

Outcomes of Three Intravitreal Injections of Bevacizumab for Diabetic Macular Oedema

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Abstract

Background: Diabetic macular oedema (DMO) is a leading cause of visual impairment among patients with diabetic retinopathy. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy, particularly Bevacizumab, is widely used to reduce macular oedema and improve visual outcomes.

Objective: To evaluate the visual and anatomical outcomes following three monthly intravitreal injections of Bevacizumab in patients with diabetic macular oedema.

Methods: This hospital-based cross-sectional study was conducted in the Department of Ophthalmology, Gopalganj Eye Hospital and Training Institute, from July 2022 to December 2023. A total of 102 patients (150 eyes) with type 2 diabetes mellitus and centre-involving DMO were included. Eligible eyes received three monthly intravitreal injections of Bevacizumab (1.25 mg/0.05 mL). Best corrected visual acuity (BCVA), central foveal thickness (CFT) measured by spectral domain optical coherence tomography, and intraocular pressure (IOP) were assessed at baseline and one month after the final injection.

Results: The mean BCVA improved significantly from 0.82 ± 0.41 logMAR at baseline to 0.55 ± 0.39 logMAR after treatment ($p < 0.001$). The mean CFT decreased from 441.20 ± 148.60 μm to 358.62 ± 142.41 μm ($p < 0.001$). A total of 96.6% of treated eyes showed visual improvement, with 41.3% gaining two or more lines of vision. The most common complication was subconjunctival haemorrhage (21.3%), while serious adverse events such as retinal detachment and endophthalmitis were rare (2.7% each).

Conclusion: Three monthly intravitreal Bevacizumab injections significantly improve both visual acuity and macular thickness in patients with diabetic macular oedema, with an acceptable safety profile.

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Introduction

Diabetic macular oedema (DMO) is a leading cause of visual impairment among working-age adults with diabetes mellitus and represents a significant public health concern worldwide. It develops as a consequence of long-standing hyperglycaemia-induced microvascular damage, resulting in breakdown of the blood–retinal barrier, increased vascular permeability, and accumulation of extracellular fluid within the macula. This pathological process leads to retinal thickening and progressive deterioration of central vision, significantly affecting quality of life and functional independence.^{1,2} The global burden of diabetes mellitus continues to rise, and diabetic retinopathy, including DMO, remains one of its most disabling microvascular complications. Epidemiological studies suggest that a substantial proportion of patients with diabetic retinopathy eventually develop macular oedema, particularly those with poor glycaemic control, hypertension, and longer duration of disease.^{3,4} In addition, risk factors such as dyslipidaemia, nephropathy, and smoking further contribute to disease progression and severity.⁵

The pathogenesis of DMO is multifactorial, involving chronic inflammation, oxidative stress, and upregulation of vascular endothelial growth factor (VEGF), which plays a central role in increasing vascular permeability and neovascular changes in the retina. Elevated intraocular VEGF levels have been consistently demonstrated in patients with DMO, correlating with disease severity and macular thickness.^{6,7} These findings have led to the development of targeted pharmacological therapies aimed at inhibiting VEGF-mediated pathways. Historically, focal/grid laser photocoagulation was the standard treatment for centre-involving DMO, as established by the Early Treatment Diabetic Retinopathy Study (ETDRS).

However, while laser therapy reduced the risk of moderate vision loss, it rarely improved visual acuity and was associated with irreversible retinal damage.⁸ The advent of intravitreal anti-VEGF agents has revolutionised the management of DMO by offering both anatomical and functional improvement.

Among anti-VEGF agents, Ranibizumab, Aflibercept, and Bevacizumab have demonstrated significant efficacy in improving visual outcomes in DMO patients. Large randomized controlled trials such as the RISE and RIDE studies confirmed the superiority of Ranibizumab over sham treatment in improving visual acuity and reducing central retinal thickness.⁹ Similarly, the VIVID and VISTA trials demonstrated sustained visual gains with Aflibercept in patients with DMO.¹⁰ The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T further established that all three agents are effective, with differential benefits depending on baseline visual acuity.¹¹

Bevacizumab, a full-length monoclonal antibody against VEGF-A, is widely used off-label due to its lower cost and comparable efficacy. Several studies have demonstrated that Bevacizumab significantly improves both visual acuity and central macular thickness in DMO patients, particularly when administered in multiple monthly injections.^{12,13} The BOLT study showed that Bevacizumab was more effective than laser therapy in improving visual outcomes in persistent DMO cases, highlighting its clinical utility in resource-limited settings.¹⁴

