http://doi.org/10.48165/ijabms.2021.23122

EFFICACY OF MACULAR PHOTOCOAGULATION WHEN GIVEN IN THE EARLY OR LATE PERIOD AFTER SINGLE INTRAVITREAL BEVACIZUMAB INJECTION IN TERMS OF CENTRAL FOVEAL THICKNESS CHANGE AND VISUAL ACUITY GAIN

Author: -
Dr. Aaska Sapan Shah (Vitreo-retinalsurgeon, C H Nagri Hospital) shah7aashi@yahoo.com
Dr. Naimish Haribhai Mahaliya (3rdyear resident doctor, LG Hospital) mahaliyanaimish@gmail.com
Dr. Sapan Snehalbhai shah (Oculoplastysurgeon, LG Hospital) sapan_sha@yahoo.com
Dr. Jigar Jitendrabhai Joshi (2nd year resident doctor, LG Hospital) jigarjoshi2@gmail.com

ABSTRACT:
AIM: To find out the efficacy of macular photocoagulation when given in the early or late period after single intravitreal bevacizumab injection in terms of central foveal thickness change and visual acuity gain.
METHODS:40 patient eyes were studied and they were divided into groups based on sex, age, hba1c levels, severity of disease and treatment received over the period of 6months.
RESULT: patients receiving deferred macular photocoagulation after a single intravitreal injection of bevacizumab had better outcomes regarding reduction of central foveal thickness and improvement in visual acuity at the end of 6-month observation period compared to those patients receiving prompt macular photocoagulation.

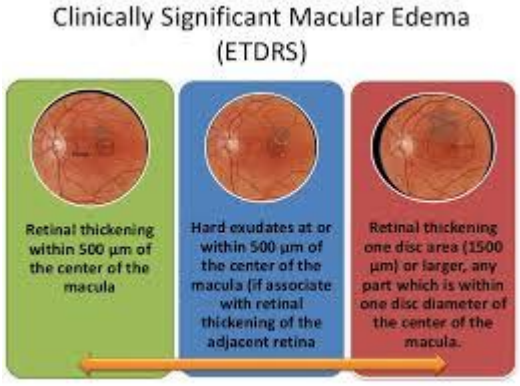
Keywords: bevacizumab, laser photocoagulation, diabetic retinopathy

INTRODUCTION:

Diabetic retinopathy is an ocular manifestation of diabetes mellitus, a systemic disease, which affects up to 80 percent of all patients who have had diabetes for 10 years or more.[1]
Diabetic retinopathy (DR) is one of the leading causes of severe visual impairment. Diabetic retinopathy is the result of microvascular retinal changes. Hyperglycemia -induced intramural pericyte death and thickening of the basement membrane led to incompetence of the vascular walls. These damages change the formation of the blood-retinal barrier and also make the retinal blood vessels become more permeable.
Diabetic retinopathy can be classified as:

- Non-proliferative diabetic retinopathy
- Proliferative diabetic retinopathy
- Diabetic Maculopathy

CSME as described by the Early Treatment of Diabetic Retinopathy Study occurring in Diabetic Retinopathy is defined as:



Routine investigations include diabetes profile, haemoglobin, urine albumin, lipid profile and renal function test.

IMAGING:

