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ORIGINAL RESEARCH

Comparative Evaluation of Efficacy of Intravitreal Bevacizumab (1.25mg) and Laser Monotherapy in Treatment of Diabetic Macular Edema – A Short Term Hospital Based Study in North India

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ABSTRACT

Aims: To compare the treatment efficacy of intravitreal bevacizumab (1.25 mg) and laser monotherapy in diabetic macular edema in patients of type 2 diabetes mellitus.

Settings and Design: Randomised, non-blinded prospective interventional study conducted in a tertiary care hospital on 66 eyes of type 2 diabetes patients.

Methods and Material: After obtaining informed consent, patients diagnosed with non-proliferative diabetic retinopathy (NPDR) and DME defined as clinically significant macular edema (CSME) were recruited in the study. The selected patients were randomized into two groups – group A (n=33) - macular laser photocoagulation and group B (n=33) - three monthly intravitreal bevacizumab injections (1.25 mg). At 3 months follow up, comparison of change in central macular thickness (CMT), macular volume (MV) and best corrected visual acuity (BCVA) was done.

Statistical analysis used: SPSS 21, IBM, USA, Pearson's chi-squared test and two sample t-test.

Results: CSME resolved in 11 (33.33%) patients in laser group and 21 (63.64%) patients in the intravitreal bevacizumab group. Mean CMT decreased from 496.03µm to 339.24µm in laser group and from 516.48µm to 283.27µm in the bevacizumab group ($p<0.05$). Bevacizumab group showed greater reduction in mean MV laser group ($p<0.05$). Mean BCVA (logMAR) improved from 0.83 to 0.49 in the bevacizumab group while in the laser group, marginal improvement was seen from 0.81 to 0.76 ($p<0.001$).

Conclusions: Intravitreal bevacizumab is superior to macular laser photocoagulation in structural and functional improvement in NPDR with CSME.

Keywords: Anti-VEGF, bevacizumab, diabetic macular edema, diabetic retinopathy

INTRODUCTION

Diabetic macular edema (DME) is the commonest cause of moderate visual loss in diabetes.[1]Management of DME is emphasised upon improvement of anatomical parameters (reduction in central macular thickness) and functional parameters (improvement in visual

acuity). Anti-VEGF agents are now regarded as the first line of therapy in DME. Bevacizumab is used off-label in disorders such as age-related macular degeneration, diabetic retinopathy, and DME. Focal or grid laser photocoagulation has been determined to be efficacious in treatment of clinically significant macular edema.[2]

We compared the efficacy of fixed regimen intravitreal bevacizumab injections to laser photocoagulation in DME.

