ORIGINAL ARTICLE

INTRAVITREAL BEVACIZUMAB ALONE VERSUS INTRAVITREAL BEVACIZUMAB IN COMBINATION WITH FOCAL MACULAR PHOTOCOAGULATION IN DIABETIC MACULAR OEDEMA

Asad Ullah Jatoi[1], Noman Ahmed Shaikh[1], Ashok Kumar Narsan[1], Asma Jatoi[2]

[1]Department of Ophthalmology, Institute of Ophthalmology, [2]Department of Radiology, Liaquat University of Medical & Health Sciences, Jamshoro-Pakistan

Background: To compare the mean best corrected visual acuity (BCVA) between intravitreal bevacizumab (IVB) and combination treatment bevacizumab and Focal Macular Photocoagulation (FMP) for diabetic macular oedema (DME). **Method:** It is a randomized control trial conducted at Department of ophthalmology at Institute of Ophthalmology, Liaquat University of medical and health sciences, Jamshoro from 1st November 2019 to 31st October 2020, in which 260 Patients between the ages of 40 to 75 years, with DME were included. While patients with macular oedema secondary to other causes than diabetic retinopathy, presence of vitreomacular traction, aphakic patients, history of glaucoma or who had received pan-retinal photocoagulation, IVB, triamcinolone within 12 months, patients with history of stroke or cardiac disease, patients with media opacities such as corneal opacities were also excluded from the study. Two hundred sixty (260) patients were divided in two groups. Group A has 130 patients and they were treated with IVB alone. Group B also included 130, and they were treated with combination of IVB+FMP. The patients were followed-up monthly for 3 months and BCVA was checked at the end of 3 months. **Results:** Patients in group B showed superior visual outcome, when they were treated with IVB+FMC as compared to patients in group A who received IVB alone. **Conclusion:** Combination treatment OF IVB+FMP is an effective treatment option for diabetic macular oedema as compared to IVB alone with better mean visual outcome.

Keywords: Diabetic Macular Oedema; Focal laser Photocoagulation; Anti-VEGF drugs

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INTRODUCTION

Diabetes mellitus (DM) consists of a group of disorders in which hyperglycaemia is main characteristic feature. Currently, it is divided into two main groups: Type 1 and Type 2 DM.[1] Worldwide, it is seventh leading cause of death with rate of mortality of 82.4 per 100,000.[2] The most common ocular complication of diabetes mellitus is Diabetic Retinopathy (DR), which is considered as a disease affecting microvasculature of retina.[3] Diabetic retinopathy is globally escalating. About 100 million people with DM are affected by DR globally.[4] The prevalence of DR in Pakistan is 28.78%.[5] Diabetic macular oedema (DME) is explained as thickening of retina involving the center or adjacent parts of the macula. It is the most common cause of loss of vision in diabetic patients with DR.[6] Poorly controlled diabetes is associated with microangiopathy and degenerative neuroretinopathy secondary to chronic hyperglycaemic state. This metabolic disturbance causes activation of many different pathways such as activation of hexoaminase pathway, protein kinase C pathway and polyol pathway, which causes production of advanced glycosylation end products (AGEs). These AGEs cause oxidative stress, which causes formation of free radicals. Free radicals damage the pericytes, proteins of tight junctions and loss of vascular endothelial cells. Damage to tight junctions' results in damage to both inner and outer blood retinal barrier (BRB), which along with loss of pericytes causes extravasation of electrolytes, large macromolecules and fluid, thus causing Diabetic Macular Oedema (DME).[7,8] Diabetic macular oedema can be classified clinically, angiographically and on the basis of OCT. The Early treatment Diabetic Retinopathy Study (ETDRS) classifies DME into clinically significant macular and non-clinically significant macular oedema. The clinically significant macular oedema is defined as (1) retinal thickening involving the center or present within 500 microns of center of macular area (2) presence of hard exudates involving the center or within 500 microns of center of macular area (3) area of retinal thickening about 1 disc diameter or greater, any part of which lies within one disc diameter of center of macular area.[9] On the basis of fluorescein angiography, DME is defined as focal or diffuse. Focal DME is caused by leakage from microaneurysm and in diffuse, there is leakage from entire capillary bed secondary to generalized break down of inner Blood retinal barrier (BRB).[9,10] On the basis of OCT, DME can be classified as focal DME, Cystoid DME, DME with posterior hyaloid

traction, DME with subretinal fluid or serous retinal detachment and DME with tractional retinal detachment.[11] Detection of DME is now mainly done through Optical Coherence Tomography (OCT), but leakage area extent or leakage point is identified through fundus fluorescein angiography (FFA).[12,13] Treatment of DME includes Anti-Vascular endothelial derived growth factor (Anti-VEGF), intravitreal corticosteroids, Focal Macular Photocoagulation and Pars plana Vitrectomy (PPV).[14]

The rationale for this study is to compare the two treatment modalities as no such study was done in Pakistan on this topic after comprehensively searching for it and internationally only few studies have been done on it. So, by comparing both the treatment modalities, we will be able to find out better treatment option for patients.

