Original Article

Relationship of HbA1c with Visual and Anatomical Outcomes of Bevacizumab in Diabetic Macular Edema

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Purpose: To find relationship of baseline Hemoglobin A1c (HbA1c) with visual outcomes, central macular thickness and number of intravitreal Bevacizumab at 12 months in patients with diabetic macular edema (DME).

Study Design: Quasi experimental study.

Place and Duration of Study: Prevention of blindness (POB) Hospital, Karachi, Pakistan between October 2018 and September 2019.

Material and Methods: Two hundred and eighty patients with Diabetic macular edema (DME) presenting to the eye OPD of POB, who did not receive any treatment for DME were recruited. Patients who had concurrent retinal disease and were treated with intravitreal injections and/or laser were excluded. All patients were evaluated with history, ophthalmological examination and SD-OCT for central subfield macular thickness. Patients received 3 intravitreal injections of Bevacizumab one month apart. OCT was done after 3 months and retreatment for diabetic macular edema was based on the persistence of macular thickness more than 300 microns. All the data was analyzed using SPSS version 20.

Results: There were 280 patients, 53.2% were males and 46.8% were females. Patients were divided into 3 groups; patients with HbA_1C < 7.0, 7.1 – 8.0 and > 8.0. Central macular thickness decreased significantly from baseline in all 3 groups. Maximum vision improvement was seen in group 1 with HbA_1C < 7.0 and group 2 with 7.1 – 8.0. Significant inverse correlation was seen between HbA_1C and vision at 12 months ($r = -0.40$, $p < 0.01$) and positive correlation with central macular thickness ($r = 0.53$ $p < 0.01$).

Conclusion: Initial baseline HbA_1C is strongly related with visual and anatomic outcome at 12 months.

Key Words: Diabetic macular edema; Bevacizumab; Hemoglobin A1C.

Approximately 21 million people are affected by diabetic macular edema worldwide[1]. By 2025, the incidence of diabetes in Pakistan will get doubled[2]. The high burden of diabetic complications is associated with uncontrolled diabetes[3]. Therefore, control of diabetes is the main pillar for prevention and delaying of diabetic complications. In diabetes mellitus, the main reason of visual loss is macular edema[4]. Evidence shows that diabetic macular edema and moderate visual loss can be reduced by tight glycemic control[5]. The Royal College of Ophthalmologists' Clinical Guidelines for Diabetic Retinopathy" recommends laser alone[6]. Until recently, macular photocoagulation was the treatment of choice for diabetic macular edema. Even with this treatment, macular edema persists in the presence of uncontrolled diabetes[7]. The entire treatment picture has changed with the introduction of anti-vascular endothelial growth factors especially for DME[8].

Not only we have seen the relationship of HbA_1C with visual and anatomical outcome like previous studies, but also seen the relationship of baseline HbA1C with frequency or number of Anti-VEGF injections in diabetic macular edema. The frequency of Anti-VEGF injections is an important aspect to know as in the developing country like Pakistan, the cost is one of the main issues. The rationale of our study was that patients with baseline lower HbA1C may have better visual and anatomical outcome and may require fewer number of Anti-VEGF injections in one duration as compared with patients having high baseline HbA1C.

The purpose of our study was to find relationship of baseline Hemoglobin A1c (HbA1c) with visual outcomes, central macular thickness and number of intravitreal Bevacizumab at 12 months in patients with diabetic macular edema (DME).

MATERIAL AND METHODS

This study was done between October 2018 to September 2019 at Prevention of Blindness, a charity based hospital where approximately 100 patients receive Anti-VEGF injections weekly for different ocular conditions. Ethical approval was taken before the start of study.

Two hundred and eighty patients diagnosed with diabetic macular edema with initial HbA1C of less than or more than 7.0, who received at least three Anti-VEGF injections were recruited for the study. They were followed up for 12 months. The exclusion criteria of our study was those individuals who had concomitant retinal disease or who had macular edema due to reasons other than diabetes or had previous treatment with pan-retinal photocoagulation or macular photocoagulation or macular ischemia or did not have baseline HbA1C or those who were lost to follow-up.

