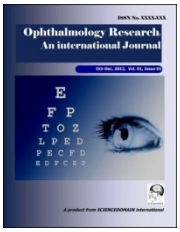

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Visual Outcome versus Vision Satisfaction after Intravitreal Bevasizumb Injection in Diabetic Retinopathy

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Authors' contributions

This work was carried out in collaboration between all authors. Author GY designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author MAY managed the literature searches, analyses of the study performed the spectroscopy analysis and author SM managed the experimental process. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Introduction: Diabetic retinopathy as an important complication of diabetes mellitus is a common cause of blindness in diabetic people. A cure or treatment is not available yet. This study was designed to investigate the effectiveness of the intravitreal injection of Avastin on patient's visual satisfaction with diabetic retinopathy.
Materials and Methods: This study included 30 eyes of thirty diabetic retinopathy patients (mean age: 60.47±8.94 years) showing no recovery with common treatments. After the intravitreal injection of 1.25mg/0.05ml of Avastin, the examination was performed after injection. In this examination, the resolution of neovascularization, clearance of vitreous and visual acuity were evaluated versus visual satisfaction.
Results: 60% of patients were women (n=18) and 40% were men (n=12). All patients had type 2 diabetes for a period of 8. 47±5.28 years (range 2-25 years). The observed change

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was 0.22±0.63 log MAR in the best corrected visual acuity (BCVA) in right eye which was statistically significant (p=0.010). The BCVA in left eye was 0.31±0.74 log mar, also showing significant relation (p=0.020). BCVA Changes did not have a meaningful relationship with age and sex of patients, but these changes were negatively related to duration of diabetes retinopathy in both right and left eyes (p=0/048, p=0/006 respectively).

Conclusion: Avastin showed short-term statistically significant visual benefits and also, improvements in ophthalmic pathology in clinical examination versus visual satisfaction, however it was not compatible to ask all of the patient's visual satisfaction. Therefore, further studies will be needed to determine the therapeutic effects of this treatment option.

Keywords: Diabetic retinopathy; vision satisfaction; avastin.

1. INTRODUCTION

The early treatment diabetic retinopathy study (ETDRS) demonstrated that immediate focal photocoagulation reduced moderate visual loss by 50, This suggests that a distinct subgroup of eyes exists with diabetic macular edema (DME) resistant to conventional laser photocoagulation [1].

Vitrectomy or application of focal macular laser and panretinal photocoagulation at appropriate disease stages reduce the risk of further vision loss. While the three year triamcinolone visual benefit was found to be inferior to standard focal macular laser, ongoing research will be determined by the utilisation of inhibitors of vascular endothelial growth factor as an additional tool in the management of diabetic retinopathy [1,2].

The M. Michaelides et al. [3] findings supported the use of bevacizumab in patients with persistent non-ischemic center-involving (clinically significant macular edema) CSME, but they were not able to find the benefit despite the relatively long duration of CSME and high number of previous laser treatments at baseline.

There were others studies indicating that intravitreal bevacizumab for DME with severe capillary loss displayed visual benefits and favorable remodeling of the macular architecture. They concluded that no major adverse event occurred related to treatment during the 54-week follow-up [4].

According to Avery and collogues, it remains unclear how frequently a repeat of anti-VEGF therapy would be necessary to ensure regression of neovascularization, and panretinal photocoagulation clearly seems to be a preferred treatment for chronic intravitreal injections [5].

The overwhelming evidence for intravitreal bevacizumab's role in the treatment of retinal disease was an encouraging sign to conduct this study which could explain the researchers' experience along with this emerging treatment.

2. MATERIALS AND METHODS

The 30 eyes of thirty patients with CSME or proliferative diabetic retinopathy participated in this study. The worth eye or only one eye underwent intravitreal injection of bevacizumab.

Exclusion criteria were intravitreal steroids within the last 4 months, of intraocular injection of anti-VEGF within the last 3 months, macular ischemia more than one disc diameter, and priors' history of intraocular surgery within the last 6 months. Patients with thomboembolic events or uncontrolled hypertension also were excluded from this study. Informed consent was obtained from all patients.

