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Original Research Article

STUDY ON CHANGE IN VISUAL ACUITY FOLLOWING INTRAVITREAL INJECTION OF ANTI VEGF (BEVACIZUMAB) IN PATIENTS WITH DIABETIC MACULAR EDEMA

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Abstract

Background: Diabetic macular edema (DME) is a common and debilitating eye illness. Although DME poses a risk to vision, it is also one of the conditions that is most easily treated. Currently, there are many therapeutic options accessible for this condition, including photocoagulation, intravitreal medicinal therapy (using either vascular endothelial growth factor inhibitors or corticosteroids treatments), and surgical removal. While laser treatment has been widely regarded as the most effective method for many years, in recent years, vascular endothelial growth factor inhibitors (anti-VEGFs) have emerged as the preferred first treatment option. **Aim:** Study on change in visual acuity following intravitreal injection of Anti VEGF (Bevacizumab) in patients with diabetic macular Edema. **Material and methods:** The research group consisted of 60 eyes belonging to 60 individuals diagnosed with Diabetic Macular Edema (DME). The study included patients of both genders, aged between 20 - 70 years, who had diabetes mellitus and diabetic macular edema (DME), regardless of the type, length, degree of control, or severity of their diabetes. DME was characterized as the presence of retinal edema or hard exudates at a distance of 500 micrometers from the center of the macula. The BCVAs before the injection were assessed using the ETDRS chart at distances of 4 meters and 1 meter. Additionally, measurements of intraocular pressure (IOP), slit lamp and fundus examination results, and central subfield macular thickness (CSMT) measurements using time domain optical coherence tomography were taken. **Results:** Prior to administering the bevacizumab injection, the median (baseline) best-corrected visual acuity (BCVA) for the eyes being treated was 48.22 (ranging from 18 to 67) ETDRS letters. Following the injections, the BCVA improved to 49.12 (ranging from 18 to 75) ETDRS letters. The pre-treatment median central subfield macular thickness (CSMT) of 428.11 (296–679) μm fell to 385.43 (249–566) μm following the bevacizumab injection. The changes in the best-corrected visual acuity (BCVA) and central subfield macular thickness (CSMT) in the eyes that received bevacizumab treatment were determined to have statistical significance (P = 0.03 and P = 0.004, respectively). **Conclusion:** Our study revealed that the direct injection of bevacizumab into the eye led to a noteworthy improvement in the clarity of vision in individuals with diabetic macular edema.

INTRODUCTION

Diabetic macular edema (DME) is a prominent contributor to central visual impairment in individuals with diabetes. Multiple pathophysiologic and biochemical alterations are involved in the development of diabetic macular edema (DME). However, an elevation in vascular endothelial growth factor (VEGF) has been identified as a significant contributing component.[1,2] A prior study revealed a notable elevation in the serum VEGF level among diabetic patients with more advanced diabetic retinopathy (DR) and greater disruption of photoreceptor outer segments (external limiting

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membrane (ELM) and ellipsoid zone (EZ)), in comparison to patients with less severe DR and healthy individuals. Furthermore, a direct correlation was shown between the severity of photoreceptor outer segment disruption and the extent of visual acuity (VA) decline.[3] Randomized clinical trials (RCTs) have shown that intravitreal anti-VEGF injection is very effective in improving both visual and anatomical results in patients with visual impairment caused by center-involved diabetic macular edema (CI-DME), as compared to macular photocoagulation.[4-7] The notable effectiveness was shown with all three available anti-VEGF drugs (bevacizumab, ranibizumab, and aflibercept) and the treatment regimens used. However, it was shown that a patient with a low baseline visual acuity who was treated with bevacizumab saw fewer improvements in their vision.[8-10] Therefore, intravitreal anti-VEGF injection is a crucial and established therapy choice for CI-DME. Although there have been gains, differences in how individuals respond to personalized treatments have been seen in both randomized controlled trials (RCTs) and real-world clinical settings.[11-13]

Bevacizumab has been used as the first anti-VEGF treatment in many clinical practices, independent of the patient's initial visual acuity and often with a lower number of injections compared to protocols generated from randomized controlled trials. This is mostly due to cost constraints. Evaluating the appropriate management requires an understanding of the therapy response pattern in different clinical contexts. Identifying the factors that affect visual outcomes after intravitreal bevacizumab injection for clinically significant diabetic macular edema (CI-DME) can impact patients' expectations and physicians' treatment decisions. This information can help adjust therapeutic regimens and their intensity, and also consider alternative treatment options.

A preliminary investigation revealed that the direct injection of bevacizumab into the eye did not have a noteworthy impact on the opposite eye in individuals with bilateral diabetic macular edema (DME).[14] Nevertheless, there have been instances when the administration of intravitreal anti-VEGF injection has resulted in an impact on the opposite eye in patients with macular edema.[11] Due to the variability in the pharmacokinetic properties of a drug administered intravitreally and the function of the blood-retinal barrier, which can differ among individuals and change in the presence of ocular disease, it is challenging to evaluate and compare the crossover effect of these two agents when used intravitreally.

