarding the status of the cornea, iris, and anterior chamber were also noted. Comprehensive dilated fundus examination was carried out using slit lamp biomicroscopy with the help of a 90D/78D lens and indirect ophthalmoscopy using a 20D condensing lens. Details regarding the fundus were noted and diagrams drawn for the same. Fundus photos were taken using Topcon TR50EX retinal camera if required in selected cases.

In cases in which fundus details were obscured by the density of the cataract, retinopathy grading was based on the 1st post-operative day examination. Grades of retinopathy were defined according to the Wisconsin epidemiologic study of diabetic retinopathy and clinically significant macular edema (CSME) was classified based on the ETDRS.

A-scan biometry noting axial length of eye and intraocular lens power calculation, measurement of macular thickness with spectral domain OCT was done. If macular thickness measurement was not possible by OCT because of hazy view secondary to the cataractous lens, then OCT was done on the immediate 1st post-operative day.

The Institutional Review Board approved all aspects of this investigation, and all subjects gave informed consent before enrollment in this study. The consent forms were explained in patients own vernacular language.

Operative Details

All phacoemulsification procedures were performed by a single surgeon using either 0.5% topical proparacaine eye drops or sub-Tenon local anesthesia as per the preference of the surgeon in individual case.

Patients' eyes were prepped and sterilized, 2.8 mm microkeratome clear corneal incision was done. Two corneal stab wounds were done using 20 gauge MVR blades. Capsulorhexis was done followed by hydro-dissection and stop and chop/direct chop phacoemulsification of the nucleus.

Foldable single piece intraocular lense (IOL) was implanted in the bag. Bevacizumab 0.05 ml (1.25 mg) was injected intravitreal using a 30-gauge needle through the pars plana (3.0–3.5 mm from the limbus) into the vitreous cavity. Subconjunctival injection of gentamicin + dexamethasone was given at the completion of surgery.

All eyes were treated postoperatively with combination of gatifloxacin 0.3% and prednisolone acetate 1% eye drops 8 times daily for 1st week then 6 times daily for 2 weeks and then tapered as 4 times daily for 2 weeks and 2 times daily for next 2 weeks.

Patients were followed postoperatively at day 1 then at 1 week and 1 month respectively for recording the CMT and best corrected visual acuity at 1 month postoperatively.

In the present study, all data were compiled and analyzed statistically by Cramer's V Test (Cross tablulations), Chi-square test, Paired-Samples *t*-test, and Repeated measure ANOVA. All the statistical methods were carried out through the SPSS for Windows (version 23.0).

$P \leq 0.05$ was considered to be statistically significant.

RESULTS

Thirty eyes of 27 patients with DR were studied and followed up for a period of 1 month. The study participants were in the age group of 43–82 years. Majority of patients were in the age group of 61–70 years. The mean age ± standard deviation (years) was 61.167 ± 8.77333.

Ninteen of 30 eyes in the study population were having history of diabetes for more than 10 year duration. Moderate NPDR was most frequent both overall and in >10 year diabetic age group. Mild NPDR was the most common type of retinopathy in <10 years diabetic age group. Stable proliferative diabetic retinopathy is seen in >10 year diabetic age group only [Figure 1].

Central Macular Thickness (CMT) Distribution

At day 1 postoperatively, the study participants were grouped according to the CMT as, Group 1 with CMT <250 μ and Group 2 with CMT value ≥250 μ 18 patients had CMT <250 μ, and in 12 patients it was >250 μ.

