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Research Article

Intravitreal Bevacizumab (Avastin) Alone Or With Laser Photocoagulation for Diabetic Macular Edema

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ABSTRACT

Background: Surgical

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INTRODUCTION

Diabetic retinopathy (DR) is a micro vascular complication of diabetes mellitus(DM) that can affect peripheral retina,the macula or both and affects 1 in 3 persons with DM. DR remains a leading cause of vision loss in working adults in developed countries. Estimates indicate that more than 360 million people will be affected by DM by 2030.[1]

With an increasing prevalence of diabetes, there is also an alarming rise in the prevalence of Diabetic retinopathy (DR) in both urban and rural India. Epidemiological data suggests the prevalence of DR is 18% in the urban and 10.4% in the rural India. It means DR is found in every 5th person with diabetes in the urban and in every 10th person with diabetes in the rural areas of India. Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study covering 3 states (Tamil Nadu, Maharashtra and Jharkhand) and 1 union territory (Chandigarh) states that the prevalence of Diabetes was between 10.4% - 13.6% and that of of Prediabetes (Impaired Fasting Glucose and/or Impaired glucose tolerance) was between 8-14.6%. [2] Retinal hypoxia is the primary cause of DR which increases the expression of vascular endothelial growth factor (VEGF) an endothelial cell-specific mitogen which induces angiogenesis and increase vascular permeability by affecting endothelial tight-junction protein.[3] Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision. It is the most common cause of vision loss in diabetic patients, with a prevalence that ranges from 19% to 65%.4 DME is associated with thickening of the basement membrane and reduction of pericytes which are believed to increase permeability of the retinal vasculature. This compromises the blood-retinal barrier

causing a leakage of plasma constituents and subsequent retinal edema and hypoxia, all of which stimulates the production of vascular endothelial growth factor (VEGF). DME damages the central retina, which impairs color and pinpoint vision, leading to blurring of vision. DME can be classified as either focal or diffuse types. Laser pan-retinal photocoagulation (PRP) is the primary treatment modality for preventing vision loss in patients with PDR(Proliferative diabetic retinopathy). Although PRP effectively reduces retinal neovascularization, it is associated with the release of cytokines, including vascular endothelial growth factor (VEGF), which can cause adverse effects in the retina.[5] including ME, thereby leading to transient or permanent loss of visual acuity [6] and contrast sensitivity. Therefore, many researchers have used anti-VEGF drugs such as intravitreal bevacizumab (IVB) injections with promising results to prevent the development of PRP-related ME.[7]

METHODOLOGY

38 eyes of 20 patients with diabetic macular edema(DME) (14 males and 6 females)were followed up for 6 months from the outpatient clinic of Ophthalmology Department. Approval of the study was obtained from the institutional ethical committee, and informed consent was obtained from all patients. The study followed the principles of Declaration of Helsinki of human subjects.

Inclusion criteria

All the diabetic patients with DME having BCVA ranged from 20/30 to 20/200 and central macular thickness on Optical coherence tomography(OCT) of >270 µm and willing for regular follow up visits were included.

Exclusion criteria

1. Patient with macular edema due to a cause other than DME.
2. Previous recent ocular surgeries, disease (uveitis, glaucoma, etc).
3. Previous intravitreal injections or argon laser retinal photocoagulation.
4. Media opacity that interfered with imaging.
5. Evidence of vitreomacular traction.
6. Evidence of ischemic maculopathy.
7. Cystoid macular edema.

After detailed history taking each patient underwent complete ophthalmological examination which including BCVA(Best corrected visual acuity)measurement with ETDRS charts and ophthalmic examination, including slit lamp bio microscopy,baseline intraocular pressure measurement with Goldmann applanation tonometry and dilated fundus examination with +90 diopter lens and indirect ophthalmoscopy. All patients had fundus fluorescien angiography (FFA).Baseline CMT was analyzed by OCT Topcon analyzer.

Patients were subdivided randomly using closed envelope technique into 2 groups:

i) 1st group received intravitreal bevacizumab only(IVB group): 10 patients,8 Males and 2 females,with mean age ± standard deviation (SD) of 58.45 ± 8.24 years.

- They received 1.25 mg bevacizumab (Avastin ®) in 0.05 ml intravitreally at baseline, 1st and 2nd month then monthly if needed “pro re nata (PRN)”.
- Retreatment was considered if there is presence of residual edema, CMT >350µ on OCT and/or unstable VA.

