Section: Ophthalmology

Original Research Article

TO DETERMINE THE CHANGES IN CENTRAL MACULAR THICKNESS AFTER THE ADMINISTRATION OF BEVACIZUMAB BY INTRAVITREAL INJECTION

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Abstract

Background: Bevacizumab, an antivascular endothelial growth factor (anti-VEGF), is often used to treat diabetic macular edema (DME). **Aim:** To determine the changes in Central macular thickness after the administration of Bevacizumab by intravitreal injection. **Material and methods:** The research group consisted of 50 eyes belonging to 50 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. 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. **Results:** The average duration of diabetes was 10.44 years with a standard deviation of 2.76 years. Among the 50 eyes included in this research, 30 eyes (60%) belonged to patients whose diabetes was managed with medication, whereas 20 eyes (40%) belonged to patients whose diabetes was not controlled despite medication. The average macular thickness before Avastin treatment was 379.98 ± 12.87 micrometers, whereas one month after Avastin treatment, the average thickness measured by OCT was 318.69 ± 11.32 micrometers. The central macular thickness decreased by an average of 61.29 ± 7.34 micrometers one month following a single intravitreal injection of 1.25mg/0.05ml of Bevacizumab. The macular thickness reduced in 49 instances and rose in one case after one month of injection. Out of the 50 patients, a substantial reduction in macular thickness of more than 10% was seen in 40 patients (80%). In 9 patients (18%), the drop in macular thickness was less than 10%. However, in 1 patient (2%), there was an increase in macular thickness. **Conclusion:** The potential advantages of intravitreal bevacizumab, even if only temporary, may be valuable in several therapeutic scenarios, such as situations where media opacity hinders the use of macular grid laser, or in instances with severe proliferative diabetic retinopathy accompanied by macular edema.

INTRODUCTION

Diabetic macular edema (DME) is a consequence of diabetic retinopathy that results in the deterioration of central vision. According to data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the prevalence of diabetic macular edema is estimated to be around 20% in patients with type 1 diabetes mellitus (DM) after 15 years of known diabetes. In patients with type 2 DM who are taking insulin, the prevalence is approximately 25%, while in patients with type 2 DM who do not take insulin, the prevalence is about 14%.[1]

Diabetic macular edema (DME) will occur in around 10% of individuals with diabetes at some point in their lives.[2] Vascular endothelial growth factor (VEGF) is a crucial element in the development of macular edema caused by diabetes. Diabetic macular

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edema often results in visual impairment in individuals with diabetes mellitus, and this impairment might be permanent.[3] Diabetes-induced vascular permeability increase causes fluid and plasma components to flow into the retina, resulting in diabetic macular edema (DME). Focal laser photocoagulation is now the preferred therapy for clinically severe macular edema. The Early Treatment Diabetic Retinopathy Study (ETDRS) has shown that focused laser photocoagulation has a positive impact and decreases the occurrence of moderate vision impairment by 50%.[4,5] In the Early Treatment Diabetic Retinopathy Study (ETDRS), 33% of the 221 eyes that were not treated and were accessible for follow-up at the 3-year visit, all of which had edema affecting the central part of the macula at the beginning, had a loss of 15 or more letters in their visual acuity score.[6] The current methods being studied to decrease the likelihood of vision loss caused by diabetic macular edema include laser photocoagulation, as shown by the ETDRS, Anti VEGF agents, intensive glycemic control, as demonstrated by the DCCT and UKPDS, and blood pressure control, as demonstrated by the UKPDS.[7-9] During the DCCT study, the implementation of rigorous glucose control resulted in a 23% decrease in the likelihood of developing diabetic macular edema compared to the standard therapy. Macular laser photocoagulation, corticosteroids, and anti-VEGF medicines are often used treatments for DME. Nevertheless, a solitary intervention is insufficient to effectively manage DME over the whole duration of the condition. Macular laser photocoagulation has been the recommended therapy since 1985, as established by the early treatment of diabetic retinopathy study (ETDRS). Its purpose is to decrease the likelihood of substantial vision impairment in individuals with clinically significant macular oedema (CSME) by about 50% during a span of 3 years. Nevertheless, fewer than 3% of cases exhibited an increase in visual acuity (VA) at the 3-year mark, specifically a gain of 15 letters.[10]

