

# Visual Outcome of Vision Threatening Diabetic Retinopathy after Various Treatment Modalities

Sidra Shakil, M. Saleh Memon, P. S. Mahar, Abdul Fattah Memon, Muhammad Faisal Fahin, Seema N. Mumtaz, Sikandar Ali Sheikh

*Pak J Ophthalmol 2019, Vol. 35, No. 1*

See end of article for  
authors affiliations

**Purpose:** To determine the visual outcome of laser treatment and intra-vitreous Avastin (Bevacizumab) injection as mono-therapy or combined, in patients with Vision Threatening Diabetic Retinopathy (VTDR).

**Study Design:** Quasi Experimental study with non-probability convenient sampling.

**Place & Duration of Study:** Isra Postgraduate Institute of Ophthalmology, Al-Ibrahim Eye Hospital, Karachi from January 2016 to December 2017.

**Material & Methods:** Patients with Diabetic retinopathy (DR) were graded according to International clinical diabetic retinopathy & macular edema disease severity scale. Patients with VTDR were offered Laser therapy, intra-vitreous Avastin injection or both.

**Results:** VTDR was witnessed in 586 patients out of 1988 patients with DR. Out of which 108 had Proliferative Diabetic Retinopathy (PDR), 382 had clinically significant macular edema (CSME) and 96 had Advanced Diabetic Eye Disease (ADED). Laser was done in 78 eyes, intravitreal Avastin was given in 340 eyes and combined laser and Avastin were given in 35 eyes. When visual outcome was correlated with treatment modalities, improvement was found in 248 eyes, deterioration in 34 eyes and stabilization in 58 eyes of Avastin group, whereas improvement was seen in 45 eyes, deterioration in 15 eyes and stabilization in 18 eyes of laser group. In combined treatment group, improvement was witnessed in 23 eyes, deterioration in 4 eyes and stabilization in 8 eyes.

Correspondence to:  
P.S. Mahar  
FRCS, DO, FRCOphth  
Professor & Dean  
Isra Postgraduate Institute of  
Ophthalmology,  
Karachi.  
**Email:** salim.mahar@aku.edu

**Conclusions:** Visual outcome of Avastin alone or combined with laser was found to be better than laser treatment alone in stabilizing the visual acuity in patients with vision threatening diabetic retinopathy.

**Keywords:** Bevacizumab, Laser, Intra vitreal Injection, Avastin.

**D**iabetic retinopathy (DR) is an important complication of diabetes and is a global cause of blindness. It is classified into non proliferative diabetic retinopathy (NPDR), proliferative retinopathy (PDR) and diabetic macular edema (DME). Involvement or threatening of the center of the macula is termed clinically significant macular edema (CSME) by the Early Treatment Diabetic Retinopathy Study (ETDRS)<sup>1</sup>. In clinical situation, CSME has become synonymous with DME. Worldwide, there are approximately 93 million people with DR, Out of which 17 million have PDR and 21 million have DME<sup>2</sup>. In Pakistan, based on National Survey of blindness carried out in 2007<sup>3</sup>, it was estimated that there were at least 90,000 to 100,000 adults with vision threatening diabetic retinopathy (VTDR) requiring immediate eye care<sup>4</sup>. Several national studies since then have shown that prevalence of diabetes is 7.5% to 11% and that of DR and VTDR is 27.43% and 8.73% respectively in Pakistan<sup>5,6</sup>. Clinical based evidence shows that control over modifiable factors like hyperglycaemia<sup>7</sup>, hypertension<sup>8</sup>, and hyperlipidemia<sup>9,10</sup> effectively prevent the development and progression of DR and DME. However this control is not possible in the developing countries making them more vulnerable to complications of diabetes. Early detection and timely treatment of diabetes and DR is necessary to prevent visual impairment. Focal/grid laser photocoagulation for CSME and Pan retinal photocoagulation (PRP) for PDR has remained the gold standard for last 30 years after monumental work of Early Treatment Diabetic Retinopathy Study (ETDRS). Recently anti-VEGF drugs have become the first line of treatment for CSME<sup>11</sup> and Laser therapy remains an adjuvant therapy to save the frequent visits, whereas PRP is still the first line of treatment for PDR<sup>12</sup>. Anti-VEGF before or along with PRP are of added benefit in high risk cases of PDR<sup>13</sup>.