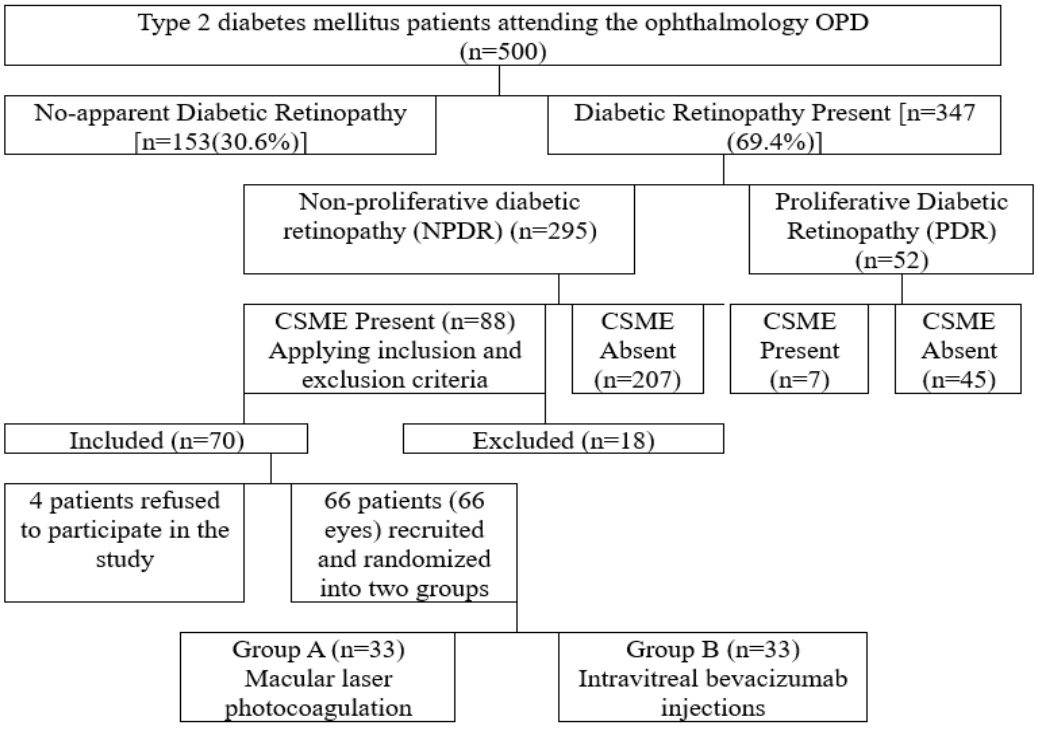
SUBJECTS AND METHODS

After taking permission from Thesis Committee and Institutional Ethics Committee of Government Medical College, Amritsar, 66 eyes of 66 patients with diabetic macular edema visiting outpatient department of Regional Institute of Ophthalmology, Govt. Medical College, Amritsar and satisfying the study criteria were selected and included in the study.

The pattern of the study was explained to the patient and written informed consent in his/her vernacular language was taken. Patient had the right to opt out of the trial at any time during the course of the study without having to give reasons for doing so.

Figure 1 shows the recruitment process followed.

Figure 1:Study Design



Inclusion critieria: Age between 40 to 70 years irrespective of sex with history of type 2 diabetes mellitus; with pure exudative diabetic maculopathy on optical coherence tomography (OCT); focal and/or diffuse DME defined as CSME with central macular thickness (CMT) on OCT of ≥300 μm.

Exclusion criteria: Patients with proliferative diabetic retinopathy (PDR); ocular diseases including glaucoma, uveitis and immature as well as mature cataract; vitreous haemorrhage / retinal detachment; patients who have already received intravitreal injections; patients with past history of laser treatment for diabetic retinopathy; pure ischemic maculopathy; already vitrectomised eyes.

STUDY PROTOCOL

A detailed clinical examination of both the eyes was done and the findings were recorded in a pre-prepared proforma: best corrected visual acuity (BCVA) by ETDRS chart; slit lamp

biomicroscopic examination of anterior segment; intraocular pressure measured by Goldmann applanation tonometer; fundus examination using indirect ophthalmoscopy with plus 20D lens and slit lamp biomicroscopy with plus 90D lens; optical coherence tomography (OCT) done with RS-330 Nidek machine using macular map scan and/or macular line scan protocols; fundus fluorescein angiography (FFA) using Topcon TRC-50DX retinal camera. Patients satisfying the inclusion criteria were then selected for this interventional study.

The selected patients were randomized into two groups using a computer based randomization program – A and B. Group A was administered macular laser photocoagulation with 532 nm Nd:YAG laser and group B was administered three monthly intravitreal bevacizumab injections (1.25 mg).

Technique of Laser photocoagulation (Group A): Preparation of the patient for laser treatment will involve informed written consent, fully dilated pupils, and application of topical anesthesia (0.5% proparacaine hydrochloride ophthalmic solution) to the eye to be treated. The treatment was done with 532 nm Nd:YAG laser slit lamp laser delivery system using Super Macula lens and Double Aspheric fundus lens.

Each patient was treated with one sitting of grid and/ or focal macular laser. The following laser parameters were used: i) focal laser to all leaking microaneurysms: spot size-50 µm; duration of pulse-0.05-0.1 sec; power- 50-100 mW; intensity- whiten or darken microaneurysm. ii) grid laser in area of diffuse diabetic macular edema: spot size-50 µm; duration of pulse-0.05-0.1 sec; power- 50-100 mW; intensity- mild light burns. Regular follow up at 1-month interval was done for a period of 3 months.

Technique for intravitreal bevacizumab injection (Group B) : Preparation of the patient for intravitreal injection of 1.25 mg bevacizumab included informed written consent and the procedure was performed following the protocol as mentioned ahead :- i) surgical mask to be used by both patient and the physician. ii) verification of the patient, agent and laterality. iii) application of topical anaesthetic drops (0.5% proparacaine hydrochloride ophthalmic solution) to minimize discomfort. iv) Application of 10% povidone-iodine solution to eyelashes and eyelid margins. iv) Insertion of a speculum to retract the eyelids away from injection site. vi) application of 5% povidone-iodine solution to the conjunctival surface at least 30 seconds before injection and it was the last agent applied to the intended injection site before injection. vii) 1.25 mg/0.05ml freshly prepared bevacizumab (Avastin®, Genentech, San Francisco, CA, USA) was then injected intravitreally using 1.0 ml disposable syringe with a 30G needle perpendicular to the sclera, 3.5 to 4.0 mm (measured with Castroviejo caliper) posterior to the limbus penetrating the pars plana between vertical and horizontal rectus muscles in the inferotemporal or superotemporal quadrant. viii) once the needle was removed, a sterile cotton applicator was used to prevent reflux. ix) the post-operative medications included antibiotic drops (gatifloxacin) for 1 week after the injection. Each patient was administered three intravitreal injections at one month intervals. Regular follow up at 1-month interval was done for a period of 3 months.

