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A STUDY ON ROLE OF INTRAVITREAL BEVACIZUMAB IN CLINICALLY SIGNIFICANT MACULAR EDEMA

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ABSTRACT The present study aims to study the anatomic and functional response of Intravitreal Bevacizumab in patients with Clinically Significant Macular Edema (CSME). This prospective study included 58 treated eyes, having diabetic retinopathy with CSME that received two intravitreal injections of Bevacizumab 1.25 mg in 0.05 ml six weeks apart and followed up at 3months and 6 months Results showed improvement in Best Corrected Visual Acuity (BCVA) and was significant throughout 6 month follow up with maximum improvement at 3 months. Also, the baseline Mean Central Macular Thickness decreased significantly. To conclude this study shows a positive effect on Visual Acuity and CSME can be established from this study and that the drug is well tolerated.

KEYWORDS : Diabetic Retinopathy, Clinically significant Macular Edema, bevacizumab

INTRODUCTION:

Diabetes mellitus (DM) has emerged as a global epidemic and Diabetic Retinopathy (DR) is a common and specific microvascular complication of Diabetes Mellitus. It is the leading cause of visual impairment and preventable blindness, and represents a significant socio-economic cost for health care systems worldwide. Population-based studies suggest that one-third of the diabetic patients have signs of diabetic retinopathy and one-tenth have vision-threatening states of retinopathy, such as Diabetic Macular Edema (DME) and Proliferative Diabetic Retinopathy (PDR) (Lamoureux et al., 2011).

DME may be present at any level of diabetic retinopathy. The prevalence of CSME in diabetic retinopathy cases is 6.27% (Raman et al., 2010) and 30% of patients with Clinically Significant Macular Edema (CSME) develop moderate vision loss. The main pathogenic element in CSME is the disruption of the blood-retinal barrier (BRB), which leads to focal hypoxia. Both hypoxia and hyperglycaemia leads to VEGF (Vascular Endothelial Growth Factor) expression (Sone et al., 1996). These VEGFs stimulate angiogenesis and microvascular permeability (Osaadon et al., 2014). Based on the crucial pathogenic role of VEGF in the development of CSME, intravitreal anti-VEGF agents have emerged as new treatments (Titchenell et al., 2013). Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF). Half-life of Bevacizumab is 4.32 days with concentrations of >10µg/ml in vitreous. Bevacizumab is maintained in the vitreous humor for 30 days. Elimination of Bevacizumab from the aqueous humor and serum paralleled that found in the vitreous humor, with half-life values of 4.88 days and 6.86 days, respectively (Bakri et al,.2007). Several studies demonstrated that Bevacizumab is able to penetrate the retina after intravitreal injection (Ferrara et al., 2005).

The purpose of this study was to evaluate the effect of intravitreal Bevacizumab on visual function and retinal thickness in patients with CSME.

MATERIALS AND METHODS:

This hospital based, prospective study was conducted during the period of February 2019 to January 2020 at Regional Institute of Ophthalmology, Gauhati Medical College. Informed consent was obtained from all patients. The study enrolled 60 subjects, of which 5 patients lost to follow-up, 1 patient developed vitreo-retinal tractional bands and 1 patient developed pleural effusion. Thus a total of 58 eyes of 53 patients were included in the study. Patients aged >50 years with T2DM and with decreased vision with clinically significant macular oedema on optical coherence tomography (OCT) were included.

Eyes that had the following features were excluded: 1. Dense media haze interfering with acquisition of good OCT/FFA image such as cataract, vitreous haemorrhage. 2. Retinal thickening due to epiretinal membranes or vitreomacular traction. 3. Macular edema due to other causes like Central Retinal Vein Occlusion or Age Related Macular Disease. 4. Angiographic evidence suggestive of ischemic maculopathy. 5. Previous history of intravitreal anti-VEGF injections or steroids or laser pan-photocoagulation received within 3 months of starting the standardised regimen. 6. Patients with uncontrolled diabetes, hypertension, chronic renal failure and history of stroke or associated with glaucoma.