The occurrence rate of an unfavorable result in terms of the percentage of eyes with improved vision after laser photocoagulation for diabetic macular edema has led to curiosity about other treatment methods. The current method used to treat DME is the use of intravitreal anti-VEGF medicines. The FDA has granted approval for the use of Ranibizumab and Aflibercept in the treatment of DME. Bevacizumab and Pegaptanib, which are other Anti VEGF medicines, are also often used for purposes not approved by regulatory authorities. Due to the substantial impact of DME on causing poor vision and blindness, it is necessary to evaluate and revise the current data on the efficacy and safety of various anti-VEGF medicines. There is an ongoing need in the medical field to produce recommendations based on solid research about anti-VEGF drugs. Eyes exhibiting pronounced macular leakage have a notably elevated quantity of VEGF in comparison to eyes with little leakage. Hence, anti-VEGF medications might be regarded as a supplementary therapy for DME. Bevacizumab is a complete antibody that blocks all variations of the VEGF-A family. It has received FDA approval for treating colorectal cancer.

MATERIALS AND METHODS

The research group consisted of 50 eyes belonging to 50 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 with a bleeding condition, an active ocular infection, a prior history of intravitreal bevacizumab (Avastin), a recent myocardial infarction, uncontrolled hypertension, pregnancy, or a previous history of focused or grid laser treatment were not included.

Following the elucidation of the study's objectives and methodology, informed permission was obtained. Proformas were completed. An first eye examination was conducted. A pre-procedure assessment of macular thickness was conducted using Topcon 3D OCT 2000, using optical coherence tomography (OCT) with a picture angle of 45 degrees and an in-depth resolution of 5 micrometers. 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 optical coherence tomography (OCT) was performed on all patients one month following the injection. The result was judged based on the change 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. The final result was calculated based on the macula's thickness. The data was analyzed using SPSS version 25.0. Age and duration of diabetes mellitus were used to construct descriptive statistics such as the mean and standard deviation (SD). Categorical characteristics such as gender, type of diabetes, severity of illness, diabetic management, and decrease in macular thickness were analyzed to determine frequencies and percentages.

RESULTS

A cohort of 50 patients was chosen for this investigation. Bevacizumab was administered by intravitreal injection in 50 eyes belonging to the

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aforementioned 50 patients. Among the group of 50 patients, there were 30 male and 20 females. The age of the patients varied between 22 and 69 years. The majority of patients fall within the age category of 45-55 years, with 22 individuals, which accounts for 44% of the total. The next largest age group is 35-45 years, with 12 patients (24%), followed by 25-35 years with 9 patients (18%). Patients beyond 55 years of age make up 10% of the total, with 5 individuals, while those below 25 years of age represent 4% of the total, with 2 individuals. The average age of the patients is 53.77 years with a standard deviation of 3.78 years. [Table 1]

The average duration of diabetes was 10.44 years with a standard deviation of 2.76 years. Out of the total number of eyes, 12 belonged to patients with Insulin dependent diabetes (IDDM) and 38 belonged to individuals with Non-insulin dependent diabetes (NIDDM). [Table 2]

Among the 50 eyes included in this research, 30 eyes (60%) belonged to patients whose diabetes was managed with medication, whereas 20 eyes (40%) belonged to patients whose diabetes was not controlled despite medication. The average macular thickness before Avastin treatment was 379.98 ± 12.87 micrometers, whereas one month after Avastin treatment, the average thickness measured by OCT was 318.69 ± 11.32 micrometers. The central macular thickness decreased by an average of 61.29 ± 7.34 micrometers one month following a single intravitreal injection of 1.25mg/0.05ml of Bevacizumab. The macular thickness reduced in 49 instances and rose in one case after one month of injection. Out of the 50 patients, a substantial reduction in macular thickness of more than 10% was seen in 40 patients (80%). In 9 patients (18%), the drop in macular thickness was less than 10%. However, in 1 patient (2%), there was an increase in macular thickness. [Table 3]