STATISTICAL ANALYSIS

Statistical analysis was done using statistics software SPSS 21, IBM, USA. Pearson's chi-squared test was used to determine whether there is a statistically significant difference between the expected frequencies and the observed frequencies in one or more categories. Two sampled t-test were used to differentiate means among two groups.

RESULTS

The present study was conducted on 66 patients (66 eyes) presenting with DME who visited the out-patient department of Regional Institute of Ophthalmology, Government Medical College, Amritsar from July 2021 to June 2022. Patients of age 40-70 years were included in the study. The mean age of the patients was 58.18±4.56 years in laser group and 58.88±8.78 years in bevacizumab group.

Table 1 shows the non-ocular baseline characteristics of the patients recruited in the study. The number of males recruited was 13 and 16, while the number of females was 20 and 17 in laser and bevacizumab groups respectively.

Table 1:

Non-ocular baseline characteristics

	Group A	Group B	p value
No. of patients (eyes)	33	33	
Mean age (years)	58.18±4.56	58.88±8.78	0.687
Males/Females	13/20	16/17	0.457
Mean duration of diabetes (years)	12.03±3.01	12.55±5.76	0.647
Mean systolic BP (mmHg)	147.15±25.45	149.21±18.94	0.710
Mean diastolic BP (mmHg)	82.67±10.03	82.24±7.26	0.845
Mean HbA1c (%)	7.98±0.54	7.74±0.96	0.212

Most number of patients had a known diabetic history since 11-15 years that is 30 (45.45%), followed by 6-10 years in 19 (28.79%), 16-20 years in 9 (13.64%), ≤5 years in 5 (7.58%) and >20 years in 3 (4.55%) patients. The mean duration of diabetes in laser group was 12.03±3.01 years and 12.55±5.76 years in the injection group. Mean HbA1c was 7.98±0.54 in laser group and 7.74±0.96 in bevacizumab group which was not significantly different ($p>0.05$).

Table 2:

Ocular characteristics at baseline

	Group A	Group B	p value
Right/left	21/12	17/16	0.319
IOP (mm Hg)	15.36±3.81	15.15±2.91	0.800
Mean BCVA (logMAR)	0.81±0.15	0.83±0.18	0.600
Mean CMT(µm)	496.03±84.69	516.48±93.5	0.289
Mean MV (mm3)	12.30±2.21	13.05±1.84	0.140

Baseline ocular characteristics are shown in Table 2. The number of patients having Moderate NPDR with CSME and Severe NPDR with CSME was respectively 22 and 11 in laser group and 15 and 18 in injection group. At the end of 3 months patients having Moderate NPDR was 8 and 15, having Severe NPDR was 3 and 6, having Moderate NPDR with CSME was 18 and 5 and having Severe NPDR with CSME was 4 and 7 in the laser and injection groups respectively. Thus, CSME was seen resolved in 11 patients in the laser group and 21 patients in the injection group after 3 months.

Mean value of BCVA at presentation in the laser group was 0.81±0.15 and in group B (Injection) was 00.83±0.18. The values changed to 0.76±0.19 in group A and to 0.49±0.24 in group B after 3 months. The change was significant only in group B (Injection). Table 3 shows the efficacy outcomes at three months.

Table:3

Efficacy outcomes at 3 months

	Group A	Group B	p value
Mean BCVA (logMAR)	0.76±0.19	0.49±0.24	<0.001
Mean CMT(µm)	339.24±96.54	283.27±89.22	0.017
Mean MV (mm3)	9.92±2.57	8.63±1.83	0.021

Mean CMT at presentation was 496.03±84.69µm in group A and 516.48±93.5µm in group B. It changed to 339.24±96.54µm in group A and 283.27±89.22µm in group B at the end of three months. Mean MV at presentation was 12.30±2.21mm^3 in group A and 13.05±1.84mm^3 in group B. It changed to 9.92±2.57mm^3 in group A and 8.63±1.83mm^3 in group B at the end of three months. Thus, the two groups were similar to each other at baseline while at three months the difference was significant.

DISCUSSION

In this study, patients with pre-diagnosed type 2 diabetes mellitus aged 40 to 70 years were enrolled over a period of one year. The mean age was 58.18+/-4.56 years in laser group and 58.88+/-8.78 in injection group. Majority patients were in 51-60 years age group, followed by 61-70 and 41-50 years.

