

Results of Intravitreal Bevacizumab as an Adjunct to mETDRS Grid Laser in Diabetic Macular Edema

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ABSTRACT

Purpose: To assess the efficacy of Intravitreal Bevacizumab as an adjuvant to grid laser photocoagulation in patients with diffuse macular edema (DME) in type II diabetes.

Study Design: Quasi experimental study.

Place and Duration of Study: Institute of Ophthalmology, Liaquat University of Medical and Health Sciences, Jamshoro, from September 2016 to November 2018.

Methods: Ninety-five type II diabetic patients with diffuse macular edema were selected by convenient sampling. Group I patients were treated with ETDRS grid laser photocoagulation. Group II patients were treated with ETDRS grid laser photocoagulation followed by intravitreal bevacizumab after one week monthly for 2 months and then as per need. All patients were examined after 1st, 2nd and 3rd month and mean change in best corrected visual acuity (BCVA) and central macular thickness (CMT) was recorded.

Results: The results of study were compared with the baseline values. The mean change in BCVA in group 1 was from 46 ± 18 letters to 52 ± 17 letters and in group 2 was from 46 ± 18 letters to 56 ± 17 letters (P < 0.001). Mean base line CMT was 504 µm (SD±189) in G-I and 506 µm (SD±189) in G-II. Mean CMT reduction was statistically significant in both groups during all follow up visits but in G-I it was 194 µm (p ≤ 0.001) and in G-II 272 µm (p ≤ 0.001) at 6 months.

Conclusion: Macular Grid laser with or without Intravitreal Bevacizumab significantly improves vision and decreases macular edema but combined treatment led to more stable improvement in DME during follow-up.

Key Words: Grid laser, Bevacizumab, Macular edema, Anti-VEGF.

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INTRODUCTION

According to International Diabetic Federation report published in 2017 there are four hundred and fifty-one

million people in the world who have diabetic mellitus. By the year 2045 this figure may reach up to six hundred and ninety-three and half of them do not know about the disease.¹ Worldwide the leading cause of visual impairment in working age group population is diabetic macular edema (DME) which is another worse manifestation of diabetic retinopathy.²

There are so many different strategies to treat diabetic macular edema (DME) but medical management of systemic risk factors should be optimized before any treatment. Otherwise, it may

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remain insufficient to control the progression of the disease and prevent recurrence of ocular complications.³ Different patients have different response to the treatment of DME. Therefore, we should adopt such strategies which give good results and have less side effects.⁴ For the management of DME laser photocoagulation was the best option few decades back. It was established by Early treatment of Diabetic Retinopathy Study (ETDRS) in 1980s.⁴ Nowadays intravitreal injection of anti-vascular endothelial growth factor (AVEGF) is more popular than laser due to easy administration and early recovery of vision.³ But a research conducted by Diabetic Retinopathy Clinical Research Network (DRCR.net) stated that modified ETDRS (mETDRS) protocol to treat DME was the best approach⁵ and protocol T clinical trial showed that 50% patients with DME required additional laser therapy within sixth months after injection of anti-VEGF.⁶ It means laser photocoagulation still has a role to treat DME but laser and anti-VEGF both have their own efficacy and visual outcomes. Macular laser therapy is a good treatment option as an adjuvant because it is able to improve macular thickness outcomes and reduce the number of injections needed.

In this study, anti-VEGF was used as an adjunct to laser photocoagulation in patients with DME to get early vision recovery and to decrease the financial burden on the society. The purpose of the study was to assess the efficacy of Intravitreal Bevacizumab as an adjuvant to grid laser photocoagulation in patients with diffuse macular edema (DME) in type II diabetes.

METHODS

Ninety-five eyes of type II diabetic patients, with diffuse macular edema (48 males and 47 females) were recruited for this prospective study, from the outpatient clinic of Institute of Ophthalmology Liaquat University of Medical and Health Sciences Jamshoro. The duration of study was from September 2016 to November 2018 after approval from Ethics Committee of the University. Written informed consent was obtained from all participating patients after explaining to them all the study procedures with its benefits and hazards.

