e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(1); 854-858

Original Research Article

Role of Intravitreal Bevacizumab on Visual Acuity and Central Macular Thickness in Diabetic Macular Edema and Cataract

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Received: 25-10-2023 / Revised: 23-11-2023 / Accepted: 26-12-2023
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Conflict of interest: Nil

Abstract:

Aim: To evaluate the role of intravitreal Avastin (Bevacizumab) on visual acuity and CMT in diabetic macular edema and cataract in a tertiary Eye Hospital in Eastern India

Methods: Diabetics with cataract and macular edema were divided into 2 groups. First group(n=17)underwent phacoemulsification and injection Avastin, the other group (n=14), phacoemulsification and SHAM injection. Both groups received focal photocoagulatin after 1 month.

Results: At 3 months Avastin group showed significant improvement in BCVA and CMT while non Avastin group showed only significant improvement in BCVA($p<0.05$). Patients in Avastin group showed better results in CMT and BCVA but the comparison with the non Avastin groups were statistically insignificant. For BCVA($p=0.883$) and CMT($p=0.184$).

Conclusion: Intravitreal Avastin has no statistically significant role in diabetic macular edema with cataract when other standardized therapy like focal photocoagulation was combined.

Keywords: Diabetic macular edema (DME), Bevacizumab (anti Vascular Endothelial Growth Factor OR anti VEGF), Central macular thickness (CMT), Best corrected visual acuity (BCVA), Ocular coherence tomography (OCT), focal photocoagulation (Focal PHC), Early Treatment Diabetic Retinopathy Study (ETDRS).

Introduction

Cataract is one of the well-recognized ocular complication of diabetes and it has been estimated that up to 20% of all cataract surgeries are performed on diabetics [10]. Diabetic macular edema is a vision threatening complication in diabetic retinopathy and a therapeutic challenge for the ophthalmologist [1].

Both cataract and clinically significant macular edema (CSME) and are leading causes of decreased vision in patients with diabetes. Diabetic macular edema is a major cause of central vision loss, resulting from excessive vascular permeability and subsequent leakage of fluid and plasma constituents such as lipoproteins, into the retina, thereby leading to subsequent retinal thickening [6].In diabetic patients, progression of clinically significant macular edema after cataract surgery frequently can be observed, especially in patients with pre-existing diabetic retinopathy and DME [13].

Macular laser photocoagulation is also a well-known effective treatment modality in CSME (clinically significant macular edema).[10] However, effective macular photocoagulation may be difficult to perform in some patients with diabetes with CSME when there is a co-existing cataract. Even uneventful cataract surgery demonstrated exacerbation of the macular edema in patients with diabetes. [6,7] Therefore, the management of CSME may be more difficult in such patients with diabetes if they first undergo phacoemulsification.

Recently, investigators have considered combining alternative treatment modalities for CSME such as intravitreal corticosteroids and antivascular endothelial growth factor agents with phacoemulsification in patients with co-existing CSME. VEGF (vascular endothelial growth factor) is considered a key player in the development of abnormal angiogenesis including diabetic macular edema [2]. Hypoxia induces VEGF gene transcription and elevated level is seen in ocular fluid in DME3. Intravitreal Bevacizumab an anti-VEGF agent used for the treatment of DME. [8, 9, 10] The ETDRS Study 1showed a significant benefit of focal laser photocoagulation for eyes with CSME.

Based on this background our study was conducted with an aim to evaluate the role of intravitreal Avastin (Bevacizumab) on visual acuity and CMT in diabetic macular edema and cataract, by

undergoing phacoemulsification and intravitreal Avastin in the same sitting.

Material and Method

A prospective interventional study was conducted on thirty one metabolically well controlled diabetic with diabetic macular edema and cataract were seen in a tertiary eye centre in Eastern India with minimum 3 months follow-up ,post intervention. Patients were randomized into 2 groups. One group (Group 1) underwent phacoemulsification and intravitreal Bevacizumab and the (Group 2) with phacoemulsification and Sham injection in the same sitting. All eyes were scheduled to undergo macular focal or modified grid laser photocoagulation 1 month after surgery. The frequency doubled (532 nm) Nd YAG laser, was used to standardize treatment of diabetic macular edema in all patient.

Patients with type 1 or 2 diabetes mellitus, CSME with central macular thickness >300 microns detected on OCT with no history of use of previous intravitreal antiVEGF or steroid within 6 months, patients with significant lens opacity (grade NO4NC4C4P3 or above, as classified by the Lens Opacities Classification System 3 preventing good macular photocoagulation, diabetic patients with nonproliferative diabetic retinopathy NPDR (mild, moderate, severe) were included in the study.