This study was designed to show the visual outcome of various treatment modalities like laser application and intravitreal Avastin (Bevacizumab) injection as monotherapy or combined in patients with VTDR in our setup where follow up is poor<sup>14</sup>.

## MATERIAL & METHODS

This was a Quasi Experimental study with non-probability convenient sampling carried out at Diabetes eye clinic of Al Ibrahim Eye Hospital (AIEH), Isra Postgraduate Institute of Ophthalmology, Karachi from January 2016 to December 2017. All the patients with diabetes mellitus type 2 attending diabetic eye clinic of AIEH were included in this study. Those with cataract, glaucoma and advanced diabetic eye disease (ADED) were excluded. Every patient had best corrected visual acuity (BCVA) recorded along with bio-microscopic examination of anterior segments and intraocular pressure using Goldman tonometer. They were all screened with Non Mydriatic Fundus Camera (NMFC) taking one view of the posterior pole. The patients without DR were examined by a general ophthalmologist and diabetologist. Patients with any DR or un-readable fundus photograph had dilated pupil examination with 90 D fundus lens. DR was graded according to International clinical diabetic retinopathy & macular edema disease severity scale.<sup>15</sup> Patients with Non vision threatening diabetic retinopathy (NVTDR) were given a follow up date as per directions of Royal college of ophthalmologist.<sup>16</sup> Patients with VTDR (PDR and DME) were all considered for intervention. Intervention advised was either monotherapy laser or intra-vitreous Avastin injection at monthly interval, or both. Patients with CSME or vitreous hemorrhage (PDR) were given intra-vitreous Avastin at monthly interval till the macular edema and hemorrhage were absorbed. It was then followed by modified grid laser for CSME and PRP for PDR. In DME patients with macular edema away from the fovea, patients were preferably treated with laser before anti VEGF. Follow up routine was according to the recommendations of Royal Collage of Ophthalmologist.<sup>16</sup> Accordingly the patients receiving only laser application were advised three to four monthly follow-ups, whereas patients having intra-vitreous Avastin injections alone or with laser were advised monthly follow-up, at least in the first year. On each follow-up visit, BCVA on Log Mar, blood sugar level, lipids and BP were checked.

Hb<sub>A1C</sub> was done in individuals with labile glycaemia. Optical coherence tomography (OCT) and Fundus Fluorescein Angiography (FFA) were carried out on all patients requiring treatment. In the present study, the criteria for labeling improved, stable or worse visual outcome were single line improvement, no change or decrease on log Mar chart.

Statistical analysis was done through Statistical Package for social sciences (SPSS) version 23.0. For continuous variable mean ± Standard deviation were presented. Qualitative variables were shown in frequency and percentages. To see the significance between treatment and visual acuity (Improved, stable or worse) Chi-square test was applied. The significance of Pre & Post visual outcome (Log Mar) was compared through Paired sample t-test. The cut off value of  $p \leq 0.05$  considered to be statistically significant.

**RESULTS**

From January 2016 to December 2017, a total number of 11,027 patients with diabetes were registered in diabetic clinic. On screening these patient, 1988 were found to have DR (18.02%) and 586 had VTDR (5.3%). Amongst the patients with VTDR, 108 (18.3%) had PDR, 382 (65.2%) had CSME and 96 (16.3%) had

ADED. (Table 1) Patients with PDR and CSME (490) were advised intervention which was accepted by 380 patients with 453 eyes. Laser was done in 78 (17.2%) eyes, Avastin injection was given in 340 (75.1%) eyes and combined treatments of intra-vitreous Avastin and Argon laser were given in 35 (7.7%) eyes. Over all BCVA improved in 316 (69.8%) eyes, remained stable in 84 (18.5%) eyes and worsened in 53 (11.7%) eyes. (Table - II). Pre and post treatment BCVA was noted in Laser, Avastin injection and combined treatment group. It was observed that laser group showed improvement in BCVA from Log Mar 0.35 ± 0.23 to 0.24 ± 0.21. In Avastin injection group improvement was from Log Mar 0.40 ± 0.24 to 0.23 ± 0.20. While in combined treatment, visual improvement was recorded from Log Mar 0.40 ± 0.24 to 0.20 ± 0.14. (Figure 1).