MATERIAL AND METHODS

It was a prospective type of study conducted at department of ophthalmology at Institute of Ophthalmology, Liaquat University of medical and health sciences, Jamshoro from 1st November 2019 to 31st October 2020. Patients between the ages of 45–75 years of either gender with diabetic macular oedema were included in our study. Patients having macular oedema secondary to causes other than diabetic retinopathy such as branch retinal vein occlusion or having vitreomacular traction, aphakia, having history of glaucoma or patients who had received pan retinal photocoagulation or macular laser and/ intravitreal bevacizumab or triamcinolone acetonide injection in last 12 months were excluded from our study and those patients with any cardiac history or history of stroke were also excluded from our study.

Patients with media opacities such as corneal opacity were also excluded from our study. Total number of patients was 260. The Patients were divided in two groups equally. Group A includes 130 patients and they were treated by Intravitreal Bevacizumab (IVB) alone. Group B also includes 130 patients and they were treated by Intravitreal Bevacizumab and focal macular photocoagulation (IVB and FMP) combined. Detailed history regarding their complaints and previous treatment was taken before examination. The best corrected visual acuity was checked using Snellen chart. Detailed ocular examination was done through biomicroscope slit lamp. Intraocular pressure was checked by applanation tonometer. Fundus examination was done using fundus contact lens. Macular oedema was accessed by slit lamp bimicroscopy with fundus contact lens and was confirmed by Spectral Domain OCT (SD-OCT). Fundus Fluorescein angiography (FFA) was done to identify the focal leakage area. Patients in group B only, had their FFA done. Complete procedure was explained to the patients and written consent was taken. Patients in group A, Received a dose of 2.5 mg in 0.1 mL of IVB. The pre-treatment best corrected visual acuity was noted and SD-OCT of macula was done before giving first dose. Three doses of IVB were given at the interval of one month. After three injections, BCVA recorded and SD-OCT of macula was done again. In group B, patients were given a dose of 2.5 mg in 0.1 mL of IVB followed by FMP within two weeks. Focal leakage area was identified through FFA and area centralis fundus contact lens was used for laser application and spot size was 50 µm and duration was 0.1 second and further two doses of IVB were given at the interval of one month each. After three injections, BCVA recorded and SD-OCT of macula was done again.

The data was entered and analyzed using SPSS version 22. Statistical differences between pre-treatment and post-treatment BCVA was assessed using a paired *t*-test. A *p*-value of less than 0.05 was considered to be statistically significant.

RESULTS

We selected 260 patients with DME. They were divided into two groups, Group A and group B. Each group includes 130 patients. Out of 260 patients, 151 (58.1%) were males and 109(41.9%) were females. Gender distribution is shown in table-1. In group A, the minimum age of patient was 45 whereas maximum age was 70 years. In group B, the minimum age of patient was 46 whereas maximum age was 74 years. Age distribution among the genders is shown in table-2.

Patients in Group A were treated by intravitreal Bevacizumab alone and patients in group B were given combination of intravitreal Bevacizumab and macular photocoagulation. Change of visual acuity after first month of treatment in group A was 1.037 and in group B was 0.93 and there was significant difference between two groups (p=0.00). Visual acuity was improved in both the group A and B, but patients in Group B showed much improved result as compared to group A. Change of visual acuity after second month of treatment in group A was 0.94 and in group B was 0.51 and there was significant difference between two groups (p=0.00). Visual acuity was improved in both group A and B group but group B showed much improved visual acuity as compared to group A. Final, visual acuity after third month of treatment in group A was 0.94 and group B was 0.51 and there was significant difference between two groups (p=0.00). (Table-3)

Table-1: Gender wise distribution

Gender	IVB	IVB+MPC	Total
Male	69	82	151
Female	61	48	109
Total	130	130	260

Table-2: Age wise distribution

Age	IVB	IVB+MPC	Total
45–55	82	69	151
56–65	40	47	87
66–75	8	14	22
Total	130	130	260

Table-3: Monthly BCVA comparison between two groups

Duration	IVB	IVB+FMP
After 1st month	1.037	0.93
After 2nd month	0.94	0.51
After 3rd month	0.94	0.51

DISCUSSION

As there is increase in diabetic population, the cases of diabetic eye disease has also increased. DME is multifactorial condition, which causes visual impairment, thus critically impairing the patient's Quality of life. (15)

According to our knowledge not many studies have been done on comparing the efficacy of IVB alone versus combination of IVB+FMP as a treatment option for DME.