(ii) Second group received Combined laser and intravitreal bevacizumab(Avastin ®) (IVB + laser group);10 patients, 6 males and 4 females with mean ages ± SD of 60.12 ± 7.34 years, who received repeated bevacizumab 1.25 mg in 0.05 ml intravitreally at baseline, 1st and 2nd months followed by focal/grid laser within 2 weeks from the first injection.

- If residual edema was still present with CMT >350 µ, patients were treated with IVB monthly till CMT ≤200 µ on OCT or no further improvement on two consecutive visits.
- Patients were followed up every month for 1 year, complete ocular examination including BCVA, IOP, and CMT was recorded at each visit
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- along with the presence of any complications or side effects.

Procedure

- All eyes had several drops of local anesthetic Paracaine with dilatation of pupil with Tropicamide+Phenylephrine eyedrop before the procedure. After the eye had been prepared in standard fashion using 5% povidone-iodine, an eye lid speculum was used to stabilize the eyelids and the injection of 1.25 mg (0.05 ml), bevacizumab was injected at 3.5mm in pseudophakic eye and 4 mm in phakic eye posterior to the limbus in the vitreous cavity with a tuberculin syringe and 30 gauge needle.
- After the injection, the optic nerve head examination with indirect ophthalmoscopy and the IOP were assessed. Paracentesis was performed if the IOP was elevated. The patient was instructed to instill topical moxifloxacin ophthalmic solution 0.5% four times daily for 1 week after the intravitreal injection.
- Laser photocoagulation: Macular grid photocoagulation was performed with an argon green laser delivering 2–3 rows of 50–100 µm spots, for 0.1 s, 100 µm apart in the parafoveal region >500 µm from the edge of the FAZ. Then, 150 µm to 200 µm spots were applied 200 µm apart to the remaining areas of retinal thickening and capillary nonperfusion. Focal leaks outside or within the zones of diffuse leakage were treated with 100 µm to 150 µm spots to achieve a mild blanching of the retinal pigment epithelium.

Statistical analysis

- Demographic and clinical characteristics of 20 randomized diabetic patients (10 patients) per treatment group were subjected to descriptive analysis (mean, standard deviation, and range) using the SPSS statistical software program (SPSS, version 21, Spss Inc, Chicago, ILL Company USA).
- The data on CMT outcome at 12 months' follow-up between the treatment groups were statistically analyzed based on two-sided 95% confidence interval on the t-distribution. The difference in least square means and two-sided 95% CI of mean average changes in the CMT, as well as average change in VA from the baseline to 12 months' follow-up, was estimated by the paired t- test. Mean and standard deviation were calculated for each variable. The significant differences among treatment groups were matched and the results were reflected to be significant at $P < 0.05$.

RESULTS

Patients were divided randomly into two groups: 10 patients (20 eyes) were treated with IVB (IVB group) and 10 patients (18 eyes) received IVB + laser (IVB + laser group). All eyes included in the study received IVB injections for 3 months then PRN, plus macular laser for the patients in

the combined group during the 12-month follow-up period. The demographic and clinical characteristics of all patients are summarized in table 1.

Table 1: The demographic analysis between the treatment groups

	IVB	IVB+laser
Age	58.45 ± 8.24	60.12 ± 7.34
Male(%)	8(80%)	6(60%)
Female(%)	2(20%)	4(40%)
Diabetes type 2	10(100%)	10(100%)
Disease duration (year)±SD	12.14±2.42	11.48±2.98
HbA1c(%)±SD	7.85±0.78	7.96±0.71
IOP (mmHg)±SD	17.60±2.51	18.15±3.21
Lens status Phakic	16 eyes (80%)	14 eyes (~78%)
Pseudophakic	4 eyes (20%)	4 eyes (~22%)
CMT (µm)±SD	396±46.85	398±51.50

IOP- Intraocular pressure, IVB- Intravitreal bevacizumab, CMT- Central macular thickness, SD- Standard deviation Central macular thickness at the baseline and 12-month follow-up

- After 12-month follow-up, the mean number of injections in IVB group was five while in the combined group it was only three during the whole year of follow-up.
- The IVB + laser group showed the highest significant decrease in CMT than that of the baseline, while the IVB-only-treated group showed the least significant change in CMT than baseline (−156.5 ± 33.47 vs. −138.3 ± 40.15, respectively).
- In addition, IVB + laser group showed a highly significant decrease in CMT when compared with IVB–only-treated group ($P < 0.0001$)