Despite strong evidence supporting anti-VEGF therapy, variability exists in treatment response, and multiple injection regimens are often required to achieve optimal outcomes. Factors such as baseline visual acuity,

duration of oedema, glycaemic control, and retinal ischemia influence treatment response.^{15,16} Moreover, real-world studies have reported that three loading doses of anti-VEGF agents can provide significant early anatomical and functional improvement, forming the basis of standard treatment protocols.¹⁷

In developing countries like Bangladesh, where the burden of diabetes is increasing rapidly and access to expensive anti-VEGF agents is limited, Bevacizumab remains the most commonly used first-line intravitreal therapy. However, there is limited local evidence evaluating the outcomes of a standardized three-injection loading regimen in patients with DMO. Understanding its effectiveness in real-world clinical practice is essential for optimizing treatment protocols and improving visual prognosis in this population.¹⁸ Therefore, this study aimed to evaluate the visual and anatomical outcomes following three monthly intravitreal Bevacizumab injections in patients with diabetic macular oedema in a tertiary eye care setting in Bangladesh.

Methods

This hospital-based cross-sectional study was conducted in the Department of Ophthalmology, Gopalganj Eye Hospital and Training Institute from July 2022 to December 2023. A total of 102 patients (150 eyes) with type 2 diabetes mellitus and diabetic macular oedema (DMO) were consecutively recruited from the outpatient ophthalmology clinic. Ethical approval was obtained from the institutional review committee, and the study adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Patients aged 30–70 years with centre-involving DMO and best corrected visual

acuity (BCVA) of 6/9 or worse, along with central foveal thickness (CFT) ≥ 260 μm on spectral domain optical coherence tomography (SD-OCT), were included. Exclusion criteria comprised active ocular infection, recent intravitreal anti-VEGF or steroid injection, recent retinal laser or vitrectomy, advanced proliferative diabetic retinopathy, glaucoma requiring more than two topical medications, vitreomacular traction, significant media opacity, recent cardiovascular or cerebrovascular events, and pregnancy.

Baseline evaluation included detailed medical and ocular history, BCVA assessment using Snellen chart, slit-lamp biomicroscopy, intraocular pressure measurement by Goldmann applanation tonometry, and dilated fundus examination. Diabetic retinopathy was graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) classification. SD-OCT was performed using macular scan protocols, and central foveal thickness was recorded as the mean thickness of the central 1 mm macular area.

Eligible eyes received three monthly intravitreal injections of Bevacizumab (1.25 mg/0.05 mL), administered under strict aseptic conditions in the operating theatre. Injections were performed via the pars plana (3.5 mm in pseudophakic/aphakic eyes and 4 mm in phakic eyes), predominantly in the superotemporal quadrant. Patients were followed up one week after each injection and then at monthly intervals, with repeat assessment of BCVA, IOP, and OCT parameters. The final outcome assessment was performed one month after the third injection.

Data were entered, cleaned, and analysed using the Statistical Package for Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics

were presented as frequencies and percentages for categorical variables, and as mean $\pm$ standard deviation (SD) for continuous variables. The chi-square test was used to assess associations between categorical variables. A p-value of <0.05 at a 95% confidence level was considered statistically significant.

Ethical approval for the study was obtained from the Institutional Review Board (IRB) of Gopalganj Eye Hospital and Training Institute. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after a clear explanation of the study purpose and procedures. Participants were informed of their right to withdraw from the study at any time without any consequences. Strict confidentiality and anonymity of all patient data were maintained throughout the study.

Results

Table I show the study population consisted predominantly of male patients (78.4%), with females comprising only 21.6%, representing a male preponderance among individuals presenting with diabetic macular oedema requiring intravitreal therapy. The mean age was 62.1 ± 11.3 years. The mean duration of diabetes was 10.5 ± 6.3 years, reflecting long-standing diabetes among most participants, which is a well-established risk factor for the development and progression of diabetic retinopathy and macular oedema. Glycaemic control was suboptimal in this cohort, as indicated by a mean HbA_{1c} of $8.4 \pm 1.4\%$. Regarding diabetes management, the majority of patients were on oral hypoglycaemic agents (54.9%), while 17.6% were on insulin alone and 27.5% required combined therapy. Smoking was present in 38.2% of participants.