In our study, we selected 260 patients on the basis of our inclusion and exclusion criteria. These 260 patients were divided into two groups. Each group contains 130 patients. Group A was treated with IVB and group B was treated with IVB+MPC. Group B yielded superior outcome after 3 months.

Lee SJ. conducted a study, in which they compare the efficacy between intravitreal bevacizumab and combination treatment (bevacizumab and macular photocoagulation) for the treatment of diabetic macular oedema (DME). According to this study both groups, i.e., intravitreal bevacizumab injection only and combination treatment achieved visual improvement in both groups. There was no significant difference in the final visual outcome of two groups. The sample size for this study was small, it was 90 as compared to sample size of our study was 260 so which provides better assessment to efficacy of IVB in patients with DME. Secondly, patients were not divided equally in two groups whereas in our study each group contains equal number of patients i.e., 130 each. Thirdly it does not specify the macular l,aser photocoagulation type, i.e., whether focal argon laser photocoagulation was done or grid laser photocoagulation was done.[16]

Another study was done by Sarireh FA. in which intravitreal bevacizumab alone versus combined with macular grid laser photocoagulation for diffuse macular oedema was done. This study shows that in both groups there was improvement in BCVA of 0.023 and 0.016 respectively with fewer need of reinjection in combined group. The results of this study are similar to ours that, there was improvement in BCVA in both groups. But in this study, grid argon laser macular photocoagulation was done as compared to our study in which we did focal argon laser macular photocoagulation.[17]

The study conducted by El Awad SM, compared the BCVA between the groups receiving IVB, intravitreal ranibizumab (IVR) and laser after 6 months. Their studies showed improvement in BCVA, in both IVB and laser groups of 0.19 line (*p*-value: 0.002) and 0.1 line (*p*-value:0.008) respectively, similar to results of our study that showed improvement in BCVA in both groups. But in this study duration of study was 6 months. In this study laser was done alone as compared to our study, in which IVB and FMP was done combined in one group.[18]

Akpolat Ç. did Study, in which he compared Intravitreal bevacizumab alone versus Intravitreal bevacizumab combined with macular photocoagulation. There was improvement in both groups in terms of BCVA. Best corrected visual acuity improved from 0.84±0.63 Log MAR to 0.55±0.48 Log MAR at 3 months in IVB alone group, whereas in IVB combine with macular photocoagulation group BCVA improved from 0.91±0.65 Log MAR improved to 0.73±0.55 Log MAR at 3 months. The BCVA was superior in combined group. This study supports our data that BCVA improved in both groups but more improvement was re seen in combined group.[19]

Faghihi H *et al*. did study in which they compared intravitreal bevacizumab with intravitreal triamcinolone with standard macular laser photocoagulation for diabetic macular oedema. Their study showed that BCVA declined in IVB alone group ($p<0.001$). In this study, single IVB was given alone as compared to our study in which IVB was given for three months. Secondly, in their study macular photocoagulation was done alone, as compared to our study, macular photocoagulation and IVB was given together. This is the reason, our study showed improvement in both groups at the end of three months.[20]

Pareja-Ríos A, conducted a study in which macular photocoagulation alone was compared with macular photocoagulation along with IVB given for three months. Their studies showed that BCVA was superior in group receiving both IVB and macular photocoagulation with BCVA improving from baseline to each follow-up visit with a median improvement of +6 (11; 1.5) letters on ETDRS chart.

This study showed the results in combined group after 12 months as compared to our study which yielded result after three months, but BCVA improved in both studies.[21]

There were some limitations of our study that sample size was small and long term follow up could not be achieved.

CONCLUSION

According to the result of our study combined IVB+MPC treatment group for diabetic macular oedema provided better and superior visual outcome as compared to IVB alone. No side effects of either IVB or MPC were seen in our study. Further studies must be conducted on this treatment option, i.e., combined treatment (IVB+MPC) for DME with more than 3 months follow up, so that we can see long term beneficial effects of this treatment option. On the basis of results of our study, we recommend combined treatment (IVB+MPC) for patients with diabetic macular oedema.

AUTHORS' CONTRIBUTION

AUJ: Conceptualization. NAS: Literature Search, data collection, interpretation. AKN, AJ: Write-up, analysis

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Address for Correspondence:

Asad Ullah Jatoi, Department of Ophthalmology, Institute of Ophthalmology, Liaquat University of Medical & Health Sciences, Jamshoro-Pakistan

Email: drasadullahjatoi87lumhs@gmail.com