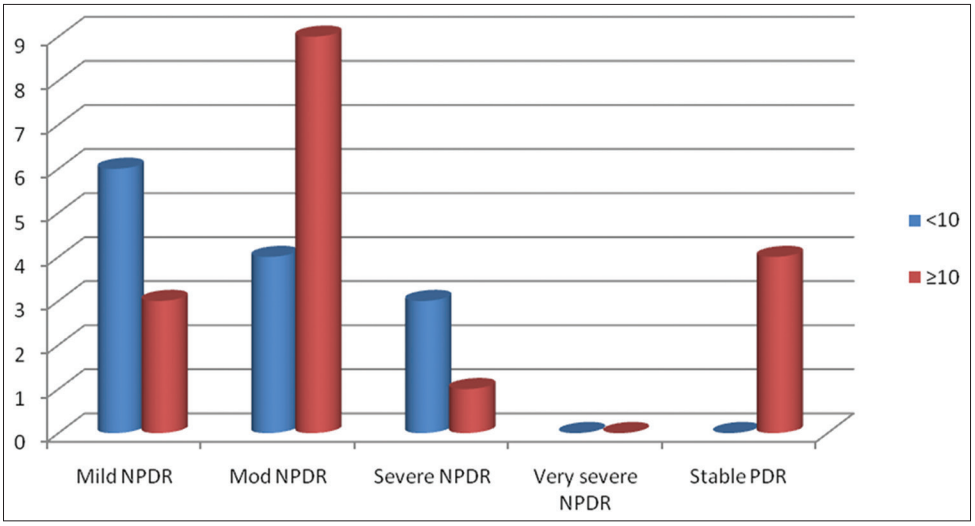

Figure 1: Duration and severity of diabetes mellitus in the study population

Change in Mean CMT at 1 Month in <250 μ and >250 μ CMT Group

The change in mean CMT is depicted in Table 1 and 2. The mean CMT for all the patients at post-operative day 1 and month 1 was 277.96 ± 142.40 and 289.50 ± 155.74, respectively.

In <250 μ CMT group, 33.33% cases showed decrease, another 33.33% cases showed no change, and remaining 33.33% cases showed increase in CMT which was <10%.

While, in >250 μ group, 58.4% cases showed increase CMT, of which in 41.7% cases the increase was >10%, while 41.7% cases showed decrease in CMT at 1 month postoperatively [Table 3].

Diabetic Age versus CMT at 1 Month

Duration of diabetes was correlated with change in CMT at 1 month.

<10 years diabetes had a mean decrease of 10.19 μm value while those with diabetes of ≥10 year duration had a mean increase of 24.11 μm at 1 month postoperatively [Table 4].

Levels of Retinopathy versus Mean CMT at 1 Month

The level of retinopathy at baseline was correlated with mean CMT at 1 month.

In mild NPDR and stable PDR group, no significant worsening occurred in CMT thickness.

While in moderate NPDR 4 (i.e., 13.33%), of 13 cases showed significant increase in CMT (>10%) at 1 month.

Table 1: <250 μ CMT group (Group 1)

CMT	Mean±SD	*P* value
Day 1	193.72±30.30	0.179
Month 1	194.22±32.05	

standard deviation

Table 2: >250 μ CMT group (Group 2)

CMT	Mean±SD	*P* value
Day 1	404.33±151.68	0.194
Month 1	432.41±158.83	

standard deviation

Table 3: Change in macular thickness at 1 month postoperatively

Column1	<250 μ CMT group	>250 μ CMT group
<10% increase	33.30%	16.70%
>10% increase	33.30%	41.70%
Decrease	0	41.70%
No change	33.33%	0
Total	100	100

In severe NPDR, of 4 cases 1 case showed significant increase in CMT while other three cases showed modest reduction of CMT [Table 5].

DISCUSSION

Diabetic patients pose a challenge due to their early formation of cataracts and propensity to develop macular edema after cataract surgery. Macular edema is a leading cause of an unfavorable visual outcome in patients with diabetes, especially in patients with pre-existing diabetic retinopathy. The most relevant angiogenic factor is VEGF. According to Patel *et al.*[6] raised VEGF levels in aqueous sample obtained from diabetic patients 1 day after surgery approximately was noted to be 10-times higher than those of controls.

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.

In the present study, those with <10 years diabetes had a mean decrease of 10.19 μm value while those with diabetes of ≥10 year duration had a mean increase of 24.11 μm at 1 month postoperatively.

