Original Article

Effectiveness of Intravitreal Bevacizumab for Diabetic Macular Edema in Eyes with Preserved Visual Acuity: A Prospective Clinical Trial

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Abstract

Purpose: To assess the effectiveness of intravitreal Bevacizumab injections in reducing central macular thickness and preserving visual acuity in diabetic patients with center-involving macular edema and good baseline vision.
Patients and Methods: This prospective clinical trial was conducted over 18 months starting in April 2017. Patients with non-proliferative diabetic retinopathy, visual acuity ≥20/25, and central macular thickness > 300 µm on OCT were included. Participants were assigned to two groups: one received intravitreal Bevacizumab (1.2 mg), and the other was monitored without treatment. Central macular thickness and best-corrected visual acuity were measured at baseline and six months postoperatively.
Results: Twenty-two eyes completed the study (12 treated, 10 control). In the treatment group, the mean macular thickness decreased from 319 µm to 301 µm (P = 0.031). In the control group, it increased from 318 µm to 328 µm. However, the intergroup difference at six months was not statistically significant (P = 0.581). Visual acuity declined slightly in both groups: from 9.05/10 to 8.7/10 in the treated group and from 9.3/10 to 9.2/10 in controls, with no significant difference between groups (P = 0.373). No adverse events were reported.
Conclusion: Bevacizumab injections led to a modest reduction in macular thickness but did not significantly improve or preserve visual acuity in diabetic patients with good baseline vision. These findings suggest that factors beyond vascular endothelial growth factor may play a role in early-stage diabetic macular edema. Further studies with a higher sample size are suggested to confirm our findings.

Keywords: Diabetic Macular Edema; Bevacizumab; Anti-VEGF; Visual Acuity; OCT.

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Introduction

Diabetic retinopathy (DR) remains a leading cause of preventable vision loss among working-age individuals worldwide, particularly in developed countries [1]. As the global prevalence of diabetes continues to rise, projected to surpass 600 million by 2040, the burden of diabetes-related ocular complications is expected to grow in parallel [2]. Diabetic macular edema (DME), a common manifestation of DR, is the most frequent cause of vision impairment in this population [3]. Epidemiological data suggest that nearly half of individuals with diabetes develop some degree of retinopathy, and approximately 10 % will experience DME and associated vision-threatening complications [2,4].

DME may develop at any stage of diabetic retinopathy and can persist or progress even in patients with good visual acuity [5]. Although in some cases it may resolve spontaneously, persistent edema, particularly involving the foveal center, can lead to structural retinal disorganization and gradual visual decline [6]. Studies have demonstrated that even in eyes with preserved Snellen visual acuity (e.g., 20/25 or better), macular edema can impair contrast sensitivity, reading speed, and overall visual quality [7].

The pathophysiology of DME is multifactorial. Among the well-characterized contributors is vascular endothelial growth factor (VEGF), a potent mediator of angiogenesis and vascular permeability [3]. VEGF is upregulated in response to retinal hypoxia and promotes breakdown of the blood-retinal barrier, leading to extravasation of fluid and plasma components into the macular region [8]. This results in extracellular fluid accumulation, cystoid space formation, and thickening of the central retina [9]. Anti-VEGF agents, such as Bevacizumab, are now widely used as first-line therapy for DME due to their ability to reduce macular thickness and improve or maintain vision [10].

Advances in retinal imaging, particularly Optical Coherence Tomography (OCT), have transformed the diagnosis and monitoring of DME [11]. OCT provides high-resolution, cross-sectional images of the retina and allows for objective measurement of macular thickness, even in cases where clinical examination alone may not reveal overt edema [12]. This has enabled earlier detection and more precise assessment of treatment response [13].

Numerous randomized controlled trials have shown that intravitreal anti-VEGF injections significantly improve visual outcomes in patients with center-involving DME and moderate to poor baseline vision (e.g., ≤ 20/40) [14-16]. However, there remains clinical uncertainty regarding the benefit of initiating anti-VEGF therapy in patients with good visual acuity and OCT-confirmed macular thickening [17]. Treating such patients may reduce retinal thickness, but the functional benefit is less clear, and treatment carries procedural risks, financial costs, and a psychological burden due to repeated injections.