A detailed ocular and systemic history was taken. Each patient underwent best corrected distance VA (Visual Acuity) measurement with LogMar equivalent of standard Snellen's chart and Snellen's near vision chart for both eyes and ophthalmic assessment including slit-lamp biomicroscopy. All the patients underwent anterior segment examination, biomicroscopic evaluation with fundus non contact +90D lens and FFA. Central macular thickness was measured with optical coherence tomography (Stratus OCT machine model 3000 (Carl Zeiss Meditec Inc.) with software version 4.0. The Fast macular thickness protocol was used. The study parameters were evaluated three months and six months after the second intravitreal injection. The intravitreal dosage of bevacizumab was 1.25mg/0.05cc. One day prior to the Intravitreal Injection topical antibiotic (Moxifloxacin) eye drop was started in the planned eye. 5% providone iodine was instilled into the conjunctival sac and then washed off. A point was marked using calipers at 3.5mm from the limbus (in pseudophakic and aphakic patients) and 4mm from limbus (phakic patients) in the superotemporal quadrant. Injection was administered using a 27 G syringe. After withdrawal of the needle, a cotton tip applicator dipped with 1 drop of betadine and 1 drop of topical antibiotic eye drop was applied for 1 min to the site of injection. Pad and bandaging was done for 24 hours. Patients were instructed to use Tab Diamox (Acetazolamide 250mg) as half tablet twice daily to be taken after food, Tab Pan 40 (Pantoprazole 40 mg) to be taken in empty stomach and Tab Diclonac (Diclofenac Sodium 50 mg) after food for the same day. Dressing was done next day with topical antibiotic drops.IOP was checked and pupils were dilated to look for any anterior or posterior segment inflammation. Patients were instructed to use topical antibiotic (Moxifloxacin) eye drops 1 hourly for 1 day followed by 6 times per day for 2 weeks postoperatively.

Six weeks after first injection, reinjection was performed in a similar way. The following study parameters were evaluated three months and six months after the second intravitreal injection:1) Visual acuity 2) Central macular thickness as measured by OCT 3) Incidence of any side-effects such as rise in intraocular pressure (IOP), inflammation or endophthalmitis 4) Any systemic side-effect such as rise in BP or any Thromboembolic event.

Statistical Methodology:

The data were presented as the mean ± standard deviation. Statistical differences between pre- and post-treatment clinical data were

assessed using a Paired t-test. To find correlation between the variables Pearson's correlation of coefficient was applied. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS:

All the patients were diagnosed cases of T2DM having Non-Proliferative Diabetic Retinopathy (NPDR) or Proliferative Diabetic Retinopathy (PDR) with CSME. The mean age of presentation was **57.64 ± 7.74 years** and **50.94%** were males (27 male 26 female). Mean duration of diabetes was found to be **14.03 ± 6.10 years**. Among the CSME patients; 87.9% of eyes were associated with NPDR whereas 12.06% were associated with PDR. Maximum no. of patients (26) had Moderate NPDR which was found in 44.82% of CSME patients at the time of presentation. Improvement in BCVA was significant throughout 6 month follow up with maximum improvement seen at 3 months. Baseline visual acuity improved from logMAR(0.737±290) to logMAR(0.534±0.235) at 6 weeks, to logMAR (0.356 ±0.166) at 3 months and to logMAR (0.434±0.182) at 6 months which was statistically significant (p<0.0001).(**Figure1)**. The baseline mean Central Macular Thickness(CMT) decreased considerably throughout the study period from **397.58µm ± 89.28 µm** to **318.06 µm ±67.92 µm** at 6 months and the maximum decrease was seen at 3 months **to 278.56±53.21µm (p<0.0001). (Figure 2).** summarises OCT-measured retinal thickness results. The CMT decreased more in the group where baseline CMT was more than 450µ and the greatest difference was seen at 3 months. Eyes with thicker retina at baseline experienced a greater absolute and relative reduction in CMT. **(Figure 3).** Also, there was positive correlation between BCVA and CMT throughout the study period such that with the decrease in central macular thickness , the vision also improved and the relation was statistically significant **(Figure 4).** At 6 weeks 55.17% eyes could maintain CMT < 350µ, 89.6% eyes at 3 months and 74.13% eyes at 6 months**.(Figure 5**) .

