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Comparing the Effect of Interavitreal Bevacizumab in Visual Acuity of Ischemic and Non-Ischemic Diabetic Macular Edema

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Abstract

***Background*:** The paper tries to examine the effect of avastin on visual acuity in patients with Ischemic and non-ischemic diabetic macular edema which was estimated convenient, inexpensive, safe, and quick in contrast to laser or deep vitrectomy.

***Materials and Methods*:** In this clinical trial study, patients with clinically significant macular edema (CSMA) were subjected to fluorescein angiography (FA) and people whose foveal avascular zones (FAZ) were over 1000 µm were defined as ischemic diabetic macular edema. Patients were divided into two ischemic and non-ischemic groups. The best corrected visual acuity (BCVA) and the central macular thickness (CMT) in all eyes were measured and recorded by optical coherence tomography (OCT). All patients received 3 vitreous injections of bevacizumab (avastin) at 1-month intervals. One month after the third injection, BCVA and CMT were measured again and patient's information was compared before and after the injection.

***Results*:** Out of 87 eyes (66 patients), 23 eyes (26.4%) belonged to ischemic group and 64 eyes (73.6%) belonged to non-ischemic group. In ischemic group, BCVA improved from 0.653 ±0.309 LogMAR to 0.404 ±0.255 LogMAR (p=0.001), while no significant change was seen in non-ischemic group (from 0.881 ±0.332 to 0.879 ±0.378). In ischemic group, CMT was increased from 362.9±34.66 to 278.76 ± 45.57 and in non-ischemic group it was enhanced from 353.47 ±67.61 to 239.87±55.44 (p=0.001).

***Conclusion*:** In spite of the great impact of vitreous injection of avastin in reducing the central macular thickness in both ischemic and non-ischemic groups and sensible improvement of patients' visibility, the visibility itself was not improved considerably in ischemic group.

Introduction

Diabetic retinopathy is one of the world most common causes of blindness among 20 to 64-year-old people [1]. Ischemia is the main cause of loss of vision in diabetic patients which finally may lead to neovascularization, diabetic macular edema and macular ischemic variations; the most common cause of loss of vision in diabetic patients is macular edema [1].

There are several measurements useful to predict blindness in such patients such as medical control (controlling blood sugar, blood pressure and blood fat), eye measurements such as laser photocoagulation and Pars Plana Vitrectomy (PPV) [2]. However, despite several treatments, diabetic retinopathy is considered as one of the most common causes of blindness and loss of vision in adults [3].

Bevacizumab (avastin) is a monoclonal antibiotic which binds all isomers of vascular endothelial growth factor. As a proper treatment for colorectal cancers, its intravenous injection was verified by Food and Drug Administration (FDA) [4]. Injecting 0.5 mg ranibizumab and also bevacizumab vitreously has decreased foveal thickness and improved visuality in a number of patients with diabetic macular edema [5]. The diabetic retinopathy is the most important cause of the new blindness among Americans less than 60 years old and the British between 30-64 years old [6]. Every year, diabetic retinopathy complications make up 12-14 percent of new blind cases in the world [7]. Although NPDR is the main cause of 80 percent of loss of vision cases, in fact macular disorders decline visibility [8].

A number of epidemiological studies have shown that in the United States about 700,000 people suffer from PDR and 500,000 suffer from diabetic macular edema. In the same direction, 65,000 new cases of PDR and 75,000 new cases of diabetic macular edema are reported annually [7].

If the same figures can be generalized to Iran, regarding its population, the mentioned disorders amount in our country is about one fourth of the mentioned figures in the United States. Although many patients lose their vision within PDR stage because of the proliferative complications, macular edema generally is the main cause of loss of vision in diabetic patients [8].

With regard to large number of diabetic patients in Iran, though there is no detailed statistics about them, and allocation of more than one trillion rials per year to treat them, according to the Diabetes Association, any action to decrease diabetic complications either eye or other complications not only will improve their life quality, but

also it will be effective in saving their treatment excessive costs and enhancing their physical ability.

In this study, we analyzed the effect of Avastin on visual acuity in patients with Ischemic and non-ischemic diabetic macular edema (DME) which was estimated as a convenient, inexpensive, safe, and quick. If DME is treated via injecting vitreous avastin, other costly treatment such as laser which needs its own special equipment and or deep vitrectomy which is a costly and dangerous surgery can be put aside.

Materials and Methods

Our study was a clinical trial one which was lasted since March 2010 to December 2010 in which 87 eyes of 66 patients who had been registered in Zahedan Al-Zahra Eye Hospital, which is the eye specialized and tertiary center of Southeastern Iran, were examined.