Duration of diabetes is a major risk factor in development and progression of diabetic retinopathy. In this study, the mean duration of diabetes was 12.03+/-3.01 in laser and 12.55+/-5.76 in bevacizumab group. Mean HbA1c was 7.98±0.54 in laser group and 7.74+/-0.96 in injection group. HbA1c level is the measure of glycemic control in diabetics and it has been postulated that with decrease of HbA1c, rate of macular edema and the subsequent micro vascular complications also decrease.[3]

Based on baseline fundus examination and OCT findings, 67% of patients in the laser group had Moderate NPDR with CSME and 33% had Severe NPDR with CSME, while the proportions were respectively 45% and 55% in injection group.

At the 3 months follow up, 55% patients had Moderate NPDR with CSME and 12% had severe NPDR with CSME in laser group, whereas the proportions were 15% and 21% respectively in the injection group. Therefore, severity of retinopathy improved in 33% cases in laser group and 64% cases in injection group with deterioration in none of the cases.

CSME was seen resolved, with CMT values less than 300 µm, in approximately one-third patients in the laser group and two-third patients in the injection group at three month follow up. In the BOLTstudy[4],(intravitreal bevacizumab or laser therapy in the management of diabetic macular edema), 8 out of 37 (21.6%) patients were early responders achieving a dry macula with CMT <270 um at 4 months after receiving three intravitreal bevacizumab injections at six week intervals which was lower as compared to this study.

BCVA was measured using ETDRS Visual acuity charts and converted to Logarithm of Minimum angle of resolution (logMAR). The mean logMAR BCVA at presentation was 0.81±0.15 and 0.83±0.18 in laser and injection groups respectively. The mean logMAR BCVA at the end of three months was 0.76±0.19 in laser group and 0.49±0.24 in injection group which was found to be statistically highly significant. In a 2007 report by Soheilian et al[5], where they compared macular laser photocoagulation, intravitreal bevacizumab injection and combined bevacizumab plus triamcinolone intravitreal injection in diffuse diabetic macular edema, it was shown that twelve weeks after interventions, visual acuity improvement compared with the baseline value was meaningful only in the IVB group (P=0.0001).

Central macular thickness (CMT) and Macular volume (MV) were measured using the Macular Map scan protocol with the help of RS-330 Nidek machine. The mean CMT and MV at presentation were calculated to be respectively 493.03±84.69 µm and 12.30±2.21 mm^3 in laser group and 516.48±93.50 µm and 13.05±-1.84 mm^3 in injection group. There was no significant difference between the two groups with respect to baseline CMT and MV.

The mean CMT and MV at the end of three months were 339.24±96.54 µm and 9.92±2.57 mm^3 in laser group and 283.27±89.22 µm and 8.63±1.83 mm^3 in injection group. The difference between means of the CMT and MV at the end of three months was found to be statistically significant. (p=0.017 for CMT and p=0.021 for MV). In contrast, Solaiman et al[6] reported that three months after a single treatment, the mean CMT was still better than baseline in all three groups of macular grid laser photocoagulation, intravitreal bevacizumab and combined laser and bevacizumab group, but this improvement was significant only in the combined group (P<0.05).

In this study, the adverse events associated with the laser treatment were transient decrease in visual acuity in 1 patient, decreased visual acuity at three month follow-up in 3 patients, vitreomacular traction in 1 patient and vitreous haemorrhage in 1 patient. Similar to this

study, Solaiman et al[6] reported there was no deterioration below baseline BCVA in all eyes included in the study, except three eyes in the macular grid photocoagulation group.

The adverse events seen in the injection group were transient decrease in visual acuity in 3 patients, transient IOP rise to more than 25 mm Hg measured 2 hours after the injection in 2 patients, transient pain during/after injection in 5 patients which was relieved with topical NSAIDs, red eye other than subconjunctival haemorrhage in 4 patients, subconjunctival haemorrhage in 1 patient and vitreomacular traction in 1 patient. There were no cases of endophthalmitis, intraocular inflammation, or retinal detachment.

There were some inherent limitations in this study. We did not correlate the functional or anatomical success in the different morphological patterns of DME between the two groups.

This study concludes that intravitreal injections of bevacizumab are superior to macular laser photocoagulation in improving BCVA in type 2 diabetes mellitus patients with DME over a follow up period of three months. Also, bevacizumab is better than laser in reducing central macular thickness as well as macular volume. Thus, intravitreal bevacizumab is more effective agent for anatomical as well as functional improvement in diabetic macular edema.

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