Original Research Paper

Volume - 10 | Issue - 7 | July - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Ophthalmology

A STUDY TO EVALUATE THE EFFICACY OF INTRAVITREAL ANTI-VEGF IN TREATMENT OF DIFFUSE DIABETIC MACULAR EDEMA WITH RESPECT TO VISUAL OUTCOME

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ABSTRACT **PURPOSE:** To evaluate the efficacy of intravitreal anti-VEGF in the reduction of foveal thickness using an interventional case series design and to see the visual prognosis using the LogMAR equivalent of standard Snellen's chart. **DESIGN:** prospective, interventional **MATERIALS AND METHODS:** 49 eyes of 30 patients were selected for the study.2 injections of intravitreal bevacizumab is given at 6 weeks interval and the patients were followed up at 1 month,3 months and 6 months period from the last injection. The patients were evaluated by measuring the visual acuity and pinhole on each visit of the patient were recorded and then evaluated for any improvement. The macular edema was confirmed by measuring the visual acuity, indirect ophthalmoscopy, direct ophthalmoscopy,oct and fundus photography. **RESULTS:** The age of presentation varied from 40-78 years and most of the patients(43.33%) belonged to the age group of 51-60 years with the mean age of presentation 56.4 years. 30 patients that were included in the study had 19(63.33%) males and 11(36.66%) females which signify that males were more affected by the disease than females. 95.92% of eyes were associated with NPDR where as 4.08% had PDR. Most of the patients having difficulty of vision had DDME in mod NPDR group. In the study it was found that most of the patients had visual acuity(VA) between >0.3- 0.6 group(21 eyes;42.86%) of logMAR equivalent of snellen's chart followed by >0.6-1 group(20 eyes;40.82%),>1 group(7 eyes;14.28%) and 0-0.3 group(1 eye;2.04%). In our study we found that the improvement of BCVA was significant throughout 6 month follow up following 2 injections of bevacizumab with maximum improvement at 3 months. At 1 month, visual acuity improved to logMAR (0.486±0.204) and at 3 months visual acuity was found to be improved to logMAR (0.345±0.155) which were statistically significant($p<0.001$) **CONCLUSION:** DDME is considered as one of the most important cause of central visual loss in patients of diabetes mellitus. Intravitreal bevacizumab has a very important role in improving the visual acuity of the patients which is the sole important symptom which the patient experience so it adds on in the wellbeing of the patient and also help the ophthalmologists to see the progress of the therapy. There was a constant improvement of visual acuity in the patients at 1month,3 months and at 6 months follow up with maximum difference from baseline at 3 months and the least from 3 month to 6 month. Thus it can be concluded that detection of visual acuity is a very import and easy tool to detect as well as to see the improvement in symptoms in patients of Diffuse Diabetic Macular Edema(DDME).

KEYWORDS : :Diffuse Diabetic Macular Edema,Visual acuity,Intravitreal bevacizumab,logMAR chart using snellen's equivalent,

INTRODUCTION:

The term diabetes mellitus(DM) describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate ,fat and protein metabolism resulting from defects in insulin secretion ,insulin action ,or both[1].The pathophysiology of Diffuse Diabetic Macular Edema(DDME) is multifactorial and the exact mechanism is yet unknown. The main etiology of DDME is thought to be due to break down of blood retinal barrier mainly in the retinal pigment epithelium and retinal endothelium junction mainly mediated by loss of tight junction protiens[2].It is also thought that increased vascular permeability in retina as well as posterior hyaloid adhesion can be associated with the pathogenesis of the disease[3,4].

India is the leading country in the number of diabetic patients. As per records 62 million Indians is having diabetes which corresponds to 7.1% of the total Indian adult population. The most important factor which cause most damage in diabetes is its microvascular complications in the retinal vasculature.

DDME is diagnosed mainly by slit lamp biomicroscopy .Fluorescein angiography is also a very important tool both in diagnosing and to estimate the progression of the disease but it is having a disadvantage of not quantifying the degree of fluid accumulated in the retina[5].

Visual acuity is also a very important and the most important tool in detecting the progress of macular DDME as well as to evaluate the outcome of any intravitreal procedures. Visual acuity is the first symptom which the patient appreciates and it has a direct correlation to the reduction of foveal thickness following anti-VEGF intravitreal injections.

Vascular Endothelial Growth Factor(VEGF) is released in the vitreous whenever there is break in blood retinal barrier. VEGF has inflammatory property and has a key role in development and progression of DDME. Bevacizumab is an immunoglobulin G(IgG) consisting of two identical light chains, consisting of 214 amino acid residues and two 453 residue heavy chains containing an N- linked oligosaccharide and has a molecular weight of approximately 149,000 daltons.

AIM OF THE STUDY:

The main aim of the study is to evaluate the efficacy of intravitreal anti-VEGF in the reduction of foveal thickness using an interventional case series design and to see the visual prognosis using the LogMAR equivalent of standard Snellen's chart.

REVIEW OF LITERATURE:

Severity of diabetic retinopathy has strong correlation with the onset of macular edema. It is also seen that more the duration of the disease more is the chance of developing DDME. Poor glycemic control also play an important role in the pathogenesis of DDME. Visual acuity and pinhole test is the first test that is done in any patient coming to an ophthalmologist and in diabetes it becomes the most important tool to rule out any macular pathology due to the disease process. The progression and the response to treatment can be easily found out by this simple test that can help the ophthalmologist to plan the future plan of action.

Haritoglou C et al.(2006)[6], has evaluated the efficacy of bevacizumab for treating DDME in 51 patients by 2 intravitreal injections and then followed up at 6,12 weeks period. A baseline mean visual acuity +/- SD was 25.88 +/- 14.43 ETDRS letters(0.86 +/- 0.38 logMAR of snellen letters) and at 6 weeks it increased to 0.75 +/- 0.37 logMAR of snellen

letters after injection. Thus they concluded that intravitreal bevacizumab improved visual acuity(VA) in DDME.

Kumar et al(2007),[7] had done a prospective study of 20 eyes with DDME and was treated with intravitreal bevacizumab. The baseline vision was recorded as 20/494(logMAR=1.338±0.455).After 3 months of two intravitreal injection at 6 weeks apart the VA improved to a mean of 20/295(logMAR=1.094±0.254) and at 6 months the VA further improved to 20/304(logMAR=1.124±0.219).

MATEIALS AND METHODS:

The present study was conducted in the Regional institute