Randomly, the diabetic patients who had referred to hospital for doing eye examination were subject to full ophthalmologic examinations including determining VA, BCVA, slate lamp examination, intraocular pressure (IOP) through Applanation Tonometer, full fundoscopy, determining marcus gunn and other complementary examinations in terms of each patient's problem.

Diabetic retinopathy stage based on the fundoscopy was recorded in the patient's case. A full description of type of diabetes and duration of suffering from diabetes since diagnosis and information about secondary diseases and associated drugs, duration of loss of visibility, if any, any previous surgery or laser therapy history.

Patients who showed thickened retina across their macula zone during the fundoscopy and who had clinically significant macular edema (CSME) were included in the study. They were completely justified about their disease and treatment diagnostic measurements involved with the study and also they were informed on advantages and disadvantages of the study and patients who were inclined to such medical treatment were attracted.

They were explained that they are allowed to quit the study anytime they prefer. The exclusion criteria were involvement of only an eye, any history of other eye diseases such as glaucoma, uveitis and obstruction of retinal vessels, vitreous hemorrhage, eye trauma history and any history of eye surgery except cataract surgery. If the mentioned issues were seen during the study, they will be excluded immediately.

In our study, two eyes subjected to vitreous hemorrhage and another eye experienced diabetic dense premacular hemorrhage, so all of them were excluded and started vitrectomy as their treatment. It is necessary to say that brain stroke or heart infarct were not among the exclusion criteria, although no
case was reported for our patients.

One of eyes of a patient with bilateral CSME developed central retinal vein occlusion (CRVO) during the follow-up period, so the damaged eye was excluded from the study. Another 33-year-old patient with bilateral CSME and Insulin-dependent diabetes who had developed unilateral inferotemporal branch retinal vein occlusion (BRVO) was excluded as well. Low incidence of BRVO, CRVO, and hemorrhage and their worthless statistics for each group made them unnecessary to be analyzed statistically.

All patients underwent fluorescein angiography and definitionally the patients whose FAZ size was more than 1000 µm were classified into ischemic macular edema group and the patients whose FAZ size was less than 1000 µm were classified into non-ischemic macular group. Then the macular central zone thickness was measured and recorded using OCT.

Patients were admitted in the hospital. Before bringing the patient into the operating room, two acetazolamide tablets (250 mg) (Diamox) were prescribed and a timolol drop was instilled in their damaged eye with the aim of decreasing intraocular pressure.

Under the sterile condition of the operating room and after applying an eye speculum, a 27 gauge insulin syringe was used to inject 1.25 mg of avastin 4 mm from the limbus in phakic patients and 3.5 mm from the limbus in aphakic and pseudo-phakic patients across the superotemporal quadrant of macula. Then the eye was washed completely with sterile normal saline and the prophylactic ciprofloxacin drop was instilled once every 4 hours for a week.

All patients were examined through slate lamp and their intraocular inflammation and IOP were determined through applanation tonometer and fundoscopy. Again patent's BCVA was determined and recorded exactly in the same room and in the same condition under which the BCVA had been determined before operation.

A month after the first injection, the second injection in the same eye was done exactly like the first one for those patients who were inclined to continue. Since most patients experienced improved VA even a day after the injection, most of them were inclined to continue.

Similarly, the third injection was applied in the same eye a month after the second injection under the similar condition. The exact BCVA of all patients was recorded one month after the third injection and the full eye examinations were repeated; OCT was repeated for patients and CMT was recorded.

Patient's BCVA was measured in terms of decimal and Log MAR systems; CMT before injection and a month after the third injection was compared and statistically analyzed in the two ischemic and non-ischemic macular edema groups. With the aim of facilitating evaluation and analysis, patient's profile statistical information including name, age, sex, how long does the patient suffer from diabetes, type of diabetes, diabetic retinopathy stage, patient's visual acuity before and after injection, CMT before and after injection, type of CSME and other certain information necessary for conclusion was recorded in a numbered questionnaire for each patient. It is remarkable to say that "$p < 0.05$" has been defined as the significant value and the confidence interval was set as 95%. The statistical information was interpreted using SPSS-9 and Mann Whitney *U* test.

Results

In this study, a total of 87 eyes from 66 patients including 38 women (57.6%) and 28 men (42.4%) were examined. The patients ranged from 33 to 72 years old (average year: 53.77). 45 right eyes (51.7%) and 42 left eyes (48.3%) suffered from the disease (Table 1).

Totally, 23 eyes (26.4%) had ischemic CSME and 64 eyes (73.6%) had non-ischemic CSME. As you can see in OCT was carried out for 76 eyes from 87 patients before and after injection, out of which 21 eyes (27.6%) had ischemic CSME and 55 eyes (72.3%) had non-ischemic CSME. The before injection OCT ranged from 217 to 559 µm (average: 356.08) and the after injection OCT ranged from 178 to 400 µm (average: 250.62) (Table 2).