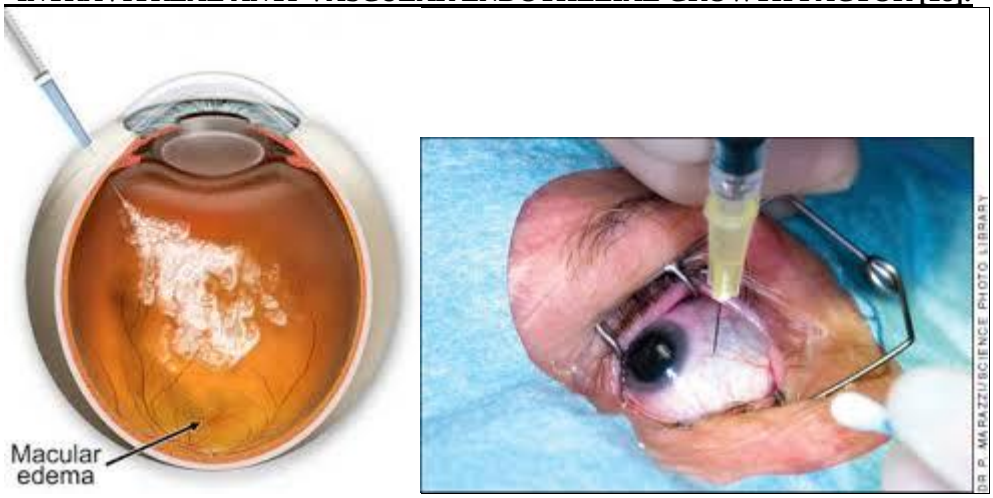
- **Fundus Fluorescein Angiography (FFA)**
- **Optical Coherence Tomography (OCT)**
- **Fundus Photography**
- **Indirect Ophthalmoscopy**

.

MANAGEMENT:

Laser photocoagulation
Medical treatment

***INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR [18]:**



- **Out of all Anti-VEGF molecules available for treatment of diabetic macular edema Bevacizumab (Avastin) is used most widely in off-label use [19] as the molecule is cost-effective and equally potent in treating macular edema.[17]**

AIMS OF STUDY:

- **To find out the efficacy of macular photocoagulation when given in the early or late period after single intravitreal bevacizumab injection in terms of central foveal thickness change and visual acuity gain.**

MATERIALS AND METHOD:

40 EYES HAVE BEEN INCLUDED IN THE STUDY.

INCLUSION CRITERIA:

- Age ≥ 40 years
- Type 2 diabetes
- DME which is diagnosed as diffuse DME on fundus flourescein angiography.
- Visual acuity (EDTRS charting) 20/320 or better

EXCLUSION CRITERIA:

- Systemic
  - Significant renal disease
  - Uncontrolled diabetes
  - BP > 180/110 mmhg
  - Cardiac event or stroke within 4 months
- Study eye
  - Prior MPC
  - Tractional retinal detachment involving the macula
  - NV of the angle
  - History of intravitreal anti-VEGF within past 2 months
  - History of corticosteriod in the past 4 months

BASELINE EVALUATION:

All patients had a complete pre-treatment evaluation.

- **HISTORY:** Detailed history including personal data like name, age, address, phone number was taken.
- Detailed systemic history was elicited including the type of diabetes, its duration, whether patient is on oral treatment or insulin, and whether having associated concomitant systemic illness like hypertension, nephropathy or hypercholesterolemia and Associated history of complications of diabetes in other organs like nephropathy and neuropathy was elicited.
- **BLOOD INVESTIGATIONS**: All patients were asked for routine blood investigations which included total blood count, fasting& post prandial blood sugar, HbA1c, renal function tests, serum lipid profile and urine routine examination.

- **OPHTHALMIC EXAMINATION:** Detailed ophthalmic history including history of glasses, any eye trauma or surgery, previous any lasers or intravitreal injections taken before recorded.
- Detailed ophthalmic examination was done including best corrected refraction, best-corrected visual acuity (BCVA) testing objective/subjective refraction using retro illuminated SNELLENS chart, classification of lenticular status using the Lens Opacities Classification System III & Applanation tonometry.
- A complete retinal assessment with a 90.0 diopter fundus lens, Binocular indirect ophthalmoscopy and fundus flouerescein angiography (FFA) was performed to grade the severity of the retinopathy maculopathy. Optical Coherence Tomography (OCT, stratus, Model 3000; Carl Zeiss Meditec Inc., Dublin, CA, USA) was done with six linear 6 mm scan at interval of 30 degree and central foveal thickness (CFT) was noted.