Table 1: Gender and age of the patients

	Number	Percentage	P value
Gender			0.15
Male	30	60	
Female	20	40	
Age			0.21
Below 25	2	4	
25-35	9	18	
35-45	12	24	
45-55	22	44	
Above 55	5	10	
Mean Age	53.77 ± 3.78		

Table 2: Duration of diabetes

	Number	Percentage	P value
Duration of diabetes			0.22
5-10	12	24	
10-15	27	54	
Above 15	11	22	
Mean Duration of diabetes	10.44 years ± 2.76		
Insulin dependent diabetic (IDDM) or Non-insulin dependent diabetic			0.21
Insulin dependent diabetic (IDDM)	12	24	
Non-insulin dependent diabetic (NIDDM)	38	76	
Uncontrolled or controlled through medicines			0.14
Uncontrolled through medicines	20	40	
controlled through medicines	30	60	

Table 3: Reduction in Macular thickness

	Mean	Sd	P value
Pre Avastin macular thickness	379.98	12.87	0.001
Post Avastin OCT	318.69	11.32	

Table 4 Reduction in Macular thickness following single intravitreal injection of Avastin at one month follow up

Reduction in Macular Thickness	Frequency	Percentage
Below 10%	40	80
Above 10%	9	18
Increased	1	2
Total	50	100

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DISCUSSION

Clinical evidence has established that increase in central macular thickness in diabetic macular edema results in corresponding decrease in visual acuity, and the treatment which reduces the retinal thickening improves vision. OCT can detect macular edema that is not clinically evident, and several OCT-derived biomarkers are useful predictors of its progression, severity, and visual outcome. Complete grid laser cannot usually be administered in individuals with media opacity, such as vitreous hemorrhage or cataract. In addition, individuals with iris neovascularization and neovascular glaucoma often exhibit symptoms like as hyphema or corneal edema, which hinder complete laser treatment. Moreover, there are instances when some patients still have elevated macular thickness (edema) while undergoing grid laser therapy. Nevertheless, Intravitreal Bivacizumab has shown a remarkable and fast response, proving its effectiveness in completely resolving macular edema within a few of days. At any given central macular thickness, there was a corresponding significant change in visual acuity. Many eyes with significant macular edema had very good visual acuity and eyes with mild edema exhibited a profound decrease in vision. It is also reported that there is inconsistence increase in thickness of central macular point with the increase in visual acuity as well as incongruous decrease in thickness of central retina with the decrease in visual acuity is not common. According to this, OCT measurement can be a good surrogate for visual acuity in macular edema related to diabetes.[8]

A cohort of 50 patients was chosen for this investigation. Bevacizumab was administered by intravitreal injection in 50 eyes belonging to the aforementioned 50 patients. Among them, there were 30 males and 20 female. The age of the patients varied between 20 - 70 years. The majority of patients fall within the age bracket of 45-55 years, accounting for 22 individuals or 44% of the total. The next largest age group is 35-45 years, with 12 individuals or 24%. There are 9 patients or 18% in the 25-35 years age group, 5 patients or 10% above the age of 55, and 2 patients or 4% below the age of 25. The average age of the patients is 53.77 ± 3.78 years. A significant proportion of our patients came from economically disadvantaged backgrounds. This may be related to their inadequate management of diabetes, relatively lower focus on healthcare concerns, and lack of compliance with follow-up appointments. The contributing factor to this age group was the extended duration of diabetes and its associated consequences. Nevertheless, in a comparable investigation carried out by Mason et al, the age range of the 30 participants varied from 26 to 63 years, with an average of 47.7 ± 12.5 years.[11] Avery et al. performed a research including 32 patients, whose ages varied from 27 to 82 years, with a mean age of 58 years.[12] In a research conducted by Arevalo JF et al., the average age of the participants was 57.2 years, with a range of 23 to 82 years. The study included 33 consecutive patients, totaling 44 eyes.[13] The research conducted on individuals with diabetic retinopathy revealed differences in the age demographics impacted across various geographic locations.