A complete ophthalmic examination at baseline and thereafter by every visit during the follow-up, including BCVA using standard Snellen charts, ophthalmoscopy and fluorescein angiography (Topcon, Topcon Corporation, Tokyo, Japan) and Optical coherence tomography (OCT) accordingly was conducted. All the patients completed a follow-up time of at least3-36 months and filed a satisfaction questionnaire with 1- improved vision 2- No improved vision 3-not noticeable or worst as options. Questions with similar inferences had reliable answers and the questionnaire was administered to descriptive interpretation due to no comparative study groups.

The patients retinopathy were in two groups according to the stage of retinopathy in each eye and after intervention the related right or left eye followed by 17-26 months of treatment. The small study samples of the patients were recruited in two groups that had severed diabetic maculopathy (6 cases) or proliferative diabetic retinopathy (24 cases) with vitreous hemorrhage.

Under topical anesthesia, a lid speculum was inserted and the povidone-iodine 5% was applied to conjunctiva and lid margins. The 1.25mg bevacizumab injections were undertaken with a 27-gauge needle through the supra- temporal quadrant. The patients took one to three injections and this was repeated on a monthly basis. To determine the effect of an intravitreal injection of bevacizumab on actively growing new vessels, we chose the clearance of vitreous hemorrhage and variation in vitreous leakage from retinal neovascularization as our primary outcome. The detection of neovascularization of disc and neovascularization of else clinically or FA allowed the use of a systematic anatomical approach to monitor the area of leaking new vessels over time. To determine the effect of an intravitreal injection of bevacizumab on macular edema, we detect the variation on retinal thickness clinically indeed of OCT measurement.

Patients received re injections when there was a recurrence of DME. Recurrence was defined as a decrease of BCVA associated with an increase of intraretinal fluid due to macular edema on OCT and/or FA, after complete or partial resolution in previous follow-up visits.

All visual acuities were converted to logMAR before analysis for statistical purposes. Due to the small number of patients, the Wilcoxon matched pairs test was used for the statistical analysis of the data. A p-value less than 0.05 were considered to be the threshold for significance.

The outcome of measurement was a comparison of the mean ETDRS BCVA at 3-36 months follow up between pre and post IVB injections. The other variables were related to safety in ocular and systemic side effects according to patients' complaints. The third stage was an assessment of patients' visual satisfaction from their visual outcome.

3. RESULTS

The mean age of 30 patients participating in this study, consisting of 40% (No=12) males and 60% (No= 18) females, was 60.47±8.94 years ranging from 39 to 83 years old (Table 1).

Visual acuity showed improvements objectively, but 53.4% of patients being asked subjectively, according to the questionnaire did not agree with their visual improvements, and while 26.6% of patients had noticeable visual improvements, 20% of patients had no noticeable improvements or even showed signs of a worse vision, according to before and after bevacizumb interavitreal injection in their eyes. According to Fig. 1 and Tables 2 and 3, such improvement did not have a clear subjective influence on nearly half of the patients being asked about the effect of intravitreal avastin injection on visual effects. The Vitreous hemorrhage and new vessels regressed vigorously after interavitreal injection but after one month, they reappeared gradually as the same patient in different time of appearing and disappearing rubeosis iridis was examined (Figs. 2 and 3). Complication of this study included: retinal detachment after second injection in one patient, two cases also developed the temporary mild anterior uveitis without pain or other eye complaints such as vitritis, hypopyon, and blurred vision. The inflammation resolved in few days by topical steroid treatment.