TREATMENT PROTOCOL:

- GROUP 1(20 EYES): - receiving prompt treatment in the form of photocoagulation within a week after single intravitreal bevacizumab injection.
- GROUP 2(20 EYES): - receiving deferred treatment in the form of photocoagulation after receiving intravitreal Bevacizumab in the dose of 1.25mg /0.05ml in one month.
    - **METHOD OF INTRAVITREAL BEVACIZUMAB:**
      After explaining procedure and taking written consent patient had been taken to operation theatre. After full pupillary dilation topical anaesthesia in the form of 4% lignocaine is applied in conjunctival cul-de-sac.
      5% povidone iodide on to the ocular surface is applied and allowed for adequate time (3 minutes) prior to injection as aseptic precaution. 1.25mg bevaciumab is prepared in 0.05ml of tuberculin syringe with 27-gauge needle. Periocular area is cleaned with 5-10% povidone iodine.
      After applying sterile drape and adjusting microscope patient is asked tofixate in gaze away from the site of injection. Scleral injection site was marked using the gauge (the site of the needle entry should be 3.0-3.5 mm from the limbus in aphakic/pseudophakic patients, and 4.0 mm in phakic patients).
      Forceps were used to steady the eye, the needle entry perpendicular with the tip aimed towards the centre of the globe. 0.1 ml of therapeutic agent injected slowly and carefully.
      Needle is removed carefully & A sterile cotton-tipped applicator may be used to prevent reflux and to steady the eye. 1-2 drops of single use antibiotic drop or ointment is instilled into treated eye.
      Post injection care- Antibiotic drops 3-4 times a day for one week was prescribed. Patient was examined on 2nd day to check visual acuity, intraocular pressure and fundus assessment for any adverse event like Sub-conjunctival haemorrhage, floaters, pain due to sudden rise in iop or inflammation or endophthalmitis if found had been noted and managed accordingly.
    - **METHOD OF GRID/FOCAL LASER**
      It includes focal laser treatment of
      microaneurysms and grid laser of diffuse leakage and focal nonperfusion within 2DD of centre of the macula.
      Spot size: 50-100 micron is utilized.
      The burn intensity for grid laser = barely visible (light gray).
      Power of laser burn is between 120-150 mW depending on the condition
      of the laser, the opacities in the media and background pigmentation.
      Laser burns placed at width of one burn -- wider if thickening is less severe. If necessary, the grid can extend up to 2-disc diameters superiorly, inferiorly, and temporally from the centre of the macula. One should avoid treating within 500 microns of the disc margin or the centre of the macula.
      Duration of about 0.05-0.1 sec is used
      Number of spots- 100-500

FOLLOW-UP SCHEDULE:

Following parameters are checked for on follow-up visits post-injection

1. Visual Acuity
2. IOP
3. CFT (Central Foveal Thickness)
4. Clinical findings

All parameters were examined on 1st Day 1st Week 1st Month 3rd Month and 6th Month.

DATA ANALYSIS:

Out of the 40 patients studied 26 were males (65%) and 14 (35%) were females.

- AGEWISE DISTRIBUTION:

In our study our patients were of following age groups: - 7(17.5%) patients of 40-50 years age group, 21(52.5%) patients of 51-60 years age group, 10(25%) patients of 61-70 years of age and 2(5%) patients of more than 70 years of age group.
Mean age being: - 56.2 years.
Maximum number of patients having diabetic retinopathy fall into the age group of 50-60 years.
As described in our study 62.5% of the patients received prompt photocoagulation (within 1 week) after single intravitreal bevacizumab injection and 37.5% of the patients received deferred photocoagulation (>1 week and <1 month).
The severity of diabetic retinopathy in the patients presented to our tertiary eye care hospital:

- 3(7.5%) patients presented with Mild NPDR with DME
- 17(42.5%) patients presented with Moderate NPDR with DME
- 20(50%) patients presented with Severe NPDR with DME
- Of the 40 patients included in the study majority of the patients were having severe non proliferative diabetic retinopathy with clinically significant macular edema, many were having moderate NPDR with CSME, and only a minor proportion were having mild NPDR with CSME.
- Group A includes IV Avastin + Prompt Macular Photocoagulation
- Group B includes IV Avastin + Deferred Macular Photocoagulation

The points show the distribution of patients in the 2 groups of treatment.
SEXWISE DISTRIBUTION:

- Group A includes 16(64%) Males and 9(36%) Females
- Group B includes 10(66.7%) Males and 5(33.3%) Females

DISTRIBUTION ACCORDING TO HbA1c LEVELS:
According to the guidelines a HbA1c value of <= 7is considered to be as good glycaemic control of past 3 months whereas values above 8.0 indicates poor glycaemic control.