Furthermore, not all patients respond equally to anti-VEGF therapy [18]. The presence of inflammatory mediators, individual variations in retinal microstructure, and possible genetic predispositions may influence treatment response [19,20]. As such, personalized approaches to DME management are being increasingly emphasized in contemporary research.

Given these considerations, our study aims to evaluate the effectiveness of intravitreal Bevacizumab injections in diabetic patients with center-involving macular edema and good visual acuity. By focusing on this specific subgroup, we seek to clarify whether early intervention with anti-VEGF therapy provides a measurable anatomical or functional advantage compared to observation alone.

Patients and Methods

This study was designed as a prospective, interventional clinical trial conducted over a period of 18 months, beginning in April 2017. The research was carried out at the ophthalmology department of Baqiyatallah University of Medical Sciences, Tehran, Iran. Ethical approval was obtained from the university's ethics committee (Ethics ID: IR.BMSU.1397.004), and all participants provided written informed consent prior to enrollment. All ethical and procedural aspects of the study complied with the Declaration of Helsinki. Patients were fully informed about the purpose, procedures, and potential risks of participation, and their right to withdraw at any stage without consequence.

Eligible participants were adult patients with type 2 diabetes mellitus, presenting with non-proliferative diabetic retinopathy, best-corrected visual acuity of 20/25 (8/10) or better, and center-involving diabetic macular edema confirmed by Optical Coherence Tomography (OCT). Inclusion criteria required a central macular thickness greater than 300 microns, no prior history of intravitreal injection or retinal laser treatment, and no concurrent ocular pathologies that could interfere with retinal imaging or interpretation. Patients were excluded if they developed complications such as vitreous hemorrhage, tractional retinal detachment, or progression to proliferative diabetic retinopathy during the study. Individuals who could not complete scheduled follow-up visits were also excluded from final analysis.

Initially a total of 28 eyes from 18 patients with non-proliferative diabetic retinopathy, visual acuity ≥20/25, and central macular thickness > 300 μm on OCT were included. After exclusions due to inadequate follow-up or noncompliance, 22 eyes from 15 patients were included in the final analysis. Twelve eyes were in the treatment group and ten in the control group. In cases of bilateral disease, the eye with greater central thickness was selected for injection, and the fellow eye served as a control. Randomization was not employed due to ethical considerations; however, statistical analysis confirmed no significant baseline differences between groups.

The intervention consisted of intravitreal injection of 1.2 mg (0.05 mL) Bevacizumab (Avastin®), performed under sterile conditions in the operating room. Each patient in the treatment group was examined the day following injection and monthly thereafter for a total of six months. Re-injection was considered at monthly follow-ups based on OCT findings, with a maximum of three injections per eye during the study period. The control group was monitored clinically without receiving any therapeutic intervention.

The primary outcome measures were changes in central macular thickness and best-corrected visual acuity from baseline to six months. Macular thickness was measured using the Heidelberg Spectralis OCT system, while visual acuity was assessed using a standard Snellen chart and converted to LogMAR values for statistical analysis. All visual and imaging assessments were performed by a single experienced optometrist to minimize inter-observer variability.

Secondary parameters included systemic glycemic control, evaluated through measurement of glycated hemoglobin (HbA1c) and fasting blood sugar (FBS). Laboratory testing was conducted at Baqiyatallah

Hospital's central diagnostic facility.

Statistical analyses were conducted using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA). Quantitative data with normal distribution were compared using Student's t-test. Non-normally distributed data were assessed using the Wilcoxon signed-rank and Mann–Whitney U tests. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. A P-value of less than 0.05 was considered statistically significant in all comparisons.

Results

This prospective clinical trial was conducted on diabetic patients with center-involving diabetic macular edema and best-corrected visual acuity of 20/25 or better. Ultimately, 22 eyes from 15 patients were included in the study. Among these, 12 eyes received intravitreal Bevacizumab injections (treatment group), while 10 eyes were monitored without intervention (control group).

The average age in the treatment group was 55 years, compared to 52.3 years in the control group. All patients completed at least four follow-up visits during the six-month study period. In the treatment group, intravitreal injections were administered monthly as needed. On average, each treated eye received two injections (Table 1).