All patients were evaluated starting from the history and comprehensive ophthalmological examination that included best corrected visual acuity using Snellen chart, biomicroscopy to diagnose clinically significant macular edema and OCT optical coherence tomography (SD-OCT) with a central subfield macular thickness (CSMT) measurement to quantify, document and follow-up the macular thickness. The patients whose visual acuity was affected by disruptive anatomy of macula due to the intracystic spaces involving the macula or had more than 300 micron macular thickness on OCT were given intravitreal injections of Bevacizumab. Patients received 3 intravitreal injections at one-month interval. OCT was done after 3 months and retreatment for diabetic macular edema was based on the persistence of macular thickness more than 300 microns.

Patients were followed monthly and HbA_1C was recorded 3 to 4 monthly interval until 12 months. Consent was taken from all the patients after brief explanation about the study, treatment and follow-up. All the data was entered in SPSS version 20, Paired t-test, test of proportion and Pearson correlation coefficient were used for statistical analysis.

RESULTS

Out of 280 patients, 149 (53.2%) were males and 131 (46.8%) were females. Twenty (7.1%) patients had HbA_1C of < 7.0, 187 (66.8%) had 7.1-8.0 and 73 (26.1%) patients had > 8.0 HbA_1c (Table1). Central macular thickness was significantly decreased on 12 months from baseline ($p < 0.01$). Number of injections given were more according to HbA_1c (< 7.0, 7.1 – 8.0 and > 8.0) but statistically not significant ($p > 0.05$). Increase in visual acuity was more in patients with HbA1c of < 7.0 as compared to the patients with higher HbA_1C (Table 2). Initial baseline HbA_1C was strongly related with visual and anatomic outcome at 12 months.

Table 1: Demographic characteristics (n = 280).

	Frequency	Percent
Gender		
Male	149	53.2
Female	131	46.8
Age in years		
Under 50	27	9.6
50-59	158	56.4
60 & above	95	33.9
Range	44–73	
Mean ± S.D	58.1 ± 6.11	
HbA1c		
Group 1 (HbA1c ≤ 7.0)	20	7.1
Group 2 (HbA1c 7.1-8.0)	187	66.8
Group 3 (HbA1c > 8.0)	73	26.1

Table 2: Comparison of HbA1c with CMT, Number of injection and Visual status.

	HbA1c <=7.0 (n=20) n, Mean ± S.D	HbA1c 7.1-8.0 (n=187) n, Mean ± S.D	HbA1c > 8.0 (n=73) n, Mean ± S.D
HbA1c			
Base line (Day 0)	19, 6.93 ± 0.09	163, 7.49 ± 0.25	67, 9.37 ± 1.24
At 12 months	19, 7.17 ± 0.31	163, 7.38 ± 0.44	67, 8.64 ± 1.43
P-value	0.005	0.003	0.001
Duration of DM (Years)	20, 10.0 ± 2.51	180, 13.7 ± 4.71*	73, 16.4 ± 4.46* ^{o}
CMT Right			
Base line (Day 0)	19, 365 ± 72.1	161, 353 ± 81.7	67, 424 ± 138.4
At 12 months	19, 287 ± 315	161, 302 ± 60.1	67, 378 ± 135.3
P-value	0.001	0.001	0.001
CMT Left			
Base line (Day 0)	19, 292 ± 44.4	159, 324 ± 70.7	67, 389 ± 118.7
At 12 months	19, 272 ± 33.6	159, 294 ± 47.8	67, 357 ± 103.2
P-value	0.043	0.001	0.001
Number of injections used in 12 months			
Right	6, 6.67 ± 2.16	87, 7.39 ± 1.49	52, 7.94 ± 1.29
Left	2, 10.00 ± 0.00	62, 8.19 ± 1.04	44, 8.20 ± 1.30
Vision increased on 12 months			
	16 (94%) out of 17	73 (64%) out of 113 *	24 (41%) out of 59 * ^{o}
	1 Line 6 (35%)	1 Line 23 (20%)	1 line 13 (22%)
Right	2 Line 9 (53%)	2 Line 34 (30%)	2 line 7 (12%)
	3 Line 1 (6%)	3 Line 15 (13%)	3 line 3 (5%)
		4 Line 1 (1%)	4 line 1 (2%)
	5 (83%) out of 6	60 (68%) out of 88*	18 (36%) out of 50 *
		1 Line 31 (35%)	1 line 12 (24%)
Left		2 Line 20 (23%)	2 line 2 (4%)
	3 line 5 (83%)	3 Line 9 (10%)	3 line 4 (8%)