The decreased size of CMT had been 105.46 µm on the average. For the central thickness of retina in the ischemic group, we observed a decreasing trend from 362.90 µm to 278.76 µm, i.e. 84.14 µm decreasing in thickness, but for non-ischemic group we observed a decrease from 353.47 µm to 239.87 µm which shows a 113.6- µm decrease. All measures in both ischemic and non-ischemic groups, $p<0.001$, were considered significant (Table 3&4).

BCVA (Log/MAR) improved from 0.71 Log/MAR (before injection) to 0.54 Log/MAR after injection, i.e. 0.17 Log/MAR increasing in BCVA.

The visual acuity (Log/MAR) improvement was trivial in ischemic group, i.e. from 0.879 to 0.881 which has been insignificant statistically ($p=0.96$); while it was increased from 0.653 to 0.404 Log/MAR in non-ischemic group which was statistically significant.

Table1. Patients' demographic data

Variables		Non ischemic group	Ischemic group	Total
Number		49	17	66
Age (year)		52.65	57	53.77
Gender	Male	18	10	28
	Female	31	7	38
Type of diabetes	I	3	1	4
	II	46	16	62
Duration of diabetes	<5	7	1	8
	5-10	19	5	24
	>10	23	11	34
CSME	unilateral	34	11	45
	bilateral	15	6	21

Table 2. Diabetic retinopathy stage, most patients were in NPDR stage, particularly severe NPDR.

Variables	Non ischemic group	Ischemic group	Total
Number of eyes	64	23	87
OD	36	9	45
OS	28	14	42
Mild NPDR	6	0	6
Moderate NPDR	16	2	18
Severe NPDR	22	8	30
Very sever NPDR	7	5	12
PDR	13	8	21

Table 3. Retinal central zone thickness in OCT

Variables	Non ischemic group	Ischemic group	Total
Befor OCT surgery	353.47±67.61	362.90±34.66	356.08±60.24
Range (µm)	217-559	310-423	217-559
After OCT	239.87±55.44	278.76±45.57	250.62±55.43
Range (µm)	180-395	202-400	180-400
Decrease in central retinal thickness region(µm)	113.60	84.14	105.46
p-Value	0.001	0.001	0.001

Table 4. Visual acuity improvement in patients before and after injection

Variables	Non ischemic group	Ischemic group	Total
Befor Log MAR surgery	0.309±0.653	0.332±0.881	0.329±0.713
Range (µm)	0.146-1.699	0.398-1.398	0.097-1.699
After Log MAR surgery	0.255±0.404	0.378±0.879	0.358±0.530
Range (µm)	0.097-1.302	0.146-1.699	0.097-1.699
Difference before and after LogMAR Injection	0.248	0.020	0.183
p-Value	0.001	0.960	0.001

Discussion

Our study indicated that vitreous injection of Avastin is a safe and certain method to treat patients with non-ischemic macular edema; but no improvement was seen in visual acuity of patients with ischemic CSME in spite of the reduced macular edema.

Out of 66 patients, 22 ones had bilateral CSME and their other eye took CSME during the study which was treated. Such a high bilateral involvement may represent the great impact of metabolic and systemic factors and the improper control of blood sugar in provoking CSME in contrast to the focal factors. For type of diabetes, 93.9 percent of patients had type II diabetes which is justifiable regarding the high incidence of type II diabetes to type I diabetes across the society.

There was a 10-year gap between developing diabetes and diagnosis in more than half of patients with CSME. Thus with regard to the routine delay in diagnosing type II diabetes since occurring and the fact that most of our patients had type II, such a long period shows the effect of longer disease and its remained chronic vascular complications. For diabetic retinopathy stage, totally 75.9 percent of eyes were in NPDR stage while 24.1 percent of them were in PDR stage. It shows that most patients whose loss of vision was due to CSME were in NPDR stage and it also indicates that CSME is the main cause of loss of vision in diabetic patients. Other studies introduced NPDR as the cause of 80 percent of loss of vision cases which was consistent with our results [8].

The highest rate of CSME in NPDE has occurred in severe NPDR stage (34.5%), while the lowest rate of it was seen in mild NPDR stage (6.9%). It suggests that more severe retinal microvascular signs during NPDR stage play more important roles in developing CSME.

As you saw in results, the visual acuity (based on LogMAR scale) was very trivial in ischemic group and it was not considered as significant; however, the visual acuity of non-ischemic group was considerable and enjoyed a significant statistical vale. It indicates the irreversible impact of ischemia caused in capillary non-perfusion parts in performance of retina cells and clinical appearance of the disorder on rod and cone cells and their supportive cells which is recorded as decreased VA.

The decreased size of CMT due to injecting Avastain was considerable in both ischemic and non-ischemic groups which was significant statistically.