- Group A includes 4 patients having HbA1c <7 and Group B includes 3 patients having HbA1c<7
- Group A includes 8 patients having HbA1c = 7 and Group B includes 10 patients having HbA1c=7
- Group A includes 3 patients having HbA1c >8 and Group B includes 2 patients having HbA1c>8

ANALYSIS:

- Data tabulation was performed on Microsoft-excel worksheets.
- Statistical analysis was done using Graph Pad InStat-3 software.
- Comparison between pre-intervention and post-intervention values in individual groups was analysed using PAIRED T TEST (in data following normal distribution) and WILCOXON MATCHEDPAIRS TEST (in data not following normal distribution).
- While comparison between the groups for all variables was done using UNPAIRED T TEST WELCH CORRECTED (in data following normal distribution) & MANN WHITNEY TEST (in data not following normal distribution).
- A "*p*" value ≤ 0.05 was considered statistically significant.

TABLE NO.1

CFT	**NUMBER OF PATIENTS**							
(IN MICRONS)	GROUP A (IV Avastin+ PROMPT Macular photocoagulation)				GROUP B (IV Avastin + DEFERRED Macular photocoagulation)			
	Pre-treatment	1st month	3rd month	6th month	Pre-treatment	1st month	3rd month	6th month
<300	3	4	7	12	4	5	8	15
300-450	13	15	13	8	12	13	11	5
>450	4	1	0	0	4	2	1	0

- From the above table' p'value calculated came to be less than 0.0001 which shows it to be extremely significant.
- The above data has been compared for central foveal thickness at the end of 6 months between the 2 groups: of which-

- (a) first group received macular photocoagulation within 1 week of a single intravitreal bevacizumab injection.
- (b) second group received photocoagulation in the period beyond 7 days and before 30 days of receiving single intravitreal bevacizumab injection.
- The comparison showed that the group receiving deferred photocoagulation had better outcomes as seen by reduced central foveal thickness at the end of 6-month study period as compared to group receiving prompt photocoagulation.

TABLE NO.2

BCVA	IV Avastin + PROMPT Macular photocoagulation				IV Avastin + DEFERRED Macular photocoagulation			
(in logMAR)	Baseline	1st M	3rd M	6TH M	Baseline	1STM	3RDM	6THM
>1	4	3	3	2	2	2	0	0
0.48 – 0.99	18	12	12	10	10	9	6	3
< 0.48	3	10	10	13	3	4	9	12

- The p value came to be less than 0.0001 which is significant.
- The above data has been compared for outcome in visual acuity at the end of 6 months between the 2 groups: of which-
- (a) first group received macular photocoagulation within 1 week of a single intravitreal bevacizumab injection.
- (b) second group received photocoagulation in the period beyond 7 days and before 30 days of receiving single intravitreal bevacizumab injection.
- The comparison showed that the group receiving deferred photocoagulation had better outcomes regarding visual acuity at the end of 6-month study period as compared to group receiving prompt photocoagulation.

DISCUSSION:

- Diabetic macular edema is a pathology which results from leakage due to process of angiogenesis.
- Thus, our aim in the treatment of diabetic macular edema would be to reduce the edema and prevent its further occurrence.
- Hence by injecting intravitreal injection of bevacizumab, the process of angiogenesis is taken care of. It reduces formation of new vessels and thus leakage from them.
- Whereas by laser photocoagulation the already formed leaky vessels are coagulated so that edema from them does not occur.
- It is thus seen that when laser photocoagulation is done within one month of the anti-VEGF injection but greater than 1 week the results obtained are better than laser photocoagulation given within one week of the anti-VEGF injection in terms of visual acuity and central foveal thickness at the completion of 6 months; with a p value that is extremely significant.

CONCLUSION:

From our study thus it can be concluded that patients receiving deferred macular photocoagulation after a single intravitreal injection of bevacizumab had better outcomes regarding reduction of central foveal thickness and improvement in visual acuity at the end of 6-month observation period compared to those patients receiving prompt macular photocoagulation.

