

INTRAVITREAL BEVACIZUMAB AS AN ADJUNCT TO LASER FOR DIFFUSE DIABETIC MACULAR EDEMAShah Nawaz¹, Shaveta², Ishfaq Ahmad Sofi³, Tariq Querishi⁴**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: Background: Diabetic retinopathy with its manifestation in the form of diabetic macular edema has become a leading cause of blindness all over the world. **AIM:** In the present study we evaluated, the anatomical and visual acuity outcomes after intravitreal bevacizumab and laser in Diffuse DME. **MATERIALS AND METHODS:** An OCT guided pilot study, evaluating the effect of intravitreal bevacizumab as an adjunct to laser, of 40 eyes of 40 diabetic patients having diffuse diabetic macular edema with maximum retinal thickness (MRT) more than or equal to 350 μm was conducted at Government Medical College & Hospital, Chandigarh, India. The patients had minimum follow up of 6 months. **RESULTS:** There was a significant decrease in maximum retinal thickness with significant gain in visual acuity at 6 month. **CONCLUSIONS:** Intravitreal bevacizumab combined with laser photocoagulation has better outcomes in the management of patients with diffuse diabetic macular edema. Since ours is a pilot study, further studies with larger number of patients and longer follow ups are essential to conclusively establish the superiority of IVB combined with laser photocoagulation in the management of DME.

KEYWORDS: Intravitreal, Bevacizumab, Photocoagulation.

INTRODUCTION: Diabetic eye disease represents the leading cause of blindness in adults less than 75 years.¹ the most common cause of moderate visual impairment in diabetic patients is diabetic macular edema.² Data from the Wisconsin epidemiologic study of diabetic retinopathy suggest that the 14-year incidence of diabetic macular edema (DME) in patients with diabetic retinopathy is 26%.³

The improvement in visual acuity (VA) by Macular laser, which is still being the gold standard for treatment of CSME,⁴ was observed in only less than 3% of cases (15-letter gain at 3 years) in the ETDRS study and is not without complications like scarring, compromised contrast sensitivity, color vision defects & and visual field abnormalities.⁵

Recent studies show important contribution of retinal ischaemia to the pathology of DR, inducing up regulation of angiogenic growth factors, most notably vascular endothelial growth factor (VEGF).⁶ VEGF is unique in being a potent promoter of both angiogenesis and vascular permeability, properties of direct relevance to the pathophysiology of DR.⁷ Better understanding of the pathophysiology of DR, has led to the introduction of anti VEGF drugs for the treatment of DME. Intravitreal injections of anti VEGF drugs like Pegaptanib sodium & Ranibizumab have already produced encouraging results in various studies.^{8,9} The use of intravitreal bevacizumab though still off label has risen exponentially in the past few years for various retinal disorders and also is more economical as compared to the other drugs of this class.¹⁰

AIM: In the present study we evaluated, the anatomical and visual acuity outcomes after IVB and laser in Diffuse DME.

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MATERIALS AND METHODS: This study was approved by the review board of our Institute. Informed consent was obtained from all the patients and the study adhered to the provisions of the Declaration of Helsinki. 40 eyes of 40 metabolically stable newly diagnosed diabetic patients having treatment naive diffuse DME more than or equal to 350 microns on OCT, presenting to Retina clinic of Department of Ophthalmology, Government Medical College Hospital, Chandigarh were administered 0.05ml of 1.25mg of intravitreal bevacizumab (IVB) at least 3 weeks before laser under full aseptic conditions. The injection was given using a 30G needle on 1cc syringe, 4mm from limbus in phakic patients and 3.5mm from limbus in aphakics and pseudophakics,.

Best corrected visual acuity (BCVA) for all patients using log MAR chart was recorded by an independent examiner. All patients were subjected to a detailed ocular examination using macular contact lens, +90D and +20D lens to evaluate the stage of diabetic retinopathy and the extent of diabetic macular edema. Clinical findings for all eyes were confirmed by FFA and also FFA ruled out macular ischemia and any neovascularization. OCT imaging with fast macular scan with internal fixation was done for all the patients using Stratus OCT, Carl Zeiss, Model-3, Dublin, California, USA, with software 4.0. Manual placement of the computerized callipers at the inner border of nerve fibre layer and inner border of retinal pigment epithelium layer gave us the maximum Retinal Thickness (MRT) in the macular area. The macular edema was documented before and after intervention. All the patients were followed up for a minimum of 6 months. OCT was repeated before laser & then at follow up visits from the same landmark.

A detailed history was taken as regards to duration of diabetes and any other diagnosed systemic ailments. Patients with uncontrolled diabetes and hypertension, dyslipidemia, chronic renal failure and history of stroke, pregnancy, history of any ocular surgery within 3 months of the study, significant cataract precluding OCT or FFA, any ocular disease with bearing on macular edema like uveitis, central retinal vein occlusion, branch retinal vein occlusion, presence of any other macular pathology like ARMD or macular hole, OCT showing evidence of vitreomacular traction & previously treated macular edema, known glaucoma patients or glaucoma suspects were excluded from the study.

