Original Research Article

Effect of hemoglobin level on response to anti-vascular endothelial growth factor treatment for diabetic macular edema

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Abstract

Background: To evaluate the impact of hemoglobin concentration on the change in macular thickness as measured by spectral domain-optical coherence tomography (SD-OCT) findings of Diabetic Macular Edema (DME) in patients treated with intravitreal Anti-Vascular Endothelial Growth Factor[Anti-VEGF] injection. **Methods:** Patients with DME receiving intravitreal Anti-VEGF injection for the first time were included for the study. The patients were categorized based on haemoglobin levels as patients without anemia (group 1=74), mild anemia (group 2A=41), moderate anemia (group 2B=35), severe anemia (group 2C=1). The pre-injection and post injection central retinal thickness value[CRT] as recorded by SD-OCT were compared. **Results:** Among 151 patients with DME, preinjection CRT was found to be significantly different while comparing group 1 with group 2A (p=0.009) and group 2A with group 2B(p=0.01). Folowing anti-VEGF injection, no significant difference was found in the CRT values among the groups 1, 2A and 2B. The reduction in CRT after anti-VEGF injection was similar among the groups 1, 2A and 2B. **Conclusion:** Mild to moderate anemia does not affect the response to treatment with anti-VEGF in DME.

Key Word: Diabetic macular edema, Hemoglobin, Anemia, Anti-VEGF, intravitreal injection, CRT values, SD-OCT.

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Received Date: 20/10/2019 Revised Date: 24/12/2019 Accepted Date: 28/01/2020
DOI: https://doi.org/10.26611/10091421

Access this article online	
Quick Response Code:	Website: www.medpulse.in
	Accessed Date: 01 May 2020

INTRODUCTION

Diabetic Retinopathy (DR) is one of the most common microvascular complications of diabetes mellitus and is the leading cause of visual impairment in the working population among the age group of 20-74 years. Diabetic Macular Edema (DME) is the most common cause of visual loss secondary to DR and affects up to 3% of individuals with recent diagnosis of Diabetes Mellitus(DM) and about 29% in those with DM for more than 20 years.[1,2] Intravitreal inhibitors of VEGF A have become the first-line of treatment for patients with DME, thereby shifting the standard of care for DME towards intravitreal VEGF inhibitors from laser photocoagulation.[3] Previous studies have concluded that the level of hemoglobin is a predictive factor for the development and progression of proliferative DR in diabetic patients.[4,5] Other studies have demonstrated that diabetic patients with retinopathy had lower level of hemoglobin and higher frequency of anemia.[6,7] There are very few studies done to evaluate the impact of systemic factors such as diabetes medication history, serum glucose, HbA1c, renal function, BMI, and blood pressure on clinical response to VEGF inhibitors for diabetic macular edema.[8,9] Along this line we designed our study to find out whether haemoglobin levels alter the response of Anti-VEGF therapy for Diabetic Macular Edema.

MATERIALS AND METHODS

Institutional Ethical Committee clearance was taken for this study. The study was conducted in accordance with the Declaration of Helsinki. Patients visiting the Department

How to cite this article: Mamatha Reddy, Chidanand Kulkarni, Krishna A Rao. Effect of hemoglobin level on response to anti-vascular endothelial growth factor treatment for diabetic macular edema. *MedPulse International Journal of Ophthalmology.* May 2020; 14(2): 21-25. https://www.medpulse.in/Ophthlmology/