Diabetic patients having uncontrolled sugar level or other blood parameters, harbouring any major ocular complaints like glaucoma with operative interventions being done earlier or intraoperative complications such as posterior capsule rupture or severe iris damage during cataract surgery, who had received laser photocoagulation less than 3 months before and patient with previous ocular trauma or vitreoretinal surgery, vitreous haemorrhage were excluded from the study. Age, gender, initial visual acuity, past ocular history, history of any current or past medical conditions like Diabetes Mellitus, Hypertension or any other systemic illness were noted. All patients had a detailed comprehensive preoperative ocular examination, including measurement of best corrected visual acuity (BCVA) with logMAR chart.

Detailed slit lamp biomicroscopy for anterior segment and detailed posterior segment examination with slit lamp biomicroscopy using a +90 Dioptre lens or by an indirect ophthalmoscope were performed. Central macular thickness (CMT) was measured by stratus 3 OCT. A scan biometry performed for intra ocular lens (IOL) power calculation. The diagnosis of CSME for all patients was based on ETDRS criteria and the presence of concurrent significant cataract established.

All patients in (Group1) underwent phacoemulsification and intravitreal Bevacizumab and the (Group 2) with phacoemulsification and Sham injection in the same sitting with implantation of precalculated posterior chamber IOL uneventfully.

All of them were seen on Ist postoperative day, 7th postoperative day, 8 weeks and 12 weeks later. In all the visits, visual acuity (logMAR chart), posterior segment examination with slit lamp biomicroscopy using a 90 Dioptre lens or by an indirect ophthalmoscope done. Central macular thickness measured by stratus 3 OCT in all visits.

Statistical Analysis: Student's t test was performed to calculate and compare the baseline characteristics between both the groups. The means of visual outcomes and central macular thickness on periodic follow up visits were recorded and comparison between both groups was done by Students't Test. Chi-square test was used to compare and calculate p value for intergroup gender distribution in the study. P value of ≤ 0.05 was considered as statistically significant while comparing two variables. SPSS (Version=16.0) statistical program was used for the analysis.

Results

During the time line 17 patients were enrolled and treatments were given in group 1 while 14 patients were treated in the 2 groups. Age of presentation, gender (male and female), duration of diabetes and grading of cataracts were evaluated. The base line patient characteristics have been shown in table 1. Mean age was 59.23±7.20 years in group1, while mean age was 56.42±6.2 years in group2. Mean duration of diabetes for group 1 was13.1±5.5 years while it was 11.6±6.0 years for group 2. Both groups are comparable in terms of age group and duration of diabetes with the p value being statistically insignificant.

Table 1:

Parameter	Group 1	Group 2	P Value if applicable
Age (Mean ±SD)	59.23±7.2	56.42±6.2	0.251
Duration of diabetes	13.1±5.5	11.6±6.0	0.473
M: F	12:5	9:5	0.709

For both groups (Intra group comparison) pre-operative BCVA (baseline BCVA), post-operative BCVA (12 weeks), pre-operative CMT (baseline CMT) and post-operative CMT (12 weeks) were compared. Further analysis was performed for inter group comparison of Post-operative BCVA (4 weeks and 12 weeks), post-operative CMT (4 weeks and 12 weeks).

Grading of the Cataract Distribution

Table 2:

Grade of Cataract	Group '1'		Group '2'	
	No. of Patients	%	No. of Patients	%
NO4 NC4 C2 P1 and above	10	58.8	4	28.5
NO3 NC4 C2 P1	04	23.5	7	50
NO3 NC2 C2 P1	03	17.7	3	21.5

For group 1 the mean initial BCVA in LogMAR was 0.9213±0.36 while at post-operative 12 weeks was 0.4184±0.24 (P=0.0001),while foe group 2 the mean initial BCVA in LogMAR was 0.83±0.36 while at post-operative 12 weeks was 0.43±0.17(P=0.002).This has been represented in table no 3.

Table 3:

BCVA estimation in LOG MAR		Number	Mean±SD	P value
Group 1	BCVA pre op.	17	0.92±0.36	P=0.0001(statistically significant)
	BCVA post op. 12 week	17	0.41±0.24	
Group 2	BCVA pre op.	14	0.83±0.36	P=0.002 (statistically significant)
	BCVA post op. 12 week	14	0.43±0.17	

Mean BCVA in log MAR in post op 12 weeks and mean CMT in microns in post op 12 weeks was compared between the two groups and shown in table 4.