Baseline systemic parameters, including glycated hemoglobin (HbA1c) and fasting blood sugar (FBS), were also evaluated. In the treatment group, mean HbA1c was 8.2 %, and FBS was 171 mg/dL. In the control group, mean HbA1c was 8.5 %, and FBS was 167 mg/dL. No statistically significant differences were observed between the groups in either parameter (P = 0.711 for HbA1c; P = 0.962 for FBS).

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population

Variable	Treatment Group (n=12)	Control Group (n=10)
Number of eyes	12	10
Mean age (years)	55	52.3
Sex (M/F)	7/5	6/4
Mean BCVA (Decimal)	9.05/10	9.3/10
Mean CMT (µm)	319	318
Mean HbA1c (%)	8.2	8.5
Mean FBS (mg/dL)	171	167

At baseline, the mean central macular thickness in the treatment group was 319 microns. By the sixth month, this value had decreased to 301 microns. In contrast, the control group exhibited a baseline mean thickness of 318 microns, which slightly increased to 328 microns at six months. Among treated patients, 7 eyes (58 %) showed a reduction in macular thickness to below 300 microns by the end of the study period. In the control group, 5 eyes (50 %) achieved a similar outcome. The reduction in macular thickness in the treatment group was statistically significant (P = 0.031), but the difference between the treatment and control groups at six months did not reach statistical significance (P = 0.581) (Table 2). Longitudinal analysis revealed no significant intergroup difference in the trend of macular thickness changes over time.

Visual acuity was also assessed at baseline and at six months. The mean visual acuity in the treatment group at baseline was equivalent to 9.05/10 (approximately LogMAR 0.05), which slightly declined to 8.7/10 (LogMAR

0.06) by the end of the study. Visual acuity remained unchanged in 25 % of the treated eyes, improved in 33 %, and declined by approximately five letters in 42 % of cases. In the control group, baseline visual acuity was 9.3/10 (LogMAR 0.01) and decreased marginally to 9.2/10 (LogMAR 0.04) at six months. Sixty percent of control eyes maintained stable visual acuity, while 40 % experienced a decline of five letters. However, the difference in visual acuity changes between the two groups was not statistically significant (P = 0.373).

Variable	Treatment Group (n=12)	Control Group (n=10)	*P-value
Mean CMT at baseline (µm)	319	318	0.942
Mean CMT at 6 months (µm)	301	328	0.581
Eyes with CMT < 300 µm at 6 months (n, %)	7 (58 %)	5 (50 %)	0.721
Mean BCVA at baseline (Decimal)	9.05/10	9.3/10	0.367
Mean BCVA at 6 months (Decimal)	8.7/10	9.2/10	0.173
Eyes with improved BCVA (n, %)	4 (33 %)	0 (0 %)	0.101
Eyes with stable BCVA (n, %)	3 (25 %)	6 (60 %)	0.194
Eyes with decreased BCVA (n, %)	5 (42 %)	4 (40 %)	0.911

**Mann–Whitney U test was used for continuous variables.*
Fisher's Exact Test was applied for categorical comparisons.
CMT: central macular thickness; BCVA: best corrected visual acuity

In a subgroup analysis of five patients who had one eye treated and the fellow eye used as a control, non-parametric statistical comparison showed no significant inter-eye differences in either central macular thickness or visual acuity outcomes (P = 0.43).

No ocular complications or adverse events, such as endophthalmitis, increased intraocular pressure, or retinal detachment, were reported in any participants. None of the eyes demonstrated progression to proliferative diabetic retinopathy or required emergency intervention during the study period.

Discussion

This prospective clinical trial evaluated the effectiveness of intravitreal Bevacizumab in reducing central macular thickness (CMT) and preserving visual acuity in diabetic patients with center-involving macular edema and good baseline vision (≥20/25). Although the treatment group showed a statistically significant reduction in CMT over six months, this anatomical improvement did not translate into a significant functional benefit in terms of visual acuity compared to the control group. These findings underscore the complexity of diabetic macular edema (DME) pathophysiology and the limitations of anti-VEGF therapy in patients with minimal visual impairment.

