Original Article

Effect of Bevacizumab and Laser in the Management of Diabetic Maculopathy

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Purpose. To compare the best corrected visual acuity response after repeated intravitreal Bevacizumab and Argon laser alone or in combination in patients with diabetic macular edema.

Material and Methods. One hundred and twenty cases of diabetic macular edema involving the fovea were enrolled for the study. They were randomly divided in 3 groups. Group A received intravitreal Bevacizumab (ivB), Group B Argon laser alone and Group C received both. The follow up was up to 9 months. Main outcome measures were mean average change in best corrected visual acuity (BCVA) and central macular thickness (CMT) from base line until final assessment at 9 months.

Results. The baseline mean ETDRS BCVA was 58.72 ± 10.68 (range 38 – 73) in the ivB group, 55.55 ± 10.75 (range 38 – 69) in laser group and60.12 ± 10.48 (range 38 – 73) in ivB + laser group. The mean ETDRS BCVA at month 9 was68.51 ± 8.59 (range 49 – 74) in the ivB group, 56.08 ± 12.63 (range 38 – 74) in laser group and 70.2 ± 8.74 (range 49 – 78) in ivB + laser group (*P* =0.000). At 9 months, central macular thickness decreased from 411.7 ± 96.38 (range 296 – 626) at baseline to 249.65 ± 65.37 (range 193 – 454) in ivB group, 413.03 ± 96.38 (range 302 – 615) to 364.92 ± 107.11 (range 206 – 588) in laser group and 415.9 ± 97.50 (range 299 – 649) to 244.8 ± 60.83 (range 193 – 488) in ivB + laser group (P= 0.000).

Conclusion. Bevacizumab alone or in combination with argon laser provide better gain in BCVA as compared to laser alone in patients with diabetic macular edema.

Diabetic maculopathy is responsible for the visual loss in patients with diabetic retinopathy[1]. It can be prevented by good metabolic and blood pressure (BP) control[2]. According to the Early Treatment of Diabetic Retinopathy Study (ETDRS), moderate visual loss can be reduced up to 50% in patients with clinically significant macular edema (CSME) with laser photocoagulation but visual improvement was noted in less than 3% of cases[3]. Despite of other therapeutic option, macular laser therapy (MLT) remains the standard treatment for diabetic macular edema (DME) for long time[4]. The increased levels of vascular endothelial growth factor (VEGF) were found in the vitreous cavity of patients with diabetic retinopathy making anti-VEGF treatment an attractive therapeutic modality in DME[5]. Monthly injections of Ranibizumab (0.5 mg in 0.05 ml) in the RESOLVE study revealed improvement in visual acuity (mean gain of 10 letters in ETDRS VA)[6]. Another study (READ2) revealed improvement of a 7.2 – letter at 6 months in patients receiving Ranibizumab alone, compared with 3.8 letters in patients receiving combined MLT and 3 monthly Ranibizumab injections, and a 0.4 – letter loss in subjects receiving only MLT[7].

Several studies have also reported favorable effect of intravitreal bevacizumab (ivB) in the management

of nonischemic diabetic maculopathy[8-9]. We conducted this study to see the effect of ivB, laser alone and in combination of ivB and laser in the management of diabetic maculopathy.

MATERIAL AND METHODS

STUDY DESIGN: Prospective comparative intervenetional 3 arm case study.

SETTINGS: The study was conducted at College of Ophthalmology and Allied Visual sciences, Mayo Hospital Lahore.

DURATION OF STUDY. Nine months

SAMPLE SIZE: 120 cases with diabetic maculopathy were included

INCLUSION CRITERIA: The following enrollment criteria were used:

1. Diabetic patients of either sex of more than 18 years of age.
2. No previous treatment.
3. Best corrected visual acuity (BCVA) between 6/60 or 6/12.
4. Media clarity, pupillary dilation sufficient for adequate fundus imaging.
5. CSME involving the fovea and central macular thickness (CMT) of more than 270 micron on optical coherence tomography (OCT).

EXCLUSION CRITERIA:

Ischemic maculopathy

1. Macular edema due to other causes
2. Any cause which will not allow the visual improvement(e.g. dense subfoveal hard exudates, macular cyst, amblyopia)
3. Proliferative diabetic retinopathy

Baseline Evaluation. After detailed history BCVA was measured using Snellen chart. Anterior segment and dilated posterior segment slit – lamp biomicroscopic examination was performed. Intraocular pressure was also noted. All subjects had colour fundus photographs, fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) imaging (Optovue).Retinal thickness was measured on a point centered at fixation. (Defined as central macular area 1000 micron in diameter from the center of fixation).

Randomization. Eligible patients were randomized into 3 groups. Group A received ivB, Group B received laser and group C received ivB + laser within 7 days of recruitment. All patients were reviewed after every 6 weeks.