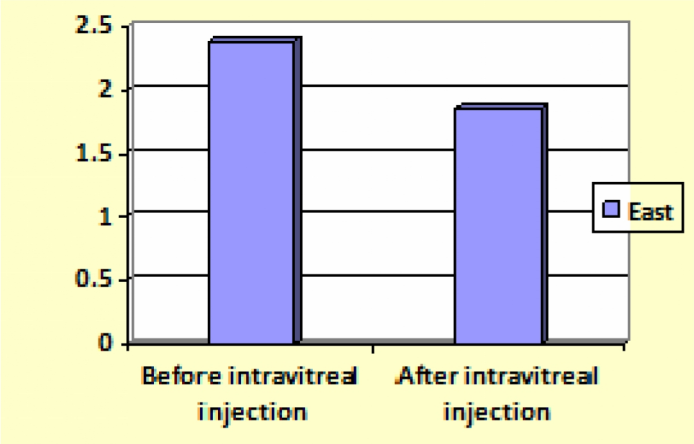

Fig. 1. Visual outcome before and after of avastin injection

Table 1. Maximum, minimum, mean and median variables under study in the studied patients

Variable	No	MiN	Max	Mean ± Sd	median
Age	30	39	83	60.47±8.94	59.5
Duration of right eye F/U	17	3	32	11.94±9.04	9
Duration of left eye F/U	26	3	36	14.23±9.84	12
Number of injection on R E during M/FU	17	1	3	1.24±0.56	1
Number of injection on L E during M/FU	26	1	2	1.23±0.43	1
Diabetes duration	30	2	25	8.47±5.28	7

F/U = Follow-up, LE = Left eye,R E = Right eye,M=Month

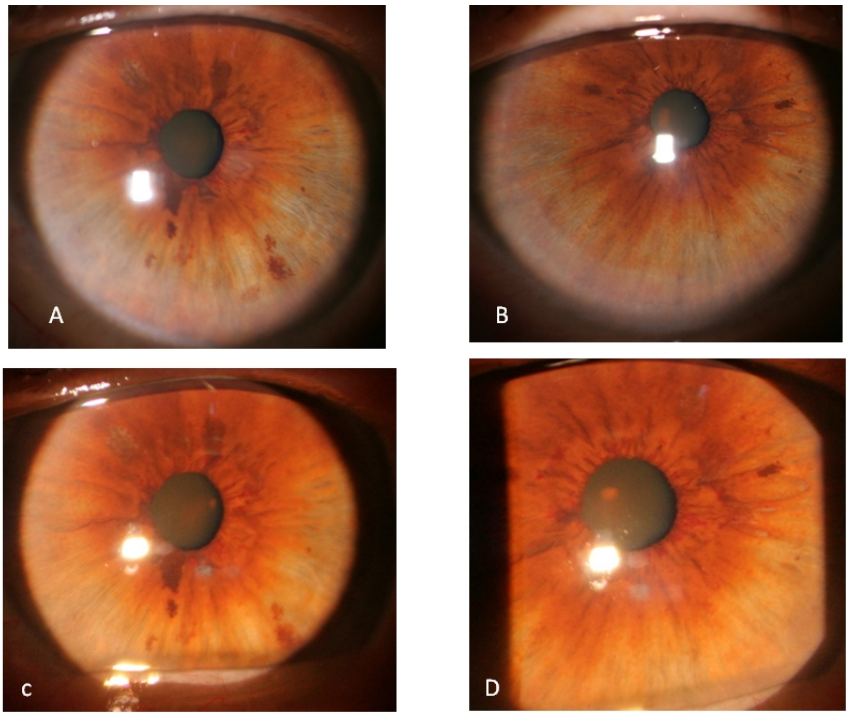

Fig. 2A and B. Right and Left iris neovascularisation Date; 7/06/2009, Date; 14/4/2010 C and D. Right and Left iris neovascularisation

Table 2. Comparative study of visual acuity difference before and after intravitreal avastin injection according to diabetes duration and age

	Diabetes duration		Age	
	Spirman	**P-Value**	**Spirman**	**P-Value**
Difference of VA of R eye (according to LOG-MAR)	-0.364	-0.048	0.230	0.222
Difference of VA of L eye (according to LOG-MAR)	-0.490	-0.006	0.021	0.913

VA= visual acuity, L = Left, R = Right, LOG-MAR = Logarythm of minimum angel resolution

Table 3. Comparative study of visual acuity difference before and after intravitreal avastin injection according to right and left eye

	Before avastin injection (according to LOG-MAR)	**After avastin injection (according to LOG-MAR)**	
	Mean ± SD	**Mean ± SD**	**P-Value**
VA of R eye	1.05±1.04	0.83±0.98	0.01
VA of L eye	1.34±0.85	1.03±0.80	0.02

VA= visual acuity, L = Left, R = Right, LOG-MAR = Logarythm of minimum angel resolution.