A study was done by Kim *et al.*[9] to assess the incidence or progression of macular edema after cataract surgery in diabetic patients where all the patients were with normal center point thickness. In their study, they found that those with diabetes duration of ≥10 years had an increase of center point thickness at 1 month of 83 μm, whereas the group with <10 years' duration had an increase of only 18 μm at 1 month postoperatively.

Table 4: Diabetic age versus CMT at 1 month

Diabetic age (years)	Mean CMT		*P* value
	Day 1	Month 1	
<10	329.09	318.9	0.508
≥10	248.36	272.47	

Table 5: Levels of retinopathy versus mean CMT at 1 month

Level of retinopathy	Mean CMT		*P* value
	Day 1	Month 1	
Stable PDR	172.5	166	0.716
Mild NPDR	282.7	282.7	
Moderate NPDR	256.46	286.23	
Severe NPDR	496	491	

In the present study, those with ≥10 year diabetic age group out of 19 cases two cases showed loss of at least one line and two more cases there was no change in Visual Acuity (VA) and the rest 15 cases showed improvement of ≥2 lines of VA (with $P < 0.05$) while all patients with diabetic age <10 year gained ≥3 lines ($P = 0.00$).

Kim *et al.*[9] also showed that the group with diabetes of ≥10 years had a modest gain of 1 line (0.10 log MAR units) of VA at 1 month, whereas the group with duration <10 years gained more than 2 lines (0.24 log MAR units) of VA ($P = 0.04$).

In the present study, in mild NPDR and stable PDR group no significant worsening occurred in CMT thickness and all showed improvement in visual acuity of ≥3 lines on Snellen visual acuity chart at 1 month. While in moderate NPDR 4 (i.e., 13.33%), of 13 cases showed significant increase in CMT (>10%) at 1 month. The findings of this study agrees with the published reports of Pollack *et al.*[10] and Malecaze *et al.*[11] who showed that level of diabetic retinopathy is a risk factor for thickening of the retina after cataract surgery. Kim *et al.*[9] in their study showed that the group with moderate or severe NPDR or proliferative diabetic retinopathy had the largest increase in center point thickness of 145 μm at 1 month after surgery, which was correlated inversely with VA improvement thus patients in these groups showed least improvement from baseline, of <1 line (0.08) of VA at 1 month after surgery.

In present study, progression of maculopathy occurred in 16.65% of the eyes at the end of 1 month. Cheema *et al.*[12] have reported that progression of diabetic maculopathy occurred in 51.51% of eyes that did not receive intravitreal bevacizumab (control group) and 5.71% of eyes that did receive intravitreal bevacizumab (intervention group) after cataract surgery with IOL implantation.

Kim *et al.*[9] demonstrated that 22% of diabetic patients developed increases in center point thickness of >30% at 4 weeks after uncomplicated phacoemulsification. While in the present study in <250 μ CMT group 2/3rd cases showed either reduction or no change and in remaining 1/3rd of the cases the increase was <10% at 1 month postoperatively.

We Acknowledge Some Limitations to Our Study

1. Small sample size and short duration of follow-up, which precludes the determination of the long-term safety and efficacy of prophylactic use of bevacizumab combined with phacoemulsification.
2. Control group was not included.

CONCLUSION

1. Intravitreal administration of 1.25 mg bevacizumab at the time of cataract surgery is a safe and effective way in avoiding new onset maculopathy in diabetic retinopathy patients.
2. It is also effective to treat pre-existing CSME and prevents its progression to some extent in few cases.

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How to cite this article: Sathyamurthy G, Kayoom NMA, Mahajan PS, Lima V, Kavitha T, Manjusha PV. Analyzing the Effect of Single Intraoperative Intravitreal Bevacizumab on Central Macular Thickness in Diabetes Mellitus Patients Undergoing Phacoemulsification Under Local Anesthesia. Int J Sci Stud 2020;8(2):1-5.

Source of Support: Nil, **Conflicts of Interest:** None declared.