References:

1. *Gale, Jason (November 7, 2010). "India's Diabetes Epidemic Cuts Down Millions Who Escape Poverty". Bloomberg*. Retrieved 8 June 2012.
2. Goldberg MF, Jampol LM. Knowledge of diabetic retinopathy before and 18 years after the Airlie House Symposium on Treatment of Diabetic Retinopathy. Ophthalmology. 1987; 94:741–746.
3. Early treatment diabetic retinopathy study research group: photocoagulation for diabetic macular edema: early treatment diabetic retinopathy study report number 9. Opthalmology1991 May;98(5 Suppl):766-85.

4. Yasser M Helmy and Heba R Atta Allah Optical coherence tomography classification of diabetic cystoid macular edema. Clin Ophthalmol. 2013; 7:10.2147/OPTH.S47987 PMCID: PMC3770711.
5. Asensio-Sánchez VM, Rodríguez-Delgado B, García-Herrero E, Cabo-Vaquero V, García-Loygorri C. [Microalbuminuria and diabetic retinopathy] Arch Soc EspOftalmol. 2008 Feb;83(2):85
6. Aksoy S, Yilmaz G, Akkoyun I, YaziciAC.Comparison of intravitreal bevacizumab and triamcinolone acetonide theraphies for diffuse diabetic macular edema. Int J Ophthalmol. 2015 Jun 18;8(3):550-5. doi: 10.3980/j.issn.2222-3959.2015.03.20.
7. Arevalo JF[1], Fromow-Guerra J, Quiroz-Mercado H, Sanchez JG, Wu L, Maia M, Berrocal MH, Solis-Vivanco A, Farah M; Pan-American Collaborative Retina Study Group Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: results from the Pan-American Collaborative Retina Study Group at 6-month follow-up. OphthalmologY. 2007 Apr;114(4):743-50.
8. Takamura Y, Tomomatsu T, Matsumura T, Arimura S, Gozawa M, Takihara Y, Inatani M. The effect of photocoagulation in ischemic areas to prevent recurrence of diabetic macular edema after intravitreal bevacizumab injection. Invest Ophthalmol Vis Sci. 2014 Jul 15;55(8):4741-6. doi: 10.1167.
9. Heier J, Bressler NM, Avery RL, Bakri SJ, Boyer DS, Brown DM, Dugel PU, Freund KB, Glassman AR, Kim JE, Martin DF, Pollack JS, Regillo CD, Rosenfeld PJ, Schachat AP, Wells JA 3rd; American Society of Retina Specialists Anti-VEGF for Diabetic Macular Edema.Comparative Effectiveness Panel.Comparison of Aflibercept, Bevacizumab, and Ranibizumab for Treatment of Diabetic Macular Edema: Extrapolation of Data to Clinical Practice JAMA Ophthalmol. 2015 Oct 29:1-6. doi: 10.1001/jamaophthalmol.2015.4110.
10. Barteselli G, Kozak I, El-Emam. results of the standardised combination therapy for diabetic macular oedema: intravitreal bevacizumab and navigated retinal photocoagulation. Br J Ophthalmol.
11. Javanović S, Canadanović V, Sabo A, Grgić Z, Mitrović M, RakićD.Intravitreal bevacizumab injection alone or combined with macular photocoagulation compared to macularphotocoagulation as primary treatment of diabetic macular edema. VojnosanitPreq. 2015 Oct;72(10).
12. Early treatment diabetic retinopathy study research group: photocoagulation for diabetic macular edema: early treatment diabetic retinopathy study report number 9. Opthalmology1991 May;98(5 Suppl):766-85.
13. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group.Ophthalmology. 1981 Jul;88(7):583-600.
14. Solaiman KA, Diab MM, Abo-Elenin.Intravitreal bevacizumab and/or macular photocoagulation as a primary treatment for diffuse diabetic macular edema. Retina. 2010 Nov-Dec;30(10):1638-45. doi: 10.1097/IAE.0b013e3181e1ed07.

Conflict of Interest:

Nil

Funding:

Nil

Acknowledgement:

Nil