When BCVA was correlated with treatment modalities separately, Laser group showed visual improvement in 45 (57.7%) eyes, stable in 18 (23.1%) eyes and worsened in 15 (19.2%) eyes. The Avastin injection group showed visual improvement in 248 (72.9%) eyes, stable in 58 (17.1%) eyes and decrease in 34 (10%) eyes. While the group given combined treatment showed visual improvement in 23 (65.7%) eyes, stable in 8 (22.9%) eyes and worsened in 4 (11.4%) eyes with P-value < 0.0001 (Table 3).

**Table 1:** Patients attended AIEH during the study period January 2016 to December 2017.

Description	Number	Percentage	
Total eye patients in OPD of AIEH	225603		
Patient with diabetes	11027	4.80%	
DR detected	1988	18%	
VTDR in all diabetics	586	5.30%	5.3% in people with diabetes
PDR, alone	108	5.4% of DR	0.979% in people with diabetes, (1.65% when PDR with CSME s included)
CSME	382 (79 CSME were associated with PDR)	19.2% of DR	3.464% in people with diabetes
ADED	96	16.30%	0.87% in people with diabetes
intervention advised	96 + 110 = 206 out of 586	100%	
Treatment accepted	380 persons (64.8) with 453 eyes	64.80%	

**Table 2:** Overall outcome of the treatment.

BCVA Log Mar (n = 453 eyes)	N (%)
Improved	316 (69.8)
Stable	84 (18.5%)
Worse	53 (11.7%)

Total	453
-------	-----

\*Best corrected visual acuity (BCVA)

**Table 3:** Association between Diagnosis, treatment and Visual outcome.

Treatment	BCVA Condition			Total		
	Improved	Stable	Worse			
LASER	CSME	4 40.0%	4 40.0%	2 20.0%	10 100.0%	
	CSME with NPDR	14 70.0%	1 5.0%	5 25.0%	20 100.0%	
	CSME with PDR	5 100.0%	0 0.0%	0 0.0%	5 100.0%	
	PDR	22 51.2%	13 30.2%	8 18.6%	43 100.0%	
	Total	45 57.7%	18 23.1%	15 19.2%	78 100.0%	
	Injection	CSME	40 65.6%	13 21.3%	8 13.1%	61 100.0%
CSME with NPDR		133 77.8%	26 15.2%	12 7.0%	171 100.0%	
CSME with PDR		34 57.6%	15 25.4%	10 16.9%	59 100.0%	
PDR		41 83.7%	4 8.2%	4 8.2%	49 100.0%	
Total		248 72.9%	58 17.1%	34 10.0%	340 100.0%	
Both Laser and Injection		CSME with NPDR	7 77.8%	0 0.0%	2 22.2%	9 100.0%
	CSME with PDR	12 80.0%	3 20.0%	0 0.0%	15 100.0%	
	PDR	4 36.4%	5 45.5%	2 18.2%	11 100.0%	
	Total	23 65.7%	8 22.9%	4 11.4%	35 100.0%	
	Total	CSME	44 62.0%	17 23.9%	10 14.1%	71 100.0%
		CSME with NPDR	154 77.0%	27 13.5%	19 9.5%	200 100.0%
CSME with PDR		51 64.6%	18 22.8%	10 12.7%	79 100.0%	
PDR		67 65.0%	22 21.4%	14 13.6%	103 100.0%	
Total		316 69.8%	84 18.5%	53 11.7%	453 100.0%	

**Table 4:** Comparison of Visual Acuity with different treatments.

Treatments	Pre Visual Acuity	Post Visual Acuity	P-value
Laser	0.35 ± 0.23	0.24 ± 0.21	< 0.001
Injection	0.40 ± 0.24	0.23 ± 0.20	< 0.001
Both	0.40 ± 0.24	0.20 ± 0.14	< 0.001

\*Data Presented in Mean ± SD, Visual acuity was noticed on Log Mar chart.