All the patients were followed up at day 1 after injection and thorough examination was done for any signs of infection, inflammation or any other complication. Re-evaluation was done after 3 weeks for VA, raised IOP and maximum retinal thickness (MRT) on OCT. If the maximum retinal thickness was $<350\mu$, the patient were taken up for laser treatment in grid pattern using 532nm laser applying just visible burns of 100 microns in size, of 100 millisecond duration, 500 μ m away from centre as recommended by ETDRS. If maximum thickness was still more than or equal to 350 μ at 3 weeks after injection then repeat injection was planned.

Follow up with detailed evaluation was done for all patients at 3 month interval with minimum follow up of 6 months. Repeat injection & supplement laser treatment were given as per required, depending on the thickness of OCT, at follow ups.

Statistical analysis was performed with SPSS 21.0. The quantitative parameters were represented as mean \pm SD and comparison was carried out using paired t-test and student's t-test. p value of <0.05 was taken as significant.

RESULTS: The mean age of patients was 58.0 ± 5.36 years (Range 50-68 years). All the 40 patients in the present study had type II diabetes and all of them were on oral hypoglycemic agents. The mean logMAR visual acuity at baseline was 0.92 ± 0.38 and the mean initial MRT before laser was $410.65\pm 38.90 \mu$ m. All the patients had diffuse macular edema evident on both OCT & FFA.

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The mean logMAR visual acuity at 3 month was 0.46 ± 0.33 & at 6 month was 0.52 ± 0.28 . The change though significant from baseline at 3 and 6 month (p value = 0.0, p value = 0.0), got slightly blunted at 6 month, but still was statistically significant from the baseline at 6 month.

The mean MRT at 3 month was 297.750 ± 43.5 and at 6 month was $309.550\pm 87.16\mu$. This decrease in MRT at 3 & 6 month when compared to baseline was highly significant (p value=0.0, p=0.0).

At 3 month, 26 patients (65%) showed a resolution of CSME while 6 (30%) had residual CSME $<350\mu$ and 2 (5%) had residual CSME $>350\mu$. The patients with MRT $<350\mu$ were taken up for supplement laser. The patient with $>350\mu$ was reinjected with IVB. The patient responded well and was taken up for laser.

At 6 month, 30 patients (75%) showed a resolution of CSME while 5(25%) had residual CSME. Out of these 10, 6 patients (15%) with residual CSME $<350\mu$ were subsequently lasered while 4 patients (10%) had CSME $>350\mu$ and were re injected with IVB. 2 were subsequently lasered and 2 patients showed no response to repeat injection and developed vitreomacular traction on OCT.

In the entire course of six months, none of the patient had any significant inflammation, raised IOP, endophthalmitis or retinal detachment. Most common complication noted was painless sub conjunctival haemorrhage at the injection site.

DISCUSSION: Diffuse diabetic macular edema (DDME) is a difficult entity to treat and as most of the eyes with DDME treated with laser photocoagulation show no improvement in edema or VA, there has been a lot of interest in other treatment modalities for diabetic macular edema such as pharmacological therapy. The use of antibodies targeted at VEGF has generated considerable interest in the recent times.¹¹

The vitreous fluid of subjects with DME has been shown to have raised levels of VEGF, which plays a major role in increasing vascular permeability causing the progression of DME.¹² These anti VEGF antibodies down regulate VEGF and reduce capillary permeability thus decreasing the resultant edema. Decreased foveal thickness facilitates laser treatment and reduces the need for high laser energy. However, VEGF is not the only factor implicated in the complex pathophysiology of DME, macular hypoxia is also troublesome.¹³ This may explain the rapid recurrence of macular edema and thus deterioration of visual acuity a few weeks after injection when VEGF levels again increase in the vitreous.

The current study of 40 diabetic patients with diffuse edema shows the additive synergistic effect of laser to anti-VEGF treatment. We saw a significant anatomical improvement in macular edema at 3 & 6 month and functional improvement significant at 3 months, but slightly blunted, though significant from baseline, at 6 months.

There are several studies in the literature on the intravitreal administration of antibodies against VEGF for DDME. Various studies have established the role of Pegabtinib sodium & Ranibizumab for the treatment of DME and hence have laid a foundation for the use of other intravitreal anti VEGF drugs like bevacizumab.

Kumar and Sinha reported results of 20 eyes with DDME treated with IVB at a dose of 1.25mg that had not responded to previous photocoagulation.¹⁴ their follow-up period was 6 months. They concluded that IVB resulted in a significant decrease in macular thickness and improvement in VA at 3 months, but that the effect was somewhat blunted, although still statistically significant, at the end of 6 months.

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Soheilian et al that reported 103 eyes with 12 weeks follow-up comparing IVB alone or combined with intravitreal triamcinolone versus macular focal or grid laser photocoagulation.¹⁵ like our study they reported better results with IVB regarding visual outcome than with laser photocoagulation alone, although it was not associated with a significant decrease in CMT.

The result of the current study parallels with the above mentioned studies and also our results show that bevacizumab is well tolerated with no systemic and significant ocular side effects.

CONCLUSION: Our pilot study concludes that combining anti-VEGF with laser photocoagulation is a complementary treatment with better efficacy than laser alone in treating DDME. To substantiate this conclusion will need larger studies.

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