It was seen that 3 out of 58 eyes had sub-conjunctival haemorrhage, which resolved completely within 2 weeks. Also, 2 of the patient developed raised IOP at 3 months follow up. One of them had received intravitreal Bevacizumab bilaterally and rise in IOP was seen in both eyes. However IOP was controlled with conservative treatment. 3 patients had developed cataract. One of the patient who had PDR with CSME developed vitreoretinal tractional bands following 1st IVB and therefore not included in the study. No other patient developed any other ocular side-effect. Among the systemic complications, we found that 3 out of 53 patients had rise in blood pressure at 3 month follow-up. No other systemic side effects were evident.

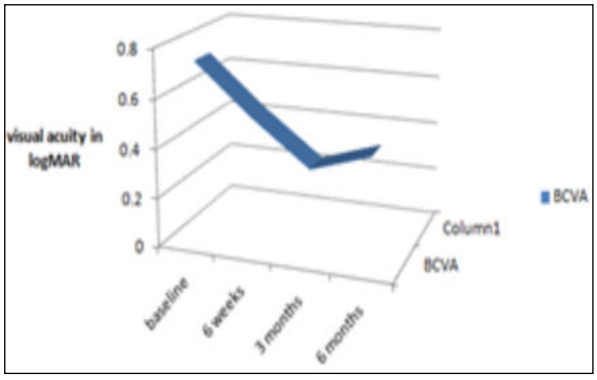

Figure1: Line Diagram Showing Visual Acuity At 6 Weeks, 3 Months And 6 Months

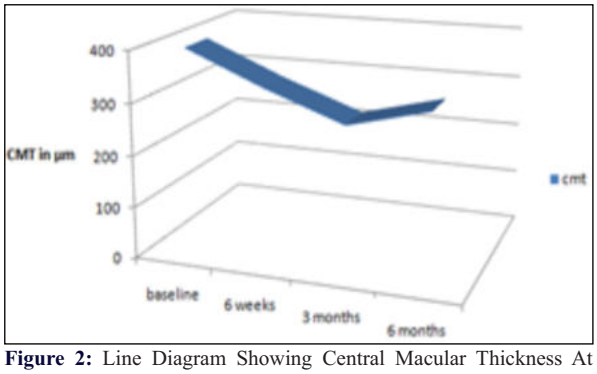

Figure 2: Line Diagram Showing Central Macular Thickness At Baseline, 6 Weeks, 3 Months And 6 Months

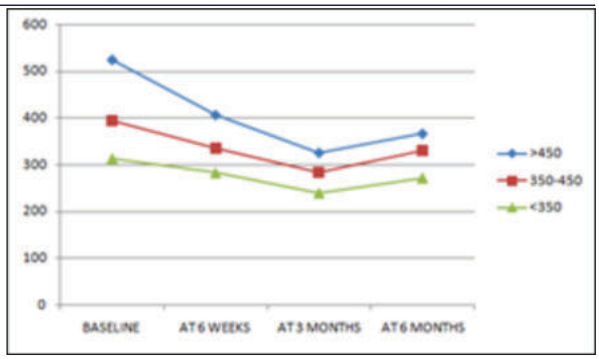

Figure3: Line Diagram Showing Improvement Among Patients Having Different Range Of CMT