Table 2: Distribution of visual acuity at baseline and 1-year follow-up

	IVB Group (n=20 eyes)	IVB+Laser (n=18 eyes)
Baseline VA letter score		
Median (25^{th} , 75^{th} percentile)	55.0(52,62)	56(49,70)
≥ 55 (better than 20/70)%	10(50)	9(50)
< 55 (20/70 or worse)%	10(50)	9(50)
VA letter score at baseline,Eyes%		
78-74(20/30)	4(20)	2(11.11)
73-69(20/40)	5(25)	4(22.22)
68-64(20/60)	2(10)	5(27.7)
63-54(20/80)	5(25)	3(16.6)
53-49(20/100)	1(5)	1(5.55)
48-39(20/150)	2(10)	2(11.11)
≤38(20/200	1(5)	1(5.55)
VA letter score at 1 year follow up		
78-74(20/30)	6(30)	5(27.7)
73-69(20/40)	4(20)	4(22.2)

68-64(20/60)	3(15)	2(11.1)
63-54(20/80)	1(5)	3(16.6)
53-49(20/100)	3(15)	2(11.1)
48-39(20/150)	2(10)	1(5.55)
≤38(20/200)	1(5)	1(5.55)

While after 12-month follow-up, the mean average change in VA letter score was significantly improved than that of the baseline in IVB, IVB + laser-treated groups ($P < 0.018$ and <0.002, respectively) Moreover, the VA letter score showed a higher significant improvement in IVB + laser group ($P < 0.007$) when compared with the IVB treated group. No ocular or systemic side effects recorded in both groups except 2 cases of subconjunctival hemorrhage at the site of injection, 3 cases in the combined group, and one case in the IVB group, also 2 cases shows transient rise in IOP in Group A.

DISCUSSION

The current gold standard therapy for DME treatment is administering anti-VEGF agents. [8-10] Other treatment modalities include Intravitreal steroid injections, Laser photocoagulation and combined approach. Current VEGF inhibitors include aflibercept (Eylea), Ranibizumab (Lucentis), pegaptanib (Macugen), and bevacizumab (Avastin). Ranibizumab and aflibercept are approved by Food and Drug Administration (FDA) for DME. Other anti-VEGF agents are also being considered due to cost effectiveness. [11] Now in our study, we tried to emphasise the significant role of combined laser and bevacizumab intravitreal injection in treating diabetic macular edema in comparison to the intravitreal bevacizumab injection alone. In comparison to the baseline, there was a significant decrease of CMT in both groups of patients which was more in the combined group than bevacizumab only group. After 12-month follow-up, the mean average change in VA letter score was significantly improved in both groups but more significant in the combined than in bevacizumab only group. These results are consistent with the previously reported results of Seo and park. [12] who stated that IVB injection resulted in significant improvement in BCVA and reduction in central retinal thickness as early as 1 week after injection, and persisted for up to 3 months. Also in consistence with Zhang et al. [13] who concluded that combining anti-VEGF with laser photocoagulation is a complementary treatment with high efficacy in treating DME and decreasing recurrence relative to other applied methods of therapy. Studies have also shown that although PRP is more cost effective in the absence of DME at the baseline but in the presence of DME, intravitreal Bevacizumab is more cost effective interm of life quality as it improves both vision and retinal anatomy and reduces the need of vitrectomy. Studies testing the efficacy of laser after anti-VEGF therapy have shown once the retina has been sufficiently thinned with anti-VEGF drugs, laser photocoagulation stabilizes the retinal thickness and reduces the treatment burden. However, there was reduction in CMT only as long as anti-VEGF injections were being given. [14] Besides, repeated IVB injection does provide a long-term benefit for the treatment of DME. Performing macular grid photocoagulation within 2-3 weeks subsequent to the initial IVB injection provides a longer disease-free intervals and reduces the burden of more frequent injections. And, this co relates with our study in which we had repeated the IVB injection for minimum three times and there was no any incidence of recurrence of DME all over the period of follow-up. On the

other hand, many previous studies have shown that adding laser photocoagulation to a regimen of intravitreal anti-VEGF injections did not improve visual outcome but contributed in reduction of the number of injections.[15] And, this co-relates with our study in which the mean number of injection is less in combined group than in the IVB group (three versus five injections). In addition, there is a potentiation of the laser treatment, after the retina has been sufficiently thinned using anti-VEGF agents which again goes in favour of our study.

CONCLUSION

From our results, it is evident that each treatment methodology potentiates the impact of the other because of different modes of action, and a combined therapy can yield more favourable outcome and may be considered a superior decision for use rather than single treatment to acquire more steady and delayed change in the treatment of DME.

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