\*Paired sample t-test was applied

## DISCUSSION

This study showed that BCVA in the laser group improved by one line or 5 letters (from  $0.35 \pm 0.23$  to  $0.24 \pm 0.21$ ). Avastin group showed improvement in BCVA by two lines or 10 letters on Log Mar (from  $0.40 \pm 0.24$  to  $0.23 \pm 0.20$ ). Visual acuity in combined group improved from  $0.40 \pm 0.24$  to  $0.20 \pm 0.14$  (2 lines or ten letters) same as monotherapy with anti-VEGF group. The present study is in accordance with many studies in favor of anti-VEGF. Brucker et al<sup>17</sup> and Elman et al<sup>18</sup> reported that results of anti VEGF vs. PRP in diabetic retinopathy have better visual acuity, less visual field loss and fewer surgical interventions in injection groups. Adam et al<sup>19</sup> and Sivaparsad S et al<sup>20</sup> has shown the superiority of anti VEGF as the more effective treatment for preserving visual function associated with DR. Present study differs from the international studies in loss of patients to follow up. Adam & Sivaparsad et al (The CLARITY trial)<sup>19, 20</sup> quoted 9% loss to follow up at 1 year. In the present study 69% were lost to follow up and only 31% individuals returned for follow-ups. Out of those who attended, 43.7% attended once, 42.65% attended twice, 4.5% attended thrice, 6.8% attended four times while 2.1% came five times. This raises the question of cautious use of anti VEGF alone as primary treatment. Anti-VEGF treatment needs multiple injections at monthly interval. At least three monthly injections and then monthly follow up for assessing need of repeat injection or laser is indicated<sup>21</sup>. Low follow up compliance mainly due to unawareness, affordability and accessibility in developing countries<sup>22-24</sup>, makes monitoring of anti-VEGF difficult. In Pakistan, health service uptake is not more than 25%<sup>14</sup>.

The ultimate result of anti-VEGF may be better than Laser alone; but it is only possible when patient can afford multiple injections and visits. In the light of this study the anti-VEGF combined with laser will be better management of CSME as well as PDR. With these considerations laser can be considered as first line of treatment in PDR without macular edema; but if the patient has CSME alone or with PDR anti VEGF can be the first line of treatment followed by laser.

Visual outcomes of VTDR after treatment with intra-vitreous Avastin (Bevacizumab) is superior to PRP alone. Keeping in view the loss to follow ups, we can suggest PRP in PDR and 1-2 injections of anti-VEGF followed by laser application in CSME. However

larger prospective studies are required to further evaluate the long term effects of these recommendation in halting the disease progression and extended improved visual outcomes. However regardless of whatever treatment is offered to the patient, it is mandatory to educate and adequately address the importance of regular follow-ups and medical compliance at patient's end. It is important that the physician should keep in mind the cost-effectivity and affordability of the patient without compromising the outcome of the treatment.

## CONCLUSIONS

Visual outcome of Avastin alone or combined with laser was found to be better than laser treatment alone in stabilizing the visual acuity in patients with vision threatening diabetic retinopathy.

### Conflict of Interest

The authors declared that there is no conflict between authors.

### Financial Disclosure

None.

### Author's Affiliation

Sidra Shakil  
Senior Registrar  
Isra Postgraduate institute of ophthalmology

M. Saleh Memon  
Director research,/Executive Director  
Isra Postgraduate institute of ophthalmology

Prof. P S Mahar  
FRCS, FRCOphth  
Professor & Dean  
Isra Postgraduate institute of ophthalmology

Abdul Fattah Memon  
Professor  
Isra Postgraduate institute of ophthalmology

Muhammad Faisal Fahin  
Statistician  
Isra Postgraduate institute of ophthalmology

Seema N Mumtaz  
Consultant Epidemiologist  
Isra Postgraduate institute of ophthalmology

Sikandar Ali Sheikh  
Project Manager  
Isra Postgraduate institute of ophthalmology

#### Author's contribution

Sidra Shakil  
Conceive the study, Manuscript writing.

M. Saleh Memon  
Manuscript writing, Critical review.

Prof. P S Mahar  
Review the final manuscript and intellectual contribution.

Abdul Fattah Memon  
Clinical evaluation and management of patients.

Muhammad Faisal Fahin  
Statistical analysis and Interpretation.

Seema N Mumtaz  
Review and final drafting of manuscript.

Sikandar Ali Sheikh  
Data collection, study design and review.