MATERIALS AND METHODS

The research group consisted of 60 eyes belonging to 60 individuals diagnosed with Diabetic Macular Edema (DME). The research received approval from the hospital's ethical review committee. The study included patients of both genders, aged between 20 - 70 years, who had diabetes mellitus and diabetic macular edema (DME), regardless of the type, length, degree of control, or severity of their diabetes. DME was characterized as the presence of retinal edema or hard exudates at a distance of 500 micrometers from the center of the macula. Additionally, it included retinal edema that was equal to or bigger than the diameter of one optic disc, with any portion of it being within one optic disc diameter from the center of the macula, as assessed by OCT. Patients who had previously been diagnosed with macular pathologies such as age-related macular degeneration (ARMD) or a vascular occlusive disease that affected the macula, those who had received intravitreal drug injections or laser photocoagulation within the past 3 months, those with associated pathologies like an epiretinal membrane or vitreomacular traction, or those with a history of retinal surgery were not included in the study.

Following the elucidation of the study's objectives and methodology, informed permission was obtained. Proformas were completed. A first eye examination was conducted. The BCVAs before the injection were assessed using the ETDRS chart at distances of 4 meters and 1 meter. Additionally, measurements of intraocular pressure (IOP), slit lamp and fundus examination results, and central subfield macular thickness (CSMT) measurements using time domain optical coherence tomography were taken. This assessment was performed one week prior to the treatment. The researcher administered an intravitreal injection of 1.25 mg/0.05ml of Bevacizumab (Avastin) around 3.5-4mm away from the limbus, using local anesthesia. Post-procedure visual acuity assessment and optical coherence tomography (OCT) was performed on all patients 4 weeks following the injection. The result was judged based on the change visual acuity and in macular thickness. An Optical Coherence Tomography (OCT) scan was conducted to verify the efficacy of the drug stated before in treating diabetic macular edema.

Outcomes

The BCVAs before the injection were assessed using the ETDRS chart at distances of 4 meters and 1 meter. Additionally, measurements of intraocular pressure (IOP), slit lamp and fundus examination results, and central subfield macular thickness (CSMT) measurements using time domain optical coherence tomography were taken. The examination results during the follow-up visits conducted 1 day and 4 weeks after the injections were assessed. The first visit included evaluating any potential issues, which included measuring intraocular pressure (IOP) using an air-puff tonometer, doing a slit-lamp examination, and performing a dilated fundus examination. During the second visit, the best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) tests were also conducted. The main outcome measures consisted of changes in best-corrected visual acuity (BCVA) and central subfield macular

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thickness (CSMT) in eyes after the administration of bevacizumab injections.

Statistical Analysis

The statistical analysis was conducted using SPSS version 25.0, a software package developed by SPSS Inc. in Chicago, IL, USA. The visual acuities and CSMT values were analyzed by doing the nonparametric Mann–Whitney U-test and the Wilcoxon signed-rank test for comparison. A probability (P) value below 0.05 was deemed statistically significant.

RESULTS

A cohort of 60 patients was chosen for this investigation. Bevacizumab was administered by intravitreal injection in 60 eyes belonging to the aforementioned 60 patients. Among the group of 60 patients, there were 37 male and 23 females. The age of the patients varied between 21 and 70 years. The majority of patients fall within the age category of 50-60 years, with 26 individuals, which accounts for 43.33% of the total. The next largest age group is 40-50 years, with 14 patients (23.33%), followed by 30-40 years with 12 patients (20%). Patients beyond 60 years of age make up 8.33% of the total, with 5 individuals, while those below 30 years of age represent 5% of the total, with 3 individuals. The average age of the patients is 52.22 years with a standard deviation of 5.76 years. [Table 1]

The average duration of diabetes was 11.37 years with a standard deviation of 3.11 years. [Table 2]

Out of the total number of patients, 10 were found to have type 1 diabetes mellitus (DM), whereas the remaining 50 were diagnosed with type 2 DM. Out of the total of 18 patients, which accounts for 30% of the sample, showed nephropathy as a consequence connected to diabetes mellitus. Additionally, 40 patients, making up 65% of the sample, had their hypertension under control. 32 of the patients (53.33%) had diabetic retinopathy in the preproliferative stage.

There were no problems, such as endophthalmitis, traumatic lens damage, increased intraocular pressure (IOP), or retinal detachment, related with the intravitreal injections. Prior to administering the bevacizumab injection, the median (baseline) best-corrected visual acuity (BCVA) for the eyes being treated was 48.22 (ranging from 18 to 67) ETDRS letters. Following the injections, the BCVA improved to 49.12 (ranging from 18 to 75) ETDRS letters. The pre-treatment median central subfield macular thickness (CSMT) of 428.11 (296–679) μm fell to 385.43 (249–566) μm following the bevacizumab injection. The changes in the best-corrected visual acuity (BCVA) and central subfield macular thickness (CSMT) in the eyes that received bevacizumab treatment were determined to have statistical significance (P = 0.03 and P = 0.004, respectively). [Table 3]