of Ophthalmology, Kasturba Hospital, Manipal, receiving first dose of intravitreal injection of Anti-VEGF [Bevacizumab/Ranibizumab] - a standard care of treatment for Diabetic Macular Edema [DME], from September 2015 to September 2017 were asked to participate in the study. Inclusion criteria were patients of either sex, patients with DME admitted for receiving intravitreal Anti-VEGF injection for the first time. Exclusion criteria were patients with pre-existing non-diabetic retinopathy and maculopathy (Central Serous Retinopathy, Age Related Macular Degeneration, Central retinal vein occlusion, Branch retinal vein occlusion, Drug Induced and other Macular degeneration), patients who had undergone laser photocoagulation therapy, patients not completing follow up, patients not willing to participate. Patients were explained about the study and a written informed consent was obtained. Basic demographic profile of the patients including age, sex, place of residence was documented. Past history of diabetes mellitus, hypertension, previous surgical/ medical history was documented. Patients were then subjected to an ophthalmic evaluation which included recording of visual acuity, best corrected visual acuity in both eyes and evaluation of anterior segment using slit lamp biomicroscope and intraocular pressure (IOP) measurement by Goldmann Applanation Tonometer. Posterior segment was examined by slit lamp biomicroscopy using +90 D lens and indirect ophthalmoscopy. Patients with clinical diagnosis of DME based on ETDRS criteria underwent fundus fluorescein angiography (FFA) and Spectral Domain-Optical Coherence Tomography(SD-OCT), (Cirrus HD OCT, Carl Zeiss, software version 6.0) for confirmation, grading and classification of the DME. The patients underwent, as part of Pre-Anesthetic Checkup [PAC] investigations including blood parameters (complete hemograincluding Hb level, Fasting blood sugar, post prandial blood sugar, serum electrolytes, complete blood picture, renal function tests), chest x-ray, electrocardiogram (ECG). Once the diagnosis was confirmed, patients were advised to receive intravitreal Anti-VEGF injection as the standard treatment. Intravitreal Bevacizumab (0.5 mg/0.05 ml) or Ranibizumab (1.25mg/0.05ml) was administered and the patient was discharged after 24 hours of observation. The follow-up was scheduled after 4 weeks. At the time of follow up, BCVA was tested and SD-OCT was done. The patients were grouped as 'without anemia'(group 1) and 'with anemia'(group 2). The patients with anemia were further subdivided based on severity as per the level of hemoglobin into mild (group 2A), moderate(group 2B) and severe(group 2C) categories. Haemoglobin levels (g/dl) to diagnose anaemia and for defining severity of anaemia as per WHO guidelines (Table 1).

In each of these groups:

1. BCVA was recorded before and after receiving intravitreal injection at follow- up visit.
2. Central Retinal Thickness (CRT) value was recorded on SD-OCT, before receiving injection and at the follow up visit.
3. Serum creatinine levels were also documented.
4. Reduction in CRT by 10% was considered as significant in this study. Accordingly, patients were categorized as 'with' and 'without' significant reduction.

Statistical analysis:

The collected data was tabulated and analysed using SPSS v20.0 software (IBM, Chicago, USA).Findings were described in terms of frequencies and percentages. Continuous data like BCVA, CRT value, serum creatinine levels were summarized in terms of mean and standard deviation. In this study Categorical variables were patients with anemia (mild, moderate, severe) and without anemia; patients with and without significant reduction in CRT value; Chi-square test was used to find correlation between these variables. Independent T-test was done to compare pre-injection CRT values, post injection CRT values and significant reduction values among different groups. A p value of <0.05 was considered statistically significant. Pearson's Correlation Coefficient was used to find association between hemoglobin levels and BCVA (pre and post injection) and r value was noted.

RESULTS

Over the study period 151 patients fulfilled study criteria and their records were included in the analysis. Among these 81(53.3%) were female patients and 70(46.7%) were male patients.The age range of the study population was from 45-72 years with a mean of 58.32 + 7.832.In this study population, 74(49%) were without anemia;41(27.15%) with mild anemia;35(23.17%) with moderate anemia;1(6.62%) with severe anemia. The mean CRT value before receiving injection was more among group 2A patients (471.71) when compared to patients group 1 (443.85) or group 2B (428.33). The single patient in group 2C had lowest CRT value (334.0) when compared to others.

The mean CRT value one month after injection was least among group 2B (393.0) when compared to group 1 (399.0) and group 2A (418.89). It shows there was better response to treatment in patients without anemia followed by those with moderate anemia and least outcome was seen in patients with mild anemia.

Table 2 shows the Comparison of pre injection CRT value among different study groups. The difference in CCT was statistically significant when comparing group 1 with group 2A and group 2A with group 2B. But no statistical

significant difference was found when comparing group 1 with group 2B.

Table 3 shows the Comparison of post injection CRT values between groups. There was no statistically significant difference found among group 1 and group 2A, group 1 and group 2B, group 2A and group 2B.

