



Original Research Article

Effectiveness of treatment by laser or intravitreal anti-vegf-bevacizumab or combination therapy (both Laser and Anti-VEGF) in diabetic macular edema

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ABSTRACT

Aim: This study aimed to determine the effectiveness of treatment by laser or Intravitreal anti VEGF-Bevacizumab (IVB) or combined therapy (both laser and anti-VEGF) in diabetic macular edema (DME).

Materials and Methods: A prospective observational study in which 90 eyes with diabetic macular edema (DME) were enrolled. According to patient compliance, they were divided in to 3 groups where there was 30 eyes in each group. Patients with DME who were treated with laser were observed (group A). Patients with DME who were treated with Intravitreal Bevacizumab (IVB) were observed (group B). Patients with DME who were treated with both IVB and Laser were observed (group C). All patients underwent complete ophthalmic examination at baseline and at one and three months after treatment. The outcome measures were changes in Central macular thickness (CMT) and best corrected visual acuity (BCVA). A P value less than 0.05 considered statistically significant.

Results: One month after treatment, Group B showed more statistically significant reduction in CMT and improvement in BCVA than group A and group C (P<0.05). Three months after treatment, group C showed more statistically significant reduction in CMT and improvement in BCVA when compared to other two groups (P<0.05).

Conclusions: Combined therapy with IVB and laser appeared to be superior to Laser alone or IVB alone in reducing macular thickness and improving visual acuity. Thus combined therapy can be considered as most effective treatment in DME.

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1. Introduction

Diabetic macular edema (DME) is one of the most common cause of visual impairment.¹ Three modalities of treatment for DME are laser treatment, intravitreal-bevacizumab (IVB) and combined therapy. Laser photocoagulation is the FDA approved treatment for DME.² However a previous study reported that treated eyes shows persistence of DME despite laser therapy.³

Bevacizumab is the most cost effective and widely used anti-VEGF. However, a previous study reported limitations

of IVB.³

Many ophthalmologists are also trying combination therapy. Effective treatment of DME is still controversial.^{3–5} We designed a study to evaluate effectiveness of treatment of DME by Laser, IVB or combination therapy.

2. Materials and Methods

This prospective observational study was conducted among 90 patients with diabetic macular edema aged between 55–75 years who came to ophthalmology department in a tertiary care centre in Thrissur district of Kerala for a time period of 18 months from November 2019 to May 2021,

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after acquiring approval from the Institutional Research and Ethics Committee.

Patients diagnosed with diabetic macular edema (DME) attending the ophthalmology department who satisfied the inclusion criteria were involved in the study. Written informed consent was taken from all patients. Patients were explained about the three modalities (Laser alone, IVB alone and combined therapy) of treatment of diabetic macular edema by the treating ophthalmologist. The potential adverse effects and benefits were explained to the patient. Treatment was decided according to the patient compliance by the treating ophthalmologist. Patients with DME who were treated with Laser photocoagulation alone were classified as group A. Patients with DME who were treated with one dose of Intravitreal Anti-VEGF (Bevacizumab) alone were classified as group B. Patients with DME who were treated with one dose of Anti-VEGF (Bevacizumab) followed by Laser Photocoagulation after three weeks were classified as group C.

Our definition of diabetic macular oedema was based on evidence of retinal thickening and/or hard exudates involving the centre of the macula (Clinically Significant DME as defined by ETDRS on slit-lamp biomicroscopic examination) and diffuse fluorescein leakage involving the centre of the macula on fluorescein angiography (FA) with 33% of leakage associated with microaneurysm and a significant reduction in the reflectivity of the outer retinal layers and /or subretinal fluid collection by optical coherence tomography (OCT) should be present".⁶ Inclusion criteria were 1) subjects who had diabetic macular edema with central macular thickness (CMT) of at least 350 μm measured by optical coherence tomography (OCT), 2) no previous history of any surgeries or intravitreal injection, 3) No previous history of any retinal laser therapy 4) patients who are willing to attend follow up visits. Exclusion criteria included are: 1) eyes with Vitreoretinal traction involving macular region, 2) macular ischaemia, 3) cataract, 4) Vitreous haemorrhage, 5) chronic uveitis, 6) retinal vein occlusion, 7) chronic kidney disease and 8) recent thromboembolic episode.