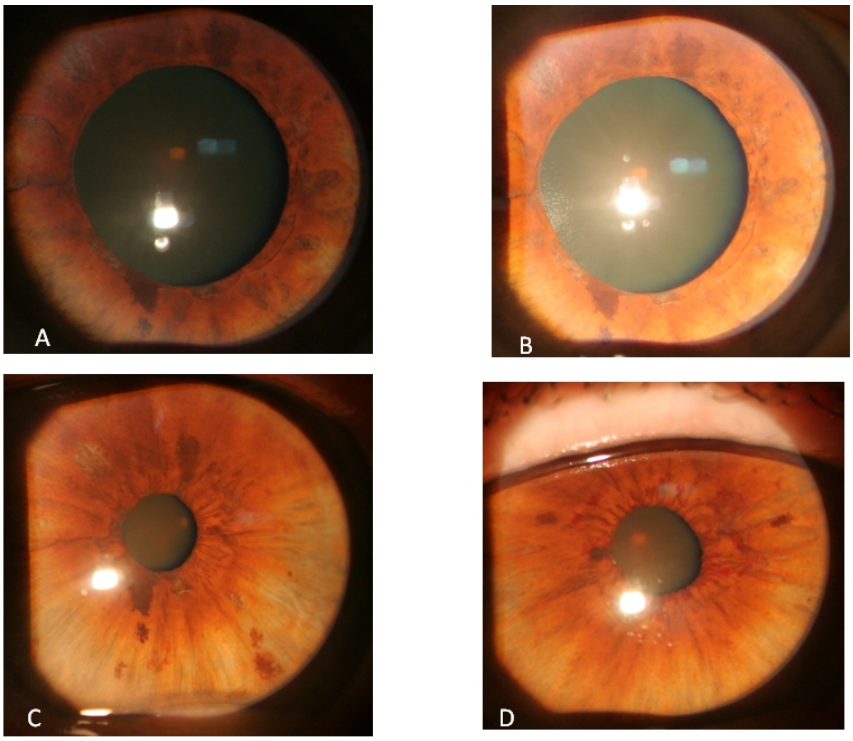

Fig. 3A and B. Disappearance of Right iris neovascularisation Date; 0/6/2010, C Disappearance of Right iris neovascularisation and D reappearance of Left iris neovascularisation Date; 18/6/2011

4. DISCUSSION

There was clinically significant difference in visual improvement at right and left eye based on the before and after injection, but subjectively, nearly half of the patients being asked about the visual improvement satisfaction ratio did not express any visual satisfaction in spite of such significant difference in objective test evaluation. Such dissatisfaction could be due to the attendant of late stage of diabetic retinopathy with severe maculopathy or proliferative diabetic retinopathy and vitreous hemorrhage (High Risk characteristic) on the patient or due to the costs of intervention and re injection due to patient' socio-economic condition. The studies by Elman and Fernando Arevalo with colugos about ranibizumab or focal/grid laser, or both indicated that additional studies are needed in order to judge the success criteria , met early in the course of treatment [6,7].

Therefore, the other researchers as described below are not sure about this therapeutic option [8-10]. They suggest that intravitreal bevacizumab is not an effective treatment for diffused DME. An explanation for this different finding was thought to be the criteria they used to define diffused DME.11 However, there are many reports emphasizing on important therapeutic role and the safety of avastin in diabetic retinopathy, which state that the retinal photocoagulation has a main stay treatment in diabetic retinopathy [12-16].

Simo and Hernandez also believed that Bevacizumab could be an off-label medicine that many ophthalmologists have used it because it was as effective as pegaptanib or ranibizumab but much cheaper. Thus, they concluded that more clinical trial designs were needed to evaluate not only effectiveness, but also systemic adverse effects of anti-VEGF therapy [9].