Group 1 Patients had higher percentage of significant reduction in CRT value (46.9%) when compared to group 2A(31.2%) and group 2B(21. 9%). However this response to treatment at one month was statistically insignificant in all the categories analysed (Table 4).

Table 5 shows that on comparison of mean reduction in CRT value no significant difference was found among group 1 and group 2A;group 1 and group 2B;group 2A and group 2B (114.33 versus 108.35; 114.33 Vs 110.71; 108.35 Vs 110.71;p>0.05). In our study 70(46.35%) patients had BCVA ≤ 6/18; 73(48.34%) patients had BCVA of 6/24-6/60 and.8 (5.29%) patients had BCVA >6/60 at diagnosis. Among patients with BCVA of ≤ 6/18, group 1(60.56%) were more compared to group 2A (20%) and group 2B (18. 57%). Among patients with BCVA of 6/24-6/60, it was observed the same as with BCVA of ≤ 6/18 i.e. group 1(41.09%) were more compared to group 2A (32.87%) and group 2B (24. 65%).Among patients with BCVA of >6/60; group 2B(50%) were more compared with group 2A(37.5%) and group 1 (12. 5%).this indicaates that most of patients without anemia had better BCVA when compared to patients with mild, moderate and severe anemia before receiving injection. After receiving the injection 85(56.3%) patients had BCVA of ≤ 6/18; 65(43.04%) had BCVA 6/24-6/60 and 1(0.66%) patient had BCVA >6/60. It shows that clinically there was improvement in visual acuity as a whole. It was observed that among patients with BCVA of ≤ 6/18 post-injection, group 1(58.53%) were more compared to group 2A (23.52%) and group 2B (20%).Among patients with BCVA of 6/24-6/60, it was observed the same as with BCVA of <6/18 i.e. group 1(38.46%) were more compared to group 2A (32.30%), group 2B (27.69%), group 2C (1. 53%).

Table 1: WHO grading of Anemia

Gender	Normal	Mild	Moderate	Severe
Female	≥12	11-11.9	8-10.9	<8
Male	≥13	11-12.9	8-10.9	<8

Table 2: Comparison of pre-injection CRT value among varying degrees of anemia

Comparison of pre-injection CRT value among varying degrees of anemia	Mean CRT values	p value
Group 1 vs Group 2A	**443.85 Vs 471.1**	**0.009**
Group 1 vs Group 2B	443.85 Vs 428.33	0.471
Group 2A vs Group 2B	**471.1 Vs 428.33**	**0.010**

Table 3: Comparison of post injection CRT value among varying degrees of anemia

Comparison of post injection CRT value among varying degrees of anemia	Mean CRT values	p value
Group 1 vs Group 2A	399.80 vs 418.83	0.158
Group 1 vs Group 2B	399.80 vs 393.0	0.657
Group 2A vs Group 2B	418.89 vs 393.0	0.219

Table 4: Reduction in CRT after Anti-VEGF injection categorized as significant and not significant among DME patients

Anemia status	Number of patients	Significant reduction	No significant reduction	p value
Group 1	74(49.0%)	30(46.9%)	44(50.57%)	0.16
Group 2A	41(27.2%)	20(31.2%)	21(24.13%)	0.10
Group 2B	35(23.17%)	14(21.9%)	21(24.13%)	0.243
Group 2C	1 (0.1%)	-	1(1.1%)	Not analysed
Total	151(100%)	64(100%)	87(100%)	

Table 5: Comparison of reduction in CRT value among varying degrees of anemia

Comparison of reduction in CRT value among varying degrees of anemia	Mean CRT values	p value
Group 1 Vs Group 2A	114.33 Vs 108.35	0.805
Group 1 Vs Group 2B	114.33 Vs 110.71	0.889
Group 2A Vs Group 2B	108.35 Vs 110.71	0.921