A detailed history of any previous ophthalmic condition and duration of diabetes mellitus was taken. All patients underwent thorough ophthalmic examination including BCVA (using LogMAR), slit lamp examination, intraocular pressure, fundus examination, optical coherence tomography (using Spectral Domain-OCT, Carl-Zeiss) and fundus fluorescein angiography before treatment at baseline. In group B and C patient, Bevacizumab was given by the treating ophthalmologist under aseptic precautions. Under topical anaesthesia, 1.25 mg in 0.05ml of Bevacizumab injection given 3.5mm to 4mm posterior to the limbus, through inferotemporal pars plana with a 30 gauge needle.

In patients treated with combined therapy, laser photocoagulation was given after three weeks of one dose of intravitreal Bevacizumab. In patients treated with laser therapy, laser photocoagulation done with argon or green laser. Two to Three rows of 75mm spots applied 100 mm apart in the parafoveal region. Remaining areas of retinal thickening and capillary non perfusion were delivered with 150 mm to 200 mm spots 200mm apart. 100 mm to 150 mm spots were applied to focal leaks outside or within the zones of diffuse leakage to form a mild whitening of the microaneurysms.

Patients were followed up at one month and three months after initial treatment. At each follow up visit, patients underwent detailed ophthalmic examination including all procedures performed at baseline except fluorescein angiography. Main outcome measures were changes in central macular thickness, best corrected visual acuity (BCVA) from baseline values. Outcome measures were assessed from baseline to one month and three months follow up.

Microsoft Office Excel 2007 spreadsheet is used to collect all data and statistically analysed using the Statistical Package for the social sciences for windows version 25.0 software. Numerical values were expressed as mean and SD and categorical values were expressed as frequency and percentage. The normality of CMT and BCVA were assessed and they were not normally distributed. To compare the mean effect of CMT and BCVA among groups, the Kruskal Wallis test was applied. A dunn bonferroni multiple comparison test was done. 95% effect sizes were calculated.

3. Results

Among the 90 patients involved in this study, 44 (48.9%) were men and 46(51.1%) were women. The mean age of all patients found to be 65 \pm 8 years. The Baseline characteristics of patients in each group given in Table 1. No significant differences was found between the 3 treatment groups with regards to sex ($P>0.05$), age ($P>0.05$) and duration of diabetes ($P>0.05$). Mean baseline CMT was 448.13 \pm 26.85 μm in group A, 482.40 \pm 46.05 μm in group B and 458.67 \pm 32.97 μm in group C. Mean Baseline BCVA was 0.59 \pm 0.03 in group A, 0.64 \pm 0.08 in group B and 0.60 \pm 0.05 in group C.

After one month, decrease in mean CMT from baseline was 49.27 \pm 11.28 μm (11.06%) in group A, 154.83 \pm 37.25 μm (31.78%) in group B and 89.30 \pm 13.19 μm (19.55%) in group C. The improvement in mean BCVA versus baseline was 0.092 \pm 0.032 (15.47%) in group A, 0.297 \pm 0.062 (46.33%) in group B and 0.169 \pm 0.079(28.16%) in group C. At the end of one month, when reduction in mean CMT and improvement in mean BCVA compared between three different groups, it was found to be statistically significant ($P<0.001$). In multiple comparison test, Group

B showed more significant improvement in BCVA and reduction in CMT after one month when compared to group A and group C ($P < 0.05$).

After three months, the reduction in mean CMT was $30.10 \pm 16.18 \mu\text{m}$ (6.72%) in group A, $109.33 \pm 36.91 \mu\text{m}$ (22.35%) in group B and $144.93 \pm 20.45 \mu\text{m}$ (31.56%) in group C. The improvement in mean BCVA versus baseline was 0.060 ± 0.036 (10.05%) in group A, 0.208 ± 0.093 (32.61%) in group B and 0.380 ± 0.059 (63.19%) in group C. At the end of three months, when reduction in mean CMT and improvement in mean BCVA compared between three different groups, it was found to be statistically significant ($P < 0.001$). After three months, Group C showed more significant improvement in BCVA and reduction in CMT when compared to group A and group B ($P < 0.05$).