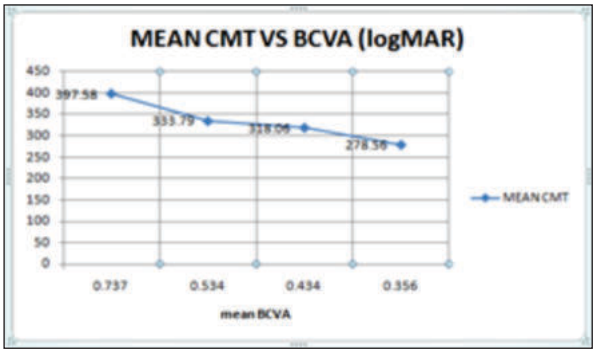

Figure 4: Relation Between CMT And BCVA At 6 Months

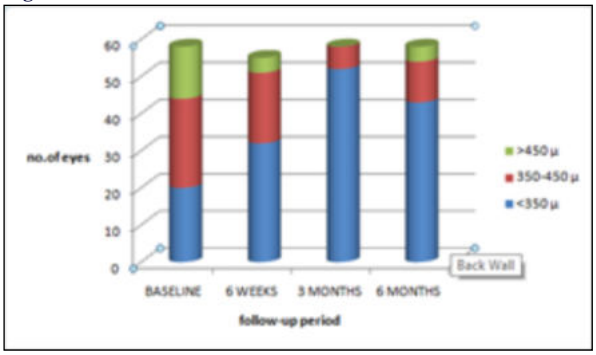

Figure 5: Bar Diagram Showing No. Of Eyes In Different CMT Groups In Subsequent Follow- Up

DISCUSSION:

In a study conducted by Haritoglou et al, 2006, it was found that after 1.25mg of intravitreal Bevacizumab injection, there was a significant reduction in macular thickness at 2 weeks and although mean visual acuity improved significantly at 6 weeks (p=0.02), this was not sustained at 12 weeks. However in the present study, we found that significant improvement in both visual acuity and central macular thickness was soon achieved at 6 weeks and the beneficial effects lasted for 6 months.

Kumar et al, 2007 demonstrated statistically significant changes in VA and CMT at 3 month after second intravitreal injection which was given at 6 weeks. Improvement in VA and CMT at month 3 was highly significant. Though the mean VA and CMT worsened marginally at 6 months the difference was still statistically significant to baseline. Similar results were seen in our study.

Mushtaq et al, 2014 demonstrated that the amount of reduction in CRT was significantly greater in group where CRT >400 µm when compared to group where CRT <400 µm. In our study also it was seen that the CMT decreased more in the group where baseline CMT was more than 450µ and the greatest difference was seen at 3 months.

Adverse events as reported by Arevalo et al., 2011, transient increased intraocular pressure in seven (5%) eyes, cataract in five (3.6%) eyes, and tractional retinal detachment in one (0.7%) eye. There were no episodes of inflammation or severe decrease of vision immediately after an injection. In our study we found raised IOP in 3.44% eyes, Sub-

conjunctival haemorrhage in 5.17% and cataract in 3.44% which is comparable with the study. No other patient developed any other ocular side-effect. Among the systemic complications, we found that 3 out of 53 patients (5.66%) had rise in blood pressure at 3 month follow-up. All 3 were hypertensive patients on anti-hypertensive drugs.No other systemic side effects were evident during 6 month follow-up.

In conclusion, Intravitreal Bevacizumab injection appears to result in significant improvement in BCVA and reduction in Clinically Significant Macular Edema as early as 6 weeks after 1st injection and this beneficial effect was shown to persist for upto 3 months following 2nd injection at 6 weeks. However the slight reduction in improvement both in BCVA and retinal thickness at 6 month follow-up suggest that repeated Bevacizumab injection might be necessary within 6 months to maintain its effect. Also it was seen that the drug is well tolerated and there are no safety concerns. Thus, a positive effect on Visual Acuity and Clinically Significant Macular Edema can be established from this study.

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