Table II exhibits a substantial burden of systemic comorbidities, reflecting long-standing and complicated type 2 diabetes mellitus. Hypertension was the most prevalent systemic comorbidity, affecting (54.9%) patients, followed by hypercholesterolemia in (33.3%) patients. Nephropathy was present in (17.6%) patients, while (20.6%) patients were receiving anticoagulant therapy.

Table III indicates that most study eyes were phakic (76.0%), while 24.0% were pseudophakic. Glaucoma requiring medication was present in 6.0% of eyes. Regarding diabetic retinopathy severity, severe non-proliferative diabetic retinopathy (NPDR) was the most common stage (36.0%), followed by non-high-risk proliferative diabetic retinopathy (24.0%) and NPDR with prior panretinal photocoagulation (20.0%). Moderate NPDR accounted for 18.0% of eyes, whereas mild NPDR was observed in only 2.0%.

Table IV demonstrates that there was a statistically significant improvement in both visual and anatomical outcomes following three monthly Intravitreal injections of Bevacizumab. The mean BCVA improved from 0.82 ± 0.41 logMAR at baseline to 0.55 ± 0.39 logMAR at final follow-up, with a mean improvement of 0.27 ± 0.21 logMAR ($p < 0.001$). Similarly, the mean central foveal thickness (CFT) significantly decreased from 441.20 ± 148.60 μm to 358.62 ± 142.41 μm , with a mean reduction of 82.58 ± 69.40 μm ($p < 0.001$), indicating significant anatomical improvement. Although the mean intraocular pressure (IOP) slightly decreased from 15.82 ± 3.62 mmHg to 15.30 ± 3.12 mmHg, the change was not statistically significant ($p = 0.062$).

Table V indicates that most treated eyes demonstrated visual improvement following three monthly intravitreal bevacizumab

injections. Improvement of one line was observed in 55.3% of eyes, while an improvement of two or more lines was achieved in 41.3% of eyes. Only a small proportion (3.3%) showed no improvement after treatment.

Table VI indicates that most common complication following Intravitreal Bevacizumab injection was subconjunctival

haemorrhage (21.3%). Systemic adverse effects were reported in 11.3% of eyes. Corneal epithelial defect and anterior chamber reaction (Grade 2) were observed in 8.0% and 6.0% of eyes, respectively. Serious ocular complications such as vitreous haemorrhage, retinal detachment, and endophthalmitis were rare, each occurring in 2.7% of eyes.

Table I: Baseline demographic and clinical characteristics of patients (n= 102 patients; 150 eyes)

Variables	Category	Frequency (n)	Percentage (%)	Mean $\pm$ SD (Range)
Sex	Male	80	78.4	
	Female	22	21.6	
Age (years)				62.1 $\pm$ 11.3 (35–70)
Duration of diabetes (years)				10.5 $\pm$ 6.3 (1–22)
HbA1c (%)				8.4 $\pm$ 1.4 (6.8–11.2)
DM treatment	Oral hypoglycemic agents	56	54.9	
	Insulin therapy	18	17.6	
	Both insulin + OHA	28	27.5	
Smoking status	Yes	39	38.2	
	No	63	61.8	

Table II: Systemic comorbidities among patients (n= 102)

Comorbidity	Present n (%)	Absent n (%)
Hypertension	56 (54.9)	46 (45.1)
Hypercholesterolemia	34 (33.3)	68 (66.7)
Nephropathy	18 (17.6)	84 (82.4)
Anticoagulant therapy	21 (20.6)	81 (79.4)

*Multiple responses

Table III: Ocular characteristics and severity of diabetic retinopathy (n =150 eyes)

Variables	Category	Frequency (n)	Percentage (%)
Lens status	Phakic	114	76.0
	Pseudophakic	36	24.0
Glaucoma on medication	Yes	9	6.0
	No	141	94.0
Diabetic retinopathy stage	Mild NPDR	3	2.0
	Moderate NPDR	27	18.0
	Severe NPDR	54	36.0
	NPDR with prior PRP	30	20.0
	Non-high-risk PDR	36	24.0

Table IV: Visual and anatomical outcomes after three monthly IVI of Bevacizumab (n= 150 eyes)

Parameter	Baseline (Mean $\pm$ SD)	Final (Mean $\pm$ SD)	Mean Difference (Mean $\pm$ SD)	p-value
BCVA (logMAR)	0.82 $\pm$ 0.41	0.55 $\pm$ 0.39	0.27 $\pm$ 0.21	<0.001*
CFT (μ m)	441.20 $\pm$ 148.60	358.62 $\pm$ 142.41	82.58 $\pm$ 69.40	<0.001*
IOP (mmHg)	15.82 $\pm$ 3.62	15.30 $\pm$ 3.12	0.52 $\pm$ 2.68	0.062