Significant from HbA1c <= 7.0 *P < 0.05 Significant from HbA1c 7.1 – 8.0 ^{o}P < 0.05

DISCUSSION

Our study showed that baseline HbA1c has positive correlation with baseline CMT (r = 0.53, p < 0.01) that means if the initial HbA1c is uncontrolled, patients can have high central macular thickness (CMT). We found that in patients with < 7.0, 7.1 to 8.0 and > 8.1 Hba1c, CMT decreased in all patients after Anti-VEGF injections. Our results also correspond to the previous studies in which the patients having low HbA1C showed greater visual improvement with the use of Anti-VEGF injections[9]. Matsuda and colleagues showed that with HbA1C of 7.0 or less there was significant decrease in CMT with the use of Bevacizumab and similar results were seen with the

use of another Anti-VEGF Ranibizumab[10,11]. Diabetic Retinopathy Research Group Vienna also showed that CMT was decreased at its maximum by using either Bevacizumab or Ranibizumab if the HbA1C was less than 7.0[12].

Diabetic macular edema is the biggest cause of visual loss in diabetic retinopathy and can happen at any stage of diabetic retinopathy[13]. Tight glycemic control < 7.0 can delay or prevent the complications in both type 1 and type 2 diabetes[14,15].

However VIVID and VISTA DME studies showed that there was no relationship of baseline HbA1C with visual and anatomical outcome. The difference in results might be because the Anti-VEGF used was Aflibercept and less or more than 8.0 HbA1C was used in the study[16].

According to Matsuda et al DME with regulated blood glucose can impact the response to Bevacizumab. The patients with a starting HbA1C of 7.0 or less showed more improvement in BCVA during the 12 months of therapy than those with starting HbA1C > 7.0[9]. Pemp and colleagues also described that the visual improvement could be gained at its highest level by using Bevacizumab or Ranibizumab if the baseline HbA1C was < 7.0 at the start of therapy[12].

Pakistan is a developing country where cost matters for everything and same is for the Ani-VEGF injections. Bevacizumab being a cost effective injection could be the reason for the increased number of injections used in our study. We did not compare among different Anti-VEGF injections like Ranibizumab or Aflibercept that might have given results at a lower number of injections as compared with Bevacizumab which is commonly used in our set up. An article showed that bevacizumab in relation with cost effectiveness is superior to other Anti-VEGF injections[17]. Another study showed that the cost of Ranibizumab is 20 to 40 folds higher than the cost of Bevacizumab and the treatment of DME is 10 to 15 million Euros higher in Netherland[18]. The Bevacizumab is the cost effective choice as compared to Ranibizumab and Aflibercept[19]. The other reason of increase number of injections in the group having < 7.0 HbA1C might be the increase in its HbA1C until 12 months.

The DRCR.net compared the efficacy of 3Anti-VEGF at 2 years. Vision improved in all 3 drug groups however, the frequency of injections became half in 2nd year[20]. Our follow up was only 1 year so future studies can check this frequency of injections for more than a year.

One study showed that despite different levels of glycemic control during the treatment the baseline HbA1C affects the visual and anatomical outcome however, the required number of Anti-VEGF injections decrease during the course of treatment if the HbA1C remains controlled[4].

Limitation of our study was the small number of patients and it was a retrospective study. There were also lesser number of patients in group 1. Future studies can be planned to investigate this group further. Only Bevacizumab was used in this study. Other Anti-VEGF like Ranibizumab and Aflibercept can be compared with Bevacizumab in future studies.

CONCLUSION

Baseline HbA1C has a strong relation with visual and anatomic outcome in diabetic macular edema.

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