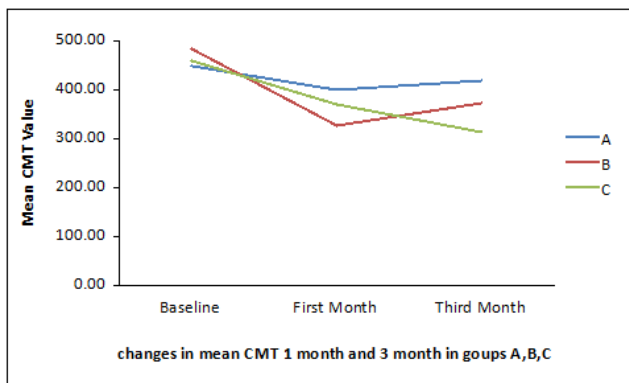


Fig. 1: Changes in mean BCVA one and three months in groups A, group B, group C

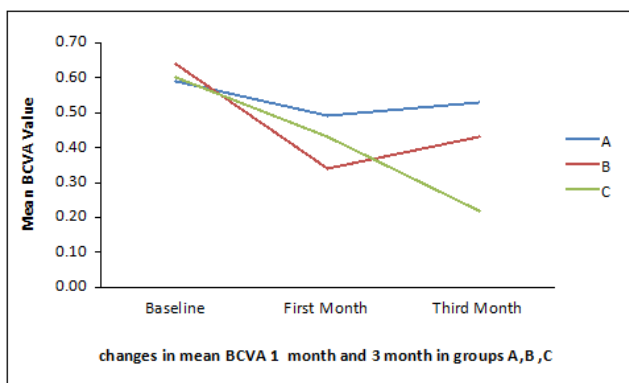


Fig. 2: Changes in mean BCVA one and three months in groups A, group B, group C

4. Discussion

Diabetic Macular Edema is the common cause of impairment of vision in diabetic retinopathy.³ Laser photocoagulation had been considered the mainstay of treatment, yet the visual outcome had been

unsatisfactory.^{5,7-9} Recently the use of IVB for treatment of Diabetic Macular Edema has resulted in promising outcome, but the effects lasts for short duration only.^{6,10-12}

In this study, It was seen that at one month, eyes received IVB alone has more reduction in CMT and improvement in BCVA when compared to other two groups. Whereas at three months follow up, eyes treated with combined therapy showed more reduction in CMT and improvement in BCVA when compared to other two groups. In combined Therapy, IVB injection which is given before laser photocoagulation reduces the macular thickness. Less thickened macula responds more to laser therapy³ and thus it is found that more prolonged outcome with laser therapy is obtained in those eyes who are previously treated with IVB than those eye who are treated with laser therapy alone. At one month, the IVB group showed a better outcome than other two groups who received laser therapy, this may be because of a transient elevation of macular oedema with Laser Therapy which may subside with time.³ It is also noted that in eyes treated with combined therapy, requirement of repeat injections of IVB is less frequent as compared to eyes treated with IVB alone.³ Thus from this study, it is found that combined therapy is more superior when compared to IVB alone or laser therapy alone.

Laser therapy was the first effective evidence-based modality of treatment for diabetic macular oedema.¹ But in our study, decrease of CMT at one and three months in those eyes with Laser alone is less when compared to other two groups. So it is found that though Laser photocoagulation may not cause more visual gain, it can prevent further deterioration of vision. And thus it is found that the efficacy of laser photocoagulation is inferior to IVB monotherapy and combined therapy. Recurrence of macular oedema after laser therapy is also noted in few patients.

The result of this study is consistent with Solaiman et al,³ Kang et al¹³ and Lam et al.¹¹ Solaiman et al concluded that combined therapy has more visual outcome when compared to Laser therapy or IVB alone.³ Kang et al. concluded more reduction in CMT at three and six months in eyes treated with combination therapy.¹³ Lam et al. also came to same conclusion suggesting that combined therapy is better than laser.¹¹ Our study is dissimilar with J.Fernando⁶ et al study which concluded that IVB alone is superior to Laser or combined therapy.