Patients older than 40 years with macular edema caused by type II Diabetes, BCVA of 6/18 to 6/60, central macular thickness (CMT) more than 300 μm ,

intra ocular pressure less than 20 mm Hg, clear optical zone with properly dilated pupils and no iris neovascularization were included in the study. Patients who had diabetic macular edema (DME) with subfoveal exudates, macular edema caused by diseases other than DM, macular ischemia & traction, CMT greater than 1000 μm , preexisting macular pathology, history of (H/O) intravitreal injection/vitreotomy, H/O cataract surgery within the past 6 months and H/O renal pathology, glaucoma/ocular hypertension, HbA1c more than 8%, blood pressure more than 150/90 mm Hg and significant media opacity were excluded from the study.

All patients who fulfilled the inclusion criteria were subjected to clinical examination and base line BCVA was recorded by Snellen Chart, intra ocular pressure (IOP) was recorded using applanation tonometer with slit lamp biomicroscope and colored fundus photograph and CMT was taken with SD-OCT. All patients were divided in two groups Group I patients were treated with ETDRS grid laser photocoagulation. Group II patients were treated with ETDRS grid laser photocoagulation combined with intravitreal bevacizumab (1.25 mg/0.05 ml). All patients were examined at baseline and followed-up at 1, 2 and 3 months after treatment. Changes in BCVA were recorded with Snellen acuity chart & converted into ETDRS letter for facilitating statistical calculation. Intravitreal injections of anti-VEGF were performed with aseptic technique and post injection Moxifloxacin 3% one drop four times a day and post laser non-steroidal anti-inflammatory one drop three times a day was advised. Combination of acetazolamide and timolol one drop twice a day was advised in patients with raised IOP.

Macular grid photocoagulation was performed with argon green laser delivering 2–3 rows using mETDRS grid Laser parameters for DME. Burn size for grid was 75 μm , burn duration was 0.05 – 0.10 s, burn separation was 2 visible burn widths apart and burn intensity was light gray

Descriptive analysis of subjects like mean, standard deviation and range was performed by using SPSS version 20. Mean change in VA and CMT was estimated with paired t-test. The level of statistical significance was set at $P < 0.05$. Changes in BCVA were recorded with Snellen acuity chart and converted into ETDRS letters for facilitating statistical calculation.

RESULTS

The demographic and base line clinical characteristics are listed in Table I. The mean age of G-1 group patients was 59.45 (SD \pm 8.23) years and of G-2

Table 1: Baseline demographic and clinical characteristics of each group of study patients

Characteristics	Group-1	Group-2
Age (years)	59.45 \pm 8.23	60.11 \pm 7.36
Male, n (%)	25 (26.31%)	23 (24.21%)
Female, n (%)	22 (23.15%)	25 (26.31%)
Disease duration (year)	11.10 \pm 2.42	12.48 \pm 2.91
HbA1c (%)	07.85 \pm 0.78	07.96 \pm 0.76
IOP (mmHg)	17.68 \pm 2.49	18.20 \pm 3.19
Blood pressure (mm Hg)		
Systole	145 \pm 17.11	138 \pm 15.90
Diastole	85 \pm 8.10	83 \pm 8.10
CMT (μ m)	504 \pm 189	507 \pm 189

patients was 60.11 (SD \pm 7.36) years. Out of ninety-five patients, 25 (26.31%) males and 22 (23.15%) females were treated with mETDRS grid laser photocoagulation and 23 (24.21%) male and 25 (26.31%) females were subjected to combined treatment.

BCVA ranged from 4 to 76 letters (Snellen equivalent 1/60 to 6/9). Eyes with poor base line BCVA achieved greatest mean improvement at 6 months (Table 2). Mean base line CMT was 504 μ m (SD \pm 189) in G-I and 506 μ m (SD \pm 189) in G-II. Mean CMT reduction was statistically significant in both groups during all follow up visits but in G-I it was 194 μ m ($p \leq 0.001$) and in G-II 272 μ m ($p \leq 0.001$) at 6 months. Only 0.045% patients of G-2 were found with raised IOP that was controlled by anti-glaucoma drops.