Arevalo et al. conducted a study in Caracas, Venezuela, and examined 110 eyes from 88 patients for six consecutive months; they injected 1.25 to 2.5 mg. intravitreal avastin in their patients; 20.5 and 7.7 percents of patients received the second and third injections, respectively. The average BCVA was improved from 0.87 LogMAR, before injection to 0.6 LogMAR after injection. The average CMT was decreased from 387µm to 275.7 µm [9]. The results of this study are consistent with our results.

Kumar and Sinha in New Delhi injected 1.25 mg bevacizumab in 20 eyes two times with 6 weeks interval. After 6 months BCVA improved from 1.338 Lg.MAR to 1.094 LogMAR and CMT decreased from 492 µm to 396 µm [10]. The improved level of BCVA in our study was more than that in this study. However, the decreased size of CMT in this study was more than that in our study.

Roh et al. in Seoul, South Korea, 31 eyes from 24 patients were injected 2 times by intravitreal bevacizumab (1.25 mg) with 22 weeks interval. Six weeks after the first injection both BCVA (3.72) and CMT (93.9 µm) got improved, but after 12 weeks they returned to the values before the injection. After the second injection again improved BCVA and decreased CMT were seen but again after 12 weeks the macular edema recurred [11]. It is necessary to say here that our study only followed the patients one month after the last injection which was significant statistically, but to perform long-term analysis some longer follow-ups are required.

Velez-Montoya et al. in Mexico City examined 22 patients with bilateral DME and CMT>275µm. they treated their patients through intravitreal injection of 2.5 mgr bevacizumab in one eye and then the two eyes of a patient were compared. BCVA and CMT did not show any considerable change in the untreated eye. It shows that the vitreous bevacizumab has not any systemic effect.

The another only study which like ours analyzed the effect of ischemia along with the effect of vitreous bevacizumab was carried out by Chung et al. in Korea. He also examined the effect of macular ischemia in how much is effective the vitreous injection of bevacizumab [13].

In this study, FA zone of 59 eyes from 59 patients who had been retroactively injected by vitreous bevacizumab were analyzed and the patients whose FAZ was more than 1000 µm or the patients who had perifoveal capillary ring obstruction in FA zone were defined as macular ischemia. The patients were divided into two groups ischemic and non-ischemic DME and their VA, OCT were examined before injection, 1 and 3 months after injection. After three months the VA level for the ischemic group decreased from 0.52 to 0.57 LogMAR while it was decreased from 0.66 to 0.59 LogMAR for non-ischemic group.

Our study did not show any considerable difference in average BCVA of Ischemic group, it was decreased from 0.881 to 0.879; however, the difference was completely considerable in the non-ischemic group in which was improved from 0.653 to 0.4.4 which was more considerable statistically than in the mentioned study.

Generally, our study as same as the abovementioned study shows the special effect of ischemia in preventing improvement of BCVA through injection of intravitreal bevacizumab in patients with ischemic DME.

In the abovementioned study, nine eyes out of 18 eyes (50%) in ischemic group and 9 eyes out of 41 eyes (21%) in the non-ischemic group experienced decreased VA for more than one line [4]. A number of 42 eyes (22%) from ischemic group and only 2 patients (5%) from the non-ischemic group experienced the loss of vision, more than three lines.

In our study, seven eyes out of 23 eyes (30.4%) in the ischemic group and 6 eyes out of 64 eyes (9.3%) in the non-ischemic group showed decreased BCVA more than one line and more than one line decrease in BCVA in ischemic group was two cases out of 23 cases (8.6%) while it was one case out of 64 cases (1.5%) in the non-ischemic group; hence in both of them our study showed higher results.

Generally it can be concluded that regarding the fact that VEGF is one of the most important inflammatory mediators which can cause vascular leakage and interstitial edema in macular zone and CSME, injection of antiVEGF can be effective in mitigating the interstitial edema; our results showed that the ischemic drug is unable to prevent the effect of antiVEGF to mitigate the edema. As it has been seen ischemia plays an important role to suppress the effect of the drug to improve VA.

Another interpretation is that even when the ischemia has been diagnosed in someone, VEGF can be treated as the main cause of interstitial edema; however, intake of this drug will be effective in treating edema in both ischemic and non-ischemic patients.

The trivial improvement of visual acuity in patients of the ischemic group in spite of the considerable improvement of interstitial edema suggested that ischemia affects the performance of retina cells despite the anatomical improvement of edema which can be irreversible. However, the irreversibility of this phenomenon needs further studies. In summary our study indicated that intravitreal injection of bevacizumab (avastin) can be a safe method to treat patients with non-ischemic macular edema. But in spite of the mitigation of the macular edema no achievement was reached in visual acuity of patients with ischemic macular edema.

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Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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