Table 4:

Parameter	Group 1 Mean±SD	Group 2 Mean±SD	P value
N	17	14	
BCVA IN LOG MAR (post op.12weeks)	0.42±0.24	0.43±0.17	P=0.88 Non-significant
CMT IN MICRONS (post op.12weeks	343.29±118.16	400.71±115.54	P=0.184 Non-significant

Comparison of BCVA between Both Groups BCVA in Log MAR: For group1 the mean initial CMT was 436.65±149.02 µ while post-operative 12 weeks was 343.29±118.16 µ (P=0.049, statistically significant), while for group 2 the mean initial CMT 424.21±136.41 µ while post-operative 12 weeks was 400.71±115.54 µ (P=0.168, statistically insignificant) as shown in table no 5

Table 5:

CMT estimation in micron		Number	Mean±SD	P value
Group 1	CMT-pre op.	17	434.65±149.02	P= .049 (statistically significant)
	Post-operative 12 weeks	17	343.29±118.16	
Group 2	CMT-pre op.	14	424.21±136.410	P=0.168 (statistically Nonsignificant)
	Post-operative 12 weeks	14	400.71±115.541	

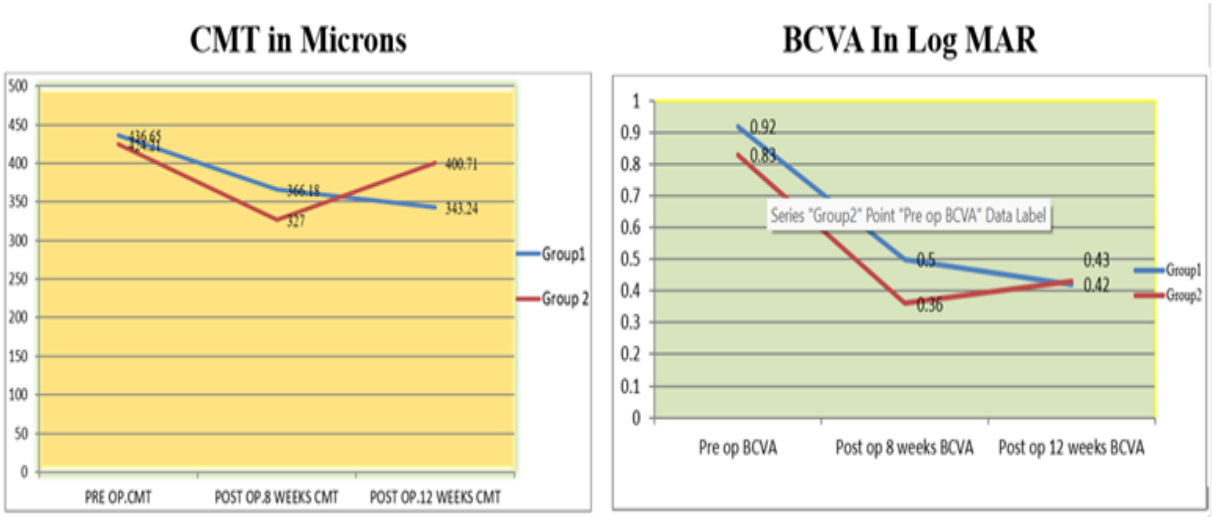

Figure 1:

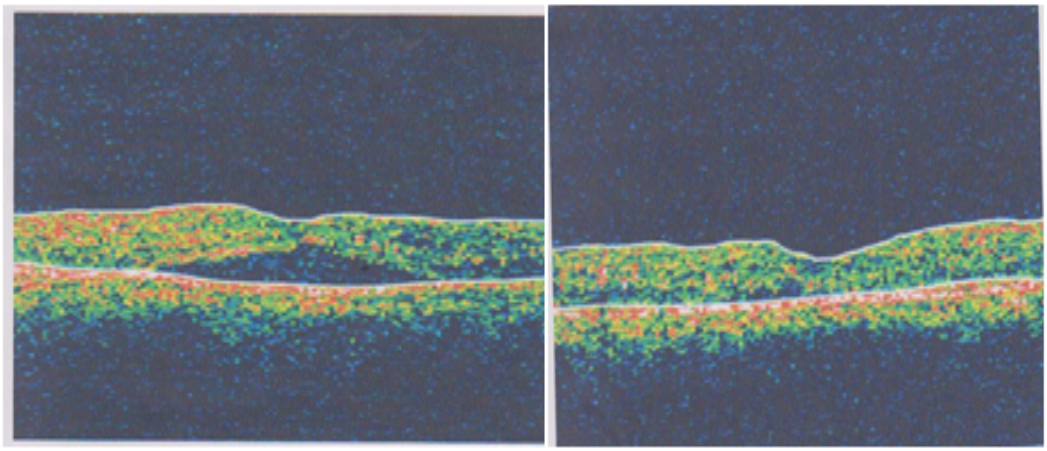

Figure 2: Improved CMT after Intravitreal Bevacizumab

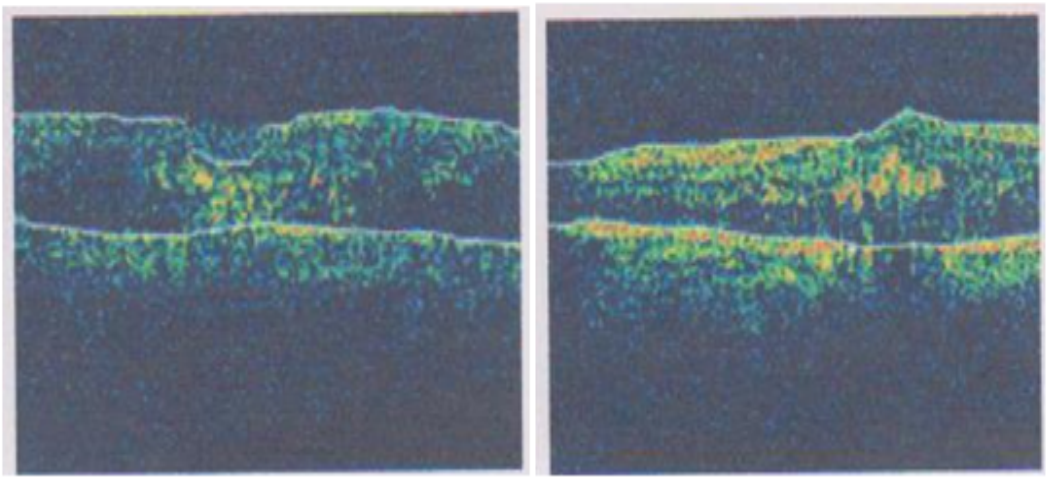

Figure 3: No Improvement in CMT after Intravitreal Bevacizumab

Discussion

With the Improvement in the knowledge of the pathophysiology of DME, various alternative therapies for the treatment of DME have emerged. Not just the treatment imaging in DME has undergone landscape change with the invention of modern imaging techniques, such as OCT. This has led to improved assessment of early DME, including subclinical DME.

There are various treatment options available for DME including corticosteroids, anti-VEGF therapy etc. Despite these newer advances, laser photocoagulation remains the standard of care and the only treatment option with proven efficacy in multiple large clinical trials. Apart from dense cataract laser photocoagulation remains the mainstay of treatment in DME.

Various studies have shown that anti-VEGF therapy reverses visual impairment, stabilizes vision loss, and to some extent prevents the future course of vision loss from DME. Bevacizumab has been considered to be a very safe drug. In our small study, there was no significant increase of IOP postoperatively and no eyes showed infection or any other severe ocular complications. However, a larger number of cases are needed to verify the safety of bevacizumab treatment. The dose of bevacizumab used in this study was 1.25 mg, which is used most commonly in clinical practice. Recurrence of CME is a possibility and may require additional multiple injections of bevacizumab. Although there were no serious adverse effects of the treatment seen in the study, the long-term efficacy is also currently unknown. In summary, our short-term data suggested that a combination of intravitreal bevacizumab plus uncomplicated cataract surgery failed to provide improvement of BCVA and CMT, when compared to controls.

At post-operative 12 weeks both groups showed significant improvement in BCVA and group 1 significant improvement in CMT. Patients in bevacizumab group showed better improvement in visual acuity (p=0.883) and CMT (p=0.184) compared to control but comparison between results of both groups were statistically insignificant.

So use of intravitreal Bevacizumab in diabetic patient with DME and cataract, undergoing phacoemulsification did not show statistically significant improvement in macular edema when compared with patient who underwent only laser photocoagulation following phacoemulsification.

Among the treatments though anti-VEGF drugs are available for DME, laser photocoagulation still remains the standard and the only treatment with proven efficacy in larger clinical trials [1,4].

A drawback of this therapy is that, the effect is not permanent and repeated injections are necessary. Though this study reports the usefulness of Bevacizumab, the application of photocoagulation should be considered for the treatment of DME.

In patients with cataract that significantly alter the view to the fundus, effective macular laser photocoagulation is more challenging, and in such patients treatment alternatives such as intravitreal Bevacizumab have been used before, during/after cataract surgery.

The present study revealed significant improvement in BCVA and CMT in patients with diabetes who underwent phacoemulsification and intravitreal bevacizumab with significant grade of cataract and diabetic macular edema but the results were comparable with that of the controls.

To our knowledge, this is one of the studies performed on Indian eyes to see the effect of bevacizumab in diabetic macular edema in patients undergoing cataract extraction. The limiting factors may be the less number of patients. Larger studies involving more number of patients are required to look into the basic pathophysiology and clinical course of the effect of intravitral Avastin injection.

Although the short follow-up precludes any specific treatment recommendations, further investigation with a longer follow-up and a larger series of patients may be needed.

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