This study showed statistically significant difference in VA outcome after intravitreal bevasizumb injection either due to diabetes maculopathy or proliferative retinopathy, and the most excellent response was in the first month post injection. After 3 months of bevacizumab injection, this research could not find stable diabetic maculopathy or proliferative diabetic retinopathy that long lasting. Our findings were not classified according to the HbA1c, so it did not agree with Matsuda S et al in one direction of their study since it did not show any significant difference related to number of intravitreal injection in the HbA1c≤7.0% group compared to HbA1c>7.0% group. They also suggested that glucose regulation can impact the response to anti-VEGF therapy in the management of DME [17].

Few patients developed mild anterior chamber reaction with full recovery by topical steroid. Except for one patient who had two injections due to macular edema and denied operation and who lost the left eye after rhegmatogenous and tractional retinal detachment. The satisfaction questionnaire was prepared subjectively to find out how many patients agreed with their visual improvements. Approximately half of the patients' satisfaction questionnaires were not compatible with the objective visual finding outcome of the second question, so this could be related to the patients' expectations of cost effect based on the procedure or may be due to the socio psychological condition in such debilitating diseases which demined the explanation of treatment outcome. The Ferenchak and Colugos study described twelve eyes of nine patients undergoing intravitreal bevacizumab for eyes with recurrent vitreous hemorrhage after vitrectomy for proliferative diabetic retinopathy. They concluded that in their study none of the twelve eyes required repeat vitrectomy for recurrent VH. Mean follow-up was 22 months (range, 8-42). A mean of 8.1 IVB (range, 1-18) given Intravitreal bevacizumab was safe and effective, adjunct in these series for the management of recurrent VH after vitrectomy for proliferative diabetic retinopathy [18]. In a review study conducted by. Nicholson B. P and Schachat A. P, it was concluded that in spite of short-term benefit in visual acuity, this treatment may be associated with tractional retinal detachment. Finally, they claimed despite promising early reports on the safety of these medications, the researchers will wait for more research results on the safety and effectiveness of anti-VEGF drugs for diabetic retinopathy [10]. This study also showed the same suggestion as above described by Nicholson and Schachat but one case developed retinal detachment.

The Spearman correlation coefficient between age and visual changes before and after injection in the right and left eyes did not demonstrate any significant relationship. ($p = 0.222$, $p=0.913$). But the Spearman correlation coefficient showed that duration of diabetes had a negative relationship in both eye visions before and after injection ($p=0.048$, $p=0.006$). This means that the longevity of diabetes duration reduced the vision improvements before and after of injection in both eyes.

Limitations of this study were non-randomized, uncontrolled, and retrospective, which precluded any estimation of effectiveness or safety of intravitreal bevacizumab. In addition, since no control group was used, the researcher could not rule out that the possibility of improvement in macular edema might be associated with systemic health attention. The retinal thickness were ≥300 micrometers and patients had controlled diabetes with a mean HbA1c of about 7.7% only in this study without information of it in past. The results were very

promising but they suggested the need for further investigation. The RESTOR study showed Ranibizumab monotherapy and combined with laser provided superior visual acuity gain over standard laser in patients with visual impairment due to DME,but the patients received ~7 (mean) ranibizumab/sham injections over 12 months [19]. So, the how many and how much should continue is now question of this palliative treatment that for long living people will be unsatisfactory.

To sum up, although it took many years of intravitreal bevacizumab injection and the preliminarily reports claimed stability and improvement in VA; the future overall argumentative reports will make specific treatment recommendations. Therefore, despite many promising results, it is too soon to judge the safety, efficacy and cost effectiveness of this treatment.

5. CONCLUSION

Intravitreal avastin injection was associated with short-term visual benefits indeed of, improvements in ophthalmic pathology in clinical examination versus visual satisfaction. Hence visual satisfaction could be related to long lasting effect of avastin injection.

CONSENT

All authors declare that written informed consent was obtained from the patients for publication of this study.

ETHICAL APPROVAL

All authors hereby declare that this study has been examined and approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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