Table 1: Gender and age of the patients

	Number	Percentage	P value
Gender			0.22
Male	37	61.67	
Female	23	38.33	
Age			0.43
Below 30	3	5	
30-40	12	20	
40-50	14	23.33	
50-60	26	43.33	
Above 60	5	8.33	
Mean Age	52.22 ± 5.76		

Table 2: Duration of diabetes

	Number	Percentage	P value
Duration of diabetes			0.16
5-10	14	23.33	
10-15	34	56.67	
Above 15	12	20	
Mean Duration of diabetes	11.37 ± 3.11		

Table 3: Visual acuity and CSMT values of untreated eyes before and after bevacizumab injection

	Before treatment		After treatment		P value
BCVA	48.22	5.43	49.12	6.35	0.03
CSMT	428.11	13.54	385.43	11.76	0.04

DISCUSSION

Previously, researchers have examined many indicators to forecast initial visual impairment and visual responses after anti-VEGF therapy in eyes with CI-DME. Quantitative retinal thickness data obtained from OCT has been widely used as a reliable indication for making decisions and tracking the evolution of diseases in both randomized controlled trials (RCTs) and clinical practice. Nevertheless, other researchers have shown the inconsistencies in the correlation between central subfield (CSFT) and visual acuity (VA) in diabetic macular edema

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(DME).[15] In clinical practice, Anti-VEGF injections are administered less frequently compared to clinical trials. The frequency of these injections is associated with the level of improvement in visual acuity. Therefore, the lower frequency of injections in real-life settings is believed to contribute to the poorer outcomes observed. Multiple evaluations have been carried out to assess the effectiveness of the two anti-VEGF drugs, bevacizumab and ranibizumab, in treating diabetic macular edema (DME).[16] Bevacizumab is a fully humanized antibody that has the ability to bind to all forms of VEGF-A. While the Food and Drug Administration has licensed it for the treatment of several types of malignancies, it is also used off-label intravitreally to treat ocular illnesses such as proliferative diabetic retinopathy and DME. Ranibizumab, a genetically engineered antibody that closely resembles a human antibody, is authorized for treating abnormal blood vessel growth in the eye in the setting of age-related macular degeneration (ARMD) and diabetic macular edema (DME). Although intravitreal bevacizumab and ranibizumab have been widely used in clinical settings, there is a lack of comprehensive research on the pharmacokinetics of these drugs in untreated eyes.

The current investigation revealed a statistically significant reduction in the central subfield macular thickness (CSMT) in untreated eyes after the administration of bevacizumab, but not after the use of ranibizumab. This discovery indicates that bevacizumab may enter the body systemically after being injected into the human eye. It also confirms a prior research which showed a significant decrease in plasma VEGF levels after an injection of bevacizumab, but not ranibizumab.[17]

Bakri et al,[18] discovered trace quantities of bevacizumab in both the serum and the uninjected eye throughout their experimental research. Avery et al,[19] observed that in some individuals with bilateral proliferative diabetic retinopathy, neovascularization regressed in both eyes after intravitreal bevacizumab injection in just one eye. The study found that unilateral intravitreal bevacizumab injections had similar effects in situations of bilateral persistent diffuse diabetic macular edema (DME) or bilateral uveitic cystoid macular edema.[20] A preliminary investigation on bilateral diabetic macular edema (DME) indicated that there were no notable impacts on the opposite, non-injected eye. Nevertheless, the researchers highlighted the limited number of participants and expressed doubts about the reliability of their own study.[14] Furthermore, Sharma et al. discovered that an intravitreal dexamethasone injection had a bilateral effect after a unilateral injection. This highlights the impact of a unilateral intravitreal injection on the other eye.[21]

The results of our study confirm prior findings that bevacizumab significantly decreased macular thickness and enhanced visual acuity in the treated eyes, consistent with previous research.[22]. Some researches shows that, the injection of bevacizumab in one eye had an impact on the untreated eye. [23]. The precise method by which intravitreally given anti-VEGFs impact an uninjected eye has not yet been fully understood. One potential explanation for this phenomenon is because the anti-VEGF substance is introduced into the circulation via the flow of blood in the choroid.[19,23] On the other hand, some scientists have proposed that bevacizumab enters the eye via the systemic circulation via the anterior pathway, where it spreads into the vitreous humor.[14]

Aflibercept, often referred to as VEGF-Trap eye, is a soluble fusion protein that specifically attaches to all variations of VEGF-A and VEGF-B, as well as placental growth factor.[24] The current authorized therapy for diabetic macular edema (DME) involves the administration of 2 mg of aflibercept by an intravitreal injection. Aflibercept's chemical structure results in an extended half-life when administered intravitreally.[25] A research evaluating the serum pharmacokinetics of three anti-VEGFs found that bevacizumab and aflibercept had higher systemic exposure and significantly reduced plasma-free VEGF levels compared to ranibizumab, which was rapidly eliminated.[25]

CONCLUSION

Our study revealed that the direct injection of bevacizumab into the eye led to a noteworthy improvement in the clarity of vision in individuals with diabetic macular edema.

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