Group A. All patients received ivB injection (1.25 mg in 0.05 ml) in the supero or infero temporal quadrant using standard aseptic intravitreal injection technique within 7 days of randomization. Two more injections were given at 6 and 12 weeks. All these patients were followed after every 6 week up to 36 weeks (6, 12, 18, 24, 30 and 36 weeks). Retreatment decision was based on achievement of stable BCVA and macular thickness. Stable BCVA was defined as no change in BCVA during the last 2 consecutive visits or having 6/6 vision. Stable macular thickness was defined as "on 3 consecutive visits with the CMT within 20 micron meter of the patient's thinnest recorded CMT".

At each visit, the patients were asked about the side effects, a complete ocular examination (including BCVA, anterior chamber reaction, IOP, and dilated fundoscopy) and OCT were performed. Color fundus photography and FFA were performed at 18 and 36 weeks.

Group B. All patients received focal or grid laser treatment within 7 days of randomization. Patients were followed up every 6 weeks. Retreatments were given according to ETDRS guidelines not earlier than 12 weeks from the last treatment (12, 24, and 36-weeks). 50 – 100 micron argon laser spot size was used to mild blanching of retinal pigment epithelium and microaneurysms. Similarly grid pattern was applied to the area of diffuse leakage. At each visit history and BCVA was recorded. A complete ocular examination (IOP, and dilated fundoscopy) and OCT were performed. Color fundus photography and FFA were performed at 18 and 36 weeks.

Group C. All patients received ivB and focal or grid laser treatment within 7 days of injection. These patients also received 2 more injection at 6 and 12 weeks times. Patients were followed up every 6 week time. At each visit, a full history and BCVA was recorded. A complete ocular examination (including anterior chamber reaction, IOP, and dilated fundoscopy) and OCT were performed. Color fundus photography and FFA were performed at 18 and 36 weeks. The data was entered and analyzed in Statistical package for social sciences version 16 (SPSS16).

Outcome Measures. The primary outcome measure was a comparison of BCVA at base line and 09 months

Table 1. Base line demographic and disease characteristics

	GROUP A	GROUP B	GROUP C
No. of patients	43	36	41
Male : Female	27:16	22:14	24:17
Mean Age ± SD Men Women	50.9 ± 6.09 53 48	50.6 ± 7.39 55 43.5	51.3 ± 4.95 53 48.5
Type of Diabetes Type I Type II	 3 40	 2 34	 4 37
Mean Duration (inyrs)	15	14	13.5
DME Type Focal Diffuse	 32 11	 25 11	 27 14

Table 2. Visual acuity letter score (approximate snellen equivalent)

ETDRS Letter Score	Approximate Snellen Equivalent
More than79	(more than 20/25)
78-69	(20/32 to 20/40)
68-59	(20/50 to 20/63)
58-49	(20/80 to 20/100
48-39	(20/125 to 20/160)
Less than 38	(less than 20/200)

Table 3. Out come measures among three groups

	GROUP A	GROUP B	GROUP C
Base line mean ETDRS BCVA	58.72 ±10.68 Range (38- 73)	55.55± 10.75 Range (38-69)	60.12± 10.48 Range (38-73)
9 months mean ETDRS BCVA	68.5 ± 8.59 Range (49-74)	56.08 ±12.63 Range (38- 74)	70.29 ± 8.74 Range (49- 78)
Mean change in BCVA from base line	9.7 ± 4.3	0.5 ± 3.9	10.1 ± 4.9
Base line mean CMT (micron meter)	411.74±96.38 Range (296- 626)	413.03± 96.38 Range (302- 615)	415.97±97.50 Range(299-649)
9 months mean CMT (micron meter)	249.65 ± 65.37 Range (193 – 454)	364.92±107.11 Range (206- 588)	244.85 ± 60.83 Range (193-488)
Mean change in CMT	-162±48.04	- 48±33.40	- 171± 56.37

Table 4. Adverse effects

	GROUP A	GROUP B	GROUP C
Angina pectoris	1	0	0
Crebro vascular Accident	0	0	0
Myocardial Infarction	0	0	0
Hypertension	2	0	2
Eye pain during &after inj or lasers	20	4	15
Subconjunctival haemorrhage	5	0	3
Floaters	4	0	2
Nausea and Vomiting during FFA.	1	2	1
Endophthalmitis	0	0	0
Intravitreal heamorrhage	0	0	0