IVB found to decrease retinal capillaries permeability and inhibit VEGF, but it does not solve macular hypoxia.^{3,10,14} Thus once the Bevacizumab is washed out from the vitreous, there is high chance of recurrence of macular edema within a few weeks. Laser therapy converts hypoxic areas into anoxic areas. Some photoreceptors are destructed by laser therapy thereby raising the inner retinal oxygen levels.³ Hence when laser photocoagulation done after three weeks of IVB treatment, macular hypoxia is improved resulting in prolonged effect of IVB and

Table 1: Baseline data of patients of Group A, Group B and Group C

	Group A	Group B	Group C
Number of eyes	30	30	30
Sex			
Male	13(43.3%)	16(53.3%)	15(50%)
Female	17(56.7%)	14(46.7%)	15(50%)
Age			
Range	55-75	56-74	55-74
Mean±SD	63.20±7.052	66.67±8.535	68.07±8.112
Duration of diabetes			
Range	10-29	10-34	10-45
Mean±SD	17.70±5.943	18.53±6.095	17.47±8.629

Table 2: Mean CMT difference from baseline to one month and three months follow up period

Groups	N	CMT			Kruskal Wallis Value	p Value
		Mean	SD	Median (IQR)		
Difference from Baseline to First month Follow up period						
1	30	49.27	11.286	51.50(42.50-56.00)	73.779	<0.001
2	30	154.83	37.255	150.5(134.00-161.25)		
3	30	89.30	13.191	89(84-98)		
Difference from Baseline to Third month Follow up period						
1	30	30.10	16.187	27(20.75-34.75)	68.071	<0.001
2	30	109.33	36.915	105.5(90.50-120)		
3	30	144.93	20.450	145(134.50-152.25)		

Table 3: Mean BCVA difference from baseline to one month and three month follow up period

Groups	N	BCVA			Kruskal Wallis Value	p Value
		Mean	SD	Median (IQR)		
Difference from Baseline to First month Follow up period						
1	30	0.092	0.032	0.10(0.09-0.10)	60.146	<0.001
2	30	0.297	0.062	0.30(0.27-0.32)		
3	30	0.169	0.079	0.15(0.10-0.20)		
Difference from Baseline to Third month Follow up period						
1	30	0.060	0.036	0.06(0.03-0.06)	71.469	<0.001
2	30	0.208	0.093	0.20(0.13-0.20)		
3	30	0.380	0.059	0.40(0.36-0.40)		

Table 4: Changes in Mean CMT (in micrometers) in groups A, B and C

Groups	Baseline	First Month	Third Month
A	448.13	398.87	418.03
B	482.40	327.57	373.07
C	458.67	369.37	313.73

Table 5: Changes in mean BCVA (logMAR) in group A, B and C

Groups	Baseline	First Month	Third Month
A	0.59	0.49	0.53
B	0.64	0.34	0.43
C	0.60	0.43	0.22

thereby decreasing recurrence rate of DME. Also in Combined therapy since macular oedema is reduced by initial treatment of IVB before treating with laser, it helps in selective delivery of laser therapy to photoreceptors.¹³ Based on all these observations both laser and IVB when given as combined therapy potentiate the effect of each other.

The limitation of the study is patient compliance to the different modalities of treatment and short follow up period. A longer follow up is needed to compare long term efficacy. It is necessary to do longer follow up in further studies.

5. Conclusion

Our study of eyes with diabetic macular edema showed that combined therapy with intravitreal bevacizumab followed by laser therapy found to be better when compared to Laser therapy alone or IVB alone in reduction of central macular Thickness and improvement of BCVA. Although IVB showed better visual outcome than combined at first month follow up, the more marked and prolonged visual outcome was obtained with combined therapy. Thus combination of IVB and sequential Laser therapy can be considered as most effective treatment in DME.

6. Source of Funding

None.

7. Conflict of Interest


The authors declare no conflict of interest.

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