The observed reduction in CMT within the treatment group aligns with previous studies that have established the anatomical efficacy of anti-VEGF agents in DME [21-23]. However, the lack of significant difference in visual outcomes between the treated and untreated groups is consistent with prior investigations reporting a "ceiling effect" in eyes with good baseline acuity [18]. For example Dugel et al., [24] demonstrated that the potential for visual improvement diminishes as baseline acuity approaches 20/20, with visual gains plateauing in patients who already possess near-normal function.

Moreover, the modest visual response in this study may be explained by the multifactorial nature of DME. While VEGF is a primary driver of vascular leakage and edema in many patients, it is not the sole pathological mechanism [25]. Inflammatory cytokines, oxidative stress, and microstructural disorganization of the retina also contribute to disease progression and treatment resistance [26]. In fact, the relative dominance of VEGF versus inflammatory factors varies across individuals, suggesting a need for personalized therapeutic approaches [27].

Advanced imaging studies have identified retinal biomarkers that may help predict functional outcomes in DME [28]. Disorganization of the retinal inner layers (DRIL), for example, has been associated with poorer visual prognosis even in cases where edema resolves [29]. It is possible that some of the treated eyes in this study had preexisting structural alterations not detectable with standard OCT parameters, limiting their potential for visual recovery.

Our findings also support emerging hypotheses that central macular edema may follow a distinct pathogenic course compared to peripheral edema. The foveal region, being naturally avascular, may rely more heavily on the metabolic function of the retinal pigment epithelium (RPE) and choriocapillaris [30]. In cases of choroidal hypoxia, the failure of the RPE pump may lead to fluid accumulation that is less responsive to VEGF blockade [31]. This mechanism could partly explain the limited functional response observed in this cohort despite anatomical improvement.

Recent advances in therapeutic targets beyond VEGF further reinforce this view. Molecules such as tyrosine kinase with immunoglobulin and EGF-like domains 2 (Tie2) and vascular endothelial protein tyrosine phosphatase (VE-PTP) are involved in vascular stabilization and blood-retinal barrier integrity [32]. Tie2 agonists and VE-PTP inhibitors, such as AKB-9778, have shown promise in preclinical and early clinical studies when used in combination with anti-VEGF agents [33]. These findings highlight the potential for multi-pathway intervention in refractory or early-stage DME.

The clinical implications of this study suggest that immediate anti-VEGF therapy may not be necessary in all patients with DME and preserved visual acuity. Observation with close OCT monitoring could be a reasonable alternative, reserving intervention for those who demonstrate anatomical progression or functional decline. This approach is supported by the Early Treatment Diabetic Retinopathy Study (ETDRS), which found no added benefit of early treatment in patients with good vision unless vision began to deteriorate [34].

Real-world treatment patterns also differ from clinical trials. It seems that the frequency of injections, follow-up compliance, and access to care might influence outcomes more than treatment type alone [35]. In resource-limited settings, avoiding unnecessary injections in asymptomatic patients may reduce costs, risks, and patient burden without compromising outcomes.

Despite its insights, this study has some limitations. The small sample size limits statistical power, and the lack of randomization introduces the possibility of selection bias. The relatively short duration of the follow up (6 months) might also be considered as a shortcoming.

Future research should aim to identify predictive biomarkers that differentiate VEGF-driven edema from inflammation-mediated or RPE dysfunction-associated fluid accumulation. Longitudinal studies incorporating multimodal imaging, such as OCT angiography, fluorescein angiography may help stratify patients based on anatomical risk factors. Additionally, randomized trials comparing anti-VEGF monotherapy with combination regimens that include corticosteroids or Tie2 pathway modulators could clarify the optimal approach for patients with preserved vision. Investigating genetic predispositions and intraocular cytokine profiles may also uncover individualized therapeutic targets. Ultimately, precision medicine strategies will be a key to optimizing outcomes while minimizing overtreatment in early-stage diabetic macular edema.

Conclusion

Bevacizumab injections led to a modest reduction in macular thickness but did not significantly improve or preserve visual acuity in diabetic patients with good baseline vision. These findings suggest that factors beyond vascular endothelial growth factor may play a role in early-stage diabetic macular edema. Further studies with a higher sample size are suggested to confirm our findings.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.