#### REFERENCES

1. **Early Treatment Diabetic Retinopathy Study Research Group.** Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Archives of Ophthalmology, 1985; 103 (12): 1796-1806.
2. **Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T et al.** Global Prevalence and Major Risk Factors of Diabetic Retinopathy. Diabetes Care, 2012; 35: 556-564.
3. **Jadoon MZ, Dineen B, Bourne RA, Shah SP, Khan MA, Johnson GJ et al.** Prevalence of Blindness and Visual Impairment in Pakistan: The Pakistan National Blindness and Visual Impairment Survey. Investigative Ophthalmol& Vis Sci. 2006; 47 (11): 4749-55.
4. **Groves N.** Diabetic retinopathy on the rise in Pakistan, Investigative Ophthalmol& Vis Sci. 2006; 47 (11): 4749-55.
5. **Hakeem R, Fawwad A.** Diabetes in Pakistan: Determinants and Prevention. Journal of Diabetology, October, 2010; 1 (3): 1-13.
6. **Mumtaz SN, Fahim MF, Arslan M, Shaikh SA, Kazi U, Memon MS.** Prevalence of diabetic retinopathy in Pakistan: A systematic review. Pak J Med Sci. 2018; 34 (2): 493-500.
7. **UK Prospective Diabetes Study Group:** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes: UKPDS 33. Lancet. 1998; 352: 837-853.
8. **UK Prospective Diabetes Study Group:** Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. Br Med J. 1998; 317: 713-720.
9. **Klein BEK, Moss SE, Klein R, Surawicz TS.** The Wisconsin Epidemiologic Study of Diabetic Retinopathy, XIII: relationship of serum cholesterol to retinopathy hard exudate. Ophthalmology, 1991; 98: 1261-1265.
10. **Gordon B, Chang S, Kavanagh M, Berrocal M, YannuzziL, Robertson C et al.** The effects of lipid lowering on diabetic retinopathy. Am J Ophthalmol. 1991; 112: 385-391.
11. **Bhagat N, Grigorian RA, Tutela A, Zarbin MA.** Diabetic macular edema: pathogenesis and treatment. Surv Ophthalmol. 2009; 54 (1): 1-32. Doi: 10.1016/j.survophthal.2008.10.001.
12. **The Diabetic Retinopathy Study Research Group.** Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report no. 14. Int Ophthalmol Clin. 1987; 27: 239-253.
13. **Osadon P, Fagan XJ, Lifshitz T, Levy J.** A review of anti-VEGF agents for proliferative diabetic retinopathy. Eye (Lond). 2014; 28 (5): 510-520.
14. **Alvi R, Memon MS, Shera S, Mumtaz SN, Shaikh SA, Fahim MF.** Visual outcome of laser treatment in diabetic macular edema: Study from an Urban Diabetes Care

- Center. Pak J Med Sci. 2016; 32 (5): 1229-1233.  
Doi: <http://dx.doi.org/10.12669/pjms.325.10597>
15. **Wilkinson CP, Ferris FL, Klien RE, et al.** Proposed International Clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*, 2003; 110 (9): 1677-82.
  16. **Ghanchi F.** A summary and the Diabetic Retinopathy Guidelines Working Group. The Royal College of Ophthalmologists' clinical guidelines for diabetic retinopathy, 2013; 27 (2): 285-287.
  17. **Brucker AJ, Qin H, Antoszyk AN, et al.** Diabetic Retinopathy Clinical Research Network. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. *Arch Ophthalmol*. 2009; 127 (2): 132-140.
  18. **Elman MJ, Aiello LP, Beck RW, et al.** Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*, 2010; 117 (6): 1064-1077.
  19. **Adam R. Glassman, MS1.** Results of a Randomized Clinical Trial of Aflibercept vs. Panretinal Photocoagulation for Proliferative Diabetic Retinopathy Is It Time to Retire Your Laser? *JAMA Ophthalmol*. 2017; 135 (7): 685-686.
  20. **Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J et al.** Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. *The Lancet*. 2017; 389 (10085): 2193-2203.
  21. **Michaelides M, Kaines A, Hamilton RD.** A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT study) 12-month data: report 2. *Ophthalmology*, 2010; 117 (6): 1078-1086.
  22. **Hakeem R, Awan Z, Memon S, Gillani M, Shaikh SA, Sheikh MA, et al.** Diabetic retinopathy awareness and practices in a low-income suburban population in Karachi, Pakistan. *J Diabetol*. 2017; 8: 49-55.
  23. **Memon MS, Mumtaz SN, Sheikh SA, Fahim MF.** Community Perception and Service Utilization of Diabetic Retinopathy Management Project in Gaddap Town. *Pak J Ophthalmol*. 2016; 32 (2): 70-77.
  24. **Memon MS, Shaikh SA, Shaikh AR, Fahim MF, Mumtaz SN, Ahamad N.** An assessment of Knowledge, attitude & Practices (KAP) towards Diabetes & Diabetic retinopathy in suburban town of Karachi. *Pak J Med Sc*. 2015; 3191): 183-188.