Table 2: Change in Base line BCVA & CMT.

Subject (ETDRS Letter Score)		Mean BCVA (letters)	P-Value	Mean CMT (μ m)	P-Value
Baseline	Baseline				
	G-1 (n = 47)	46 \pm 18		504 \pm 189	
	G-2 (n = 48)	46 \pm 18		507 \pm 189	
1 st Months PT	1st Months PT				
	G-1 (n = 47)	47 \pm 21	0.912	365 \pm 143	0.018
	G-2 (n = 48)	48 \pm 21	0.801	350 \pm 157	0.004
2 nd Months PT	2nd Months PT				
	G-1 (n = 47)	50 \pm 17	0.021	350 \pm 150	0.001
	G-2 (n = 48)	53 \pm 17	0.009	322 \pm 160	0.002
3 rd Months PT	3rd Months PT				
	G-1 (n = 47)	52 \pm 17	0.004	310 \pm 130	0.001
	G-2 (n = 48)	56 \pm 17	0.004	235 \pm 128	0.001

G-1 = Group I, G-2 = Group II, PT = Post treatment, BCVA = best corrected visual acuity, CMT = Central macular thickness
ETDRS = Early treatment of Diabetic Retinopathy Study, SD = Stander deviation

DISCUSSION

Prevalence of DME is approximately 19% to 65% and it is the main cause of severe loss of vision among patients with diabetes mellitus.⁷ Pathogenesis of DME is multi factorial like: angiogenesis, inflammation and oxidative stress.^{8,9} Therefore, a single treatment option does not show adequate response especially in diffuse, chronic and refractory DME. Various variants of VEGF increase vascular permeability by increasing phosphorylation of endothelial tight junction proteins in diabetes mellitus that may lead to DME.¹⁰ Another proposed reason of DME is the breakdown of outer

and inner retinal barrier.¹¹ Solaiman et al¹² suggested that the laser photocoagulation causes proliferation of endothelial cells in the retinal capillaries as well as retinal pigment epithelial cells thus improving the functions of outer and inner retinal barriers. Bevacizumab has the ability to block all form of VEGF receptors. This stabilizes the vascular permeability and helps to reduce DME.¹³ Since last three-decades conventional ETDRS laser photocoagulation was standard treatment for DME but results of visual outcome were modest.^{14,15} Visual acuity may decrease due to extension of macular scar,

and patients may suffer central scotoma and altered color vision.¹⁶ To avoid these complications, we used mETDRS laser treatment in this study.

As we compare the base line during each visit, we found significant reduction in CMT in both groups during each follow-up visit but at 6 months it was stable and more significant in combined group ($p \leq 0.001$). At 6 months, visual acuity letters gain was more significant in combined group than laser group.

Our results are in consistence with previous studies which reported that the combined intravitreal Bevacizumab (IVB) and laser photocoagulation was the best option not only to treat DME but also to help in decreasing the chance of recurrence.^{17,18} Shalaby et al¹⁹ reported that combined intravitreal anti VEGF and mETDRS laser had more stable functional and anatomical out comes after treating DME. We also had the same results but difference was that we applied laser before injecting IVB.

Other studies have also reported that combined treatment was more effective in treating DME than conventional macular laser photocoagulation. Adelman et al²⁰, and Do et al²¹ stated that by adding macular laser photocoagulation with IVB to treat DME may not give significant results and more extensive laser treatment may help to reduce the number of intravitreal anti-VEGF injection. That is why in this study we did first grid laser photocoagulation before injecting IVB to reduce the burden of injection to patients.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board. (LUMHS/04)

Conflict of Interest

Authors declared no conflict of interest

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Authors' Designation and Contribution

Mahtab Alam Khanzada: Associate Professor: *Concepts, Design, Manuscript preparation.*

Munawar Ahmed: Associate Professor: *Data analysis, Statistical analysis, Manuscript editing.*

Azfar Ahmed Mirza: Assistant Professor: *Literature search.*

Ghazi Khan Mari: Assistant Professor: *Data acquisition.*

Muhammad Arshad Mahmood; Professor: *Manuscript review.*