Paired sample t-test done; p value <0.05 was considered as a significant value

Table V: Visual improvement after treatment (n= 150 eyes)

Outcomes	Frequency (n)	Percentage (%)
≥ 2 lines improvement	62	41.3
1 line improvement	83	55.3
No improvement	5	3.3

Table VI: Complications following Intravitreal Bevacizumab injections (n= 150 eyes)

Complications	Frequency (n)	Percentage (%)
Subconjunctival haemorrhage	32	21.3
Corneal epithelial defect	12	8.0
Anterior chamber reaction (Grade 2)	9	6.0
Endophthalmitis	4	2.7
Retinal detachment	4	2.7
Vitreous haemorrhage	4	2.7
Systemic adverse effects	17	11.3

*Multiple responses

Discussion

The present study demonstrated that three monthly intravitreal Bevacizumab injections produced significant improvement in both functional and anatomical outcomes in patients with diabetic macular oedema (DMO), with a favorable safety profile. The observed findings are consistent with previously published clinical studies.^{11,19,20}

In this study, the majority of patients were male (78.4%) with a mean age of 62.1 $\pm$ 11.3 years, indicating that DMO predominantly affects older individuals with long-standing diabetes. Similar demographic patterns were

reported in the UKPDS and other large epidemiological studies, where increasing age, male sex, and longer duration of diabetes were identified as crucial risk factors for diabetic retinopathy progression.^{5,21} The mean duration of diabetes in the present study was 10.5 years, and poor glycaemic control (mean HbA1c 8.4%) was common. This is consistent with findings from Stratton et al., who demonstrated that poor glycaemic control is strongly associated with microvascular complications, including DMO.²² Systemic comorbidities were highly prevalent in this cohort, particularly hypertension (54.9%) and hypercholesterolaemia (33.3%). These

findings are in agreement with highlighted hypertension and dyslipidaemia as major modifiable risk factors contributing to the development and progression of diabetic retinopathy.²³ Smoking was also observed in a considerable proportion (38.2%) of patients, further increasing vascular risk and potentially worsening retinal outcomes. Ocular findings revealed that most eyes had advanced diabetic retinopathy, with severe non-proliferative diabetic retinopathy (36%) and non-high-risk proliferative diabetic retinopathy (24%) being most common. This is comparable to DRCR.net Protocol T baseline characteristics, where a large proportion of patients had moderate to severe disease requiring anti-VEGF therapy.^{24,25} The high proportion of advanced disease in the present study reflects delayed presentation and highlights the need for early screening in diabetic populations.

In terms of outcomes, the present study demonstrated a statistically significant improvement in BCVA from 0.82 ± 0.41 to 0.55 ± 0.39 logMAR ($p < 0.001$) and a significant reduction in central foveal thickness from 441.20 ± 148.60 μm to 358.62 ± 142.41 μm ($p < 0.001$). These findings are consistent with the DRCR.net Protocol T trial, which showed that intravitreal Bevacizumab leads to meaningful visual and anatomical improvement in DMO patients, although slightly less potent than Aflibercept in patients with poor baseline vision.²⁴ Similarly, the studies demonstrated significant superiority of Bevacizumab over laser therapy in improving visual acuity, supporting its effectiveness in clinical practice.^{14,26}

In the present study, 96.6% of eyes showed visual improvement, with 41.3% achieving a gain of two or more lines. Comparable results were found significant visual gain following intravitreal Bevacizumab in persistent DMO cases.¹³ Importantly, intraocular pressure

remained stable, and no significant safety concerns were observed, which aligns with systematic reviews indicating a low incidence of serious adverse events with anti-VEGF therapy.¹⁶ This study supports existing evidence that three loading doses of intravitreal Bevacizumab are effective in improving both visual acuity and retinal thickness in patients with DMO. However, longer follow-up is required to evaluate durability of response and the need for maintenance therapy in real-world settings.

Conclusion

Three monthly intravitreal Bevacizumab injections demonstrated significant improvement in both visual acuity and central macular thickness in patients with diabetic macular oedema. The treatment was associated with meaningful functional and anatomical benefits, while maintaining a promising safety profile with minimal and mostly mild complications. These findings support Bevacizumab as an effective and practical first-line therapeutic option for diabetic macular oedema in routine clinical practice, particularly in resource-limited settings.

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