According to a study conducted by El Haddad et al., the age of the patient was initially found to be related to the occurrence of retinopathy. However, after adjusting for the duration of diabetes using a logistic model, the significance of age was lost. It appeared that age was closely linked to the duration of diabetes and could not be considered as an independent risk factor.[14] The average duration of diabetes was 10.44 years with a standard deviation of 2.76 years. A research done by Mason et al. found that the average length of time that 30 individuals had diabetes was 18.4 years, ranging from 3 years to 27 years.[11] The prevalence of diabetic maculopathy increases with longer duration of diabetes. The duration of diabetes remained a significant factor in the multivariate logistic model for the development of any retinopathy. This phenomenon may be attributed to a predisposition towards inaccurately calculating the actual length of diabetes in these individuals, particularly in situations of non-insulin dependent diabetic mellitus (NIDDM) when the identification of diabetes may have been postponed.[15]

Diabetic macular edema is the prevailing complication in those diagnosed with diabetes mellitus and is a significant contributor to vision loss in those of working age. Several studies have shown significant disparities in the occurrence of diabetic retinopathy between individuals with insulin-dependent diabetes mellitus (IDDM) and those with non-insulin-dependent diabetes mellitus (NIDDM). Our research included 12 eyes from patients with insulin-dependent diabetes (IDDM) and 38 eyes from individuals with non-insulin dependent diabetes (NIDDM). Arevalo et al. performed a research with 33 patients, of whom 23 (69.7%) had IDDM and 10 (31.3%) had NIDDM.[13] In a research conducted by El Haddad, a total of 212 individuals were evaluated. Among these patients, 176 (83%) were diagnosed with NIDDM (non-insulin dependent diabetes mellitus), whereas 36 patients (17%) had IDDM (insulin dependent diabetes mellitus).[14] Mason et al. discovered that among the 30 patients included in their research, 17 were diagnosed with non-insulin-dependent diabetes mellitus (NIDDM), whereas 13 were diagnosed with insulin-dependent diabetes mellitus (IDDM).[11]

Out of the 50 eyes included in this research, 30 eyes belonged to patients whose diabetes was managed with medication, whereas 20 eyes belonged to patients whose diabetes was not well controlled with medication.

In our research, all patients with insulin-dependent diabetes mellitus (IDDM) had well-regulated blood sugar levels, whereas patients with non-insulin-

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dependent diabetic mellitus (NIDDM) exhibited varying degrees of diabetes control. Out of the total 30 patients, 60% had well-controlled diabetes, while 40% had uncontrolled diabetes. The average central macular thickness at the beginning of our trial, prior to administering the intravitreal injection of Bevacizumab (Avastin), was 379.98 ± 12.87. The minimum central macular thickness was 289.22 micrometers, while the highest thickness was 508.11 micrometers. After one month of receiving an intravitreal injection of Bevacizumab (Avastin), the central macular thickness exhibited a significant decrease. The average central macular thickness reduced to 318.69± 11.32 um, with the lowest and highest values recorded as 247.56 and 392.16 um, respectively. Haritoglou et al. conducted a study where they reported a series of cases involving patients with diabetic macular edema (DME) who were treated with a dosage of 1.25 mg of Bevacizumab. The study was prospective and noncomparative in nature. There was a notable decrease in the thickness of the macula after 2 weeks. The thickness of the central retina also decreased significantly (by 33%): from 498.96±123.99 µm at the beginning to 334.40±121.76 µm after 1 month.[16] In a separate research conducted by Arevalo JF et al., a comprehensive analysis was performed on the clinical records of 88 consecutive patients (110 eyes) with diabetic macular edema (DME). The findings of this investigation indicate... The initial central macular thickness, as measured by OCT, was 387.0±182.8 micrometers. By the conclusion of the follow-up period, it dropped to a mean of 275.7±108.3 micrometers. There were no negative effects on the eyes or the body as a whole.[13] The central macular thickness decreased by an average of 61.49 ± 33.21 micrometers one month following a single intravitreal injection of 1.25mg/0.05ml of Bevacizumab.

CONCLUSION

The potential advantages of intravitreal bevacizumab, in decreasing the central macular thickness, even if only temporary, may be valuable in several therapeutic scenarios, such as situations where media opacity hinders the use of macular grid laser, or in instances with severe proliferative diabetic retinopathy accompanied by macular edema. Administering bevacizumab during panretinal photocoagulation may help reduce the worsening of macular edema, a potential side effect of panretinal photocoagulation.

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