DISCUSSION

Very few studies have evaluated the role of metabolic parameters in the response of treatment with Anti-VEGF drugs.[8,9] In our study we attempted to find a relationship between hemoglobin levels and Anti-VEGF outcome in terms of reduction in CRT. The mean CRT value before injection in our study was 447.21 which is comparable to the mean CRT of 450.2 recorded by Mastuda *et al.*. .[10] In our study mean CRT value before receiving injection was more in group 2A (471.1) when compared to patients group 1 (443.85) group 2B (428.33) and group 2C (334.0); but the number of patients with severe anemia was insufficient to comment about CRT value when compared to others. Our study demonstrates that CRT value in mild anemia was significantly more when compared to no anemia and moderate anemia. In group 2A mean CRT value was more compared to group 1. This could be due to hypoxia induced release of vasoproliferative factors resulting in accumulation of fluid in retina, interestingly this finding was not seen in moderate anemia. These finding need to be confirmed by further evaluation with large sample size and longer follow up. In this study we did not analyse the severity of DR among varying degrees of anemia, so there could be a possibility of severe form of DR with minimal accumulation of fluid in central retina as it was already hypothesized in a study conducted by Adele *et al.*. that anemic patients were more likely to develop more advanced form of DR than patients with normal hemoglobin level.[11] The mean CRT value of study population after receiving injection was 403.60. this is higher than the value of 347.4 reported by Mastuda *et al...*[10] We found that mean CRT value after injection was least among patients with group 2B (393.0) when compared to group 1(399.0) and group 2A (418.83). Our study demonstrates that there is no significant difference in the CRT values in DME developing in patients with no anemia, mild and moderate anemia. Our study demonstrates that anti-VEGF treatment resulted in reduction of CRT values to same level by one month irrespsctive of blood haemoglobin status. In addition, patients without anemia and with moderate anemia had responded better at one month after receiving injection when compared to patients with mild anemia. This could be attributed to other factors we have not analysed in our study like uncontrolled DM, HbA1C levels, severe DR in patients with mild anemia. We found that group 1 had higher percentage of significant reduction in CRT value when compared to patients with group 2A and 2B. However, there was found to be no statistically significant difference in the CRT values after anti-VEGF injection in each category of anemia. After one month of anti-VEGF injection, the response to treatment is usually seen as change in the CRT in the OCT.[12] Our study demonstrates the hemoglobin concentration does not affect Anti- VEGF response in Diabetic Macular edema. A study conducted by Ozturk *et al.*. reported that there is a negative correlation between serum HbA1c levels and reduction in central retinal thickness following intravitreal injection, highlighting the importance of glucose regulation in treatment outcome.[13] Matsuda *et al.*. reported that patients with better glycemic control showed statistically significant improvement in Central Subfield Macular Thickness (CST) and visual outcome after intravitreal injection, and also concluded that there was no significant association with change in OCT findings, visual outcome or lipid parameters [triglycerides, HDL, and LDL].[8] They also found no significant correlation between the duration of diabetes, renal function, age, gender, BMI and blood pressure with changes in BCVA and CST following anti-VEGF therapy. We found no relationship between serum hemoglobin levels and changes in BCVA at one month in DME patients who received anti-VEGF treatment. In their study Singh *et al.*. concluded that vision improvement with ranibizumab is not influenced by non- ocular factors like duration of diabetes mellitus and its treatment history, blood glucose level, glycosylated hemoglobin level, serum creatinine level, Body Mass Index, and blood pressure.[9] The above studies indicate that visual outcome after anti-VEGF treatment is influenced by better glycemic control but not by most of other non-ocular factors considered as risk factors for developing diabetic retinopathy. In our study almost all DME patients had normal renal function implying that low hemoglobin level could not be related to renal pathology. We found that in our study population there was improvement in CRT and BCVA following Anti VEGF injection as a whole, but there was no impact of hemoglobin concentration on outcome of anti-VEGF injection. The highlight of this study is the analysis and comparison of the response to anti- VEGF treatment at different hemoglobin levels. The limitation of our study was smaller number in subgroups for comparison, patients receiving single injection were taken up for the study, the change in CRT was recorded at one month after treatment and glycosylated hemoglobin levels were not taken into consideration because of which the effect of anemia on HbA1c levels could not be studied.

CONCLUSION

Haemoglobin level in blood in absence of significant renal impairment does not have impact on response to Anti-VEGF treatment for DME. This is the first study where haemoglobin was taken as single parameter to assess its impact on Anti-VEGF outcome.

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Source of Support: None Declared
Conflict of Interest: None Declared