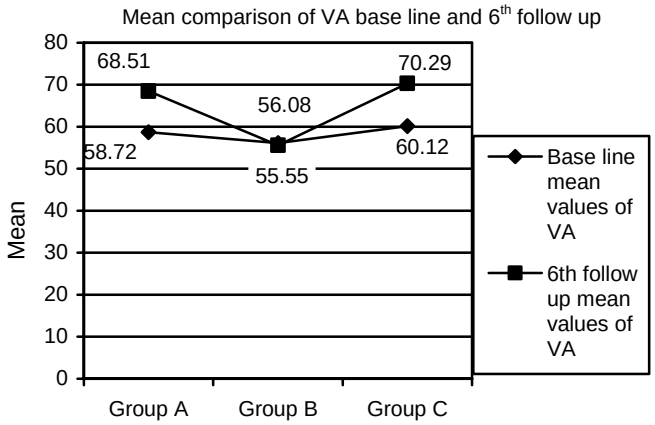

Fig. 1: Mean change in best corrected visual acuity from base line to 9 months

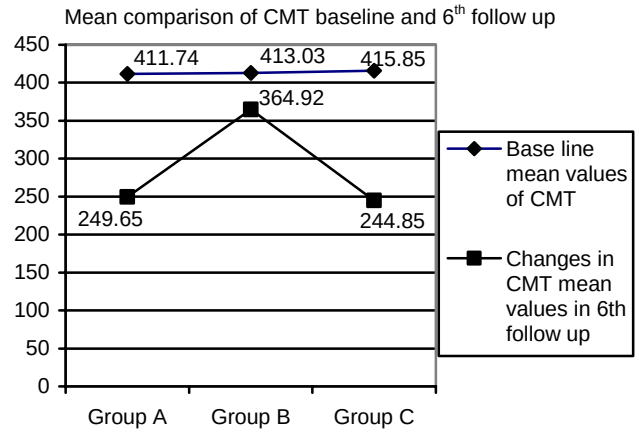

Fig. 2: Mean change in central macular thickness from base line to 9 months

between three groups. The secondary outcome measures were a comparison between three groups at 12 months with regard to:

1. Mean CMT
2. Ocular and systemic side effects

RESULTS

One hundred and twenty eyes of 120 patients were enrolled for study starting from September 2010 to May 2011. The mean age of the patients was 50.66 ± 7.66 years (range 40 – 67 years), with 47 female (39.16%) and 73 male (60.83%). Forty three patients were randomized to group A for ivB and 36 in group B for laser treatment. Forty one patients received both iv B and laser in group C. The Snellen visual acuity data was converted to ETDRS study equivalent for calculation and comparison (Table 2). Baseline demographics and diabetes characteristics were compared among three groups (Table 1).

The mean change ± SD in BCVA letter score from baseline to 9 months was 9.7 ± 4.3in the iv B group,0.5 ±3.9 in laser group and 10.1 ± 4.9 in iv B + laser group. The mean decrease in CMT from baseline to 9 month was -162 ± 48.04 in Bevacizumab group, -48 ± 33.40 in laser group and -171 ± 56.37 in laser + iv B group. The mean average change in the BCVA letter score from base line to 9 month was significant (P = 0.000) and CMT from baseline to end point (09 months) was also significantly better (P = 0.000) with Bevacizumab and Bevacizumab + laser than with laser treatment alone.

Group A and C has little difference as improvement in BCVA (P = 0.000) and reduction in CMT (P = 0.000). In the group A and C rapid improvement was noted on first post treatment follow up (at 6 week) which was continued up to month 3. These values were maintained until the last follow up at nine months except in 2 cases of group A. They were again given two more injection of iv B due to decrease in BCVA and increase on CMT. In Group B mean BCVA remain stabilized around baseline level and reached a 0.5 letter gain at 09 months.

Safety: No serious ocular side effects were noted except pain at the time of injection followed by subconjunctival hemorrhage. Few patients also noted floaters for a day or so after intravitreal injection. No case of endophthalmitis reported in any of the treatment group. Hypertension was reported after injection in 4 patients, which was controlled with medications. It was due to systemic VEGF inhibition. There was no case of myocardial infarction and stroke after iv B.

DISCUSSION

The results of the study revealed that Bevacizumab alone or combined with laser treatment is superior to laser treatment in rapidly improving and maintaining VA in patients of DME. There were no efficacy differences detected between group A and C. A greater proportion of patients treated with Bevacizumab gained BCVA letter scores from baseline as compared with the patients treated with laser. The Bevacizumab also showed significant improvement in CMT on OCT and resolution of leakage on fluorescein angiography. The results of RESTORE and DRCR.net study are consistent with our study. Results from the DRCR.net study showed that Ranibizumab combined with laser (prompt or deferred) was more effective in improving VA in DME than laser treatment alone after 1 year. The RESOLVE study also revealed rapid and continuous improvements in BCVA over a period of 12 months as compared to sham and laser treatment.

The limitations of the study are small number of patients and relatively short follow-up. Large multicenter studies are required with longer follow-up of at least 3 years which should compare laser with IVB + laser.

In conclusion Bevacizumab alone or in combination with laser is superior to standard laser in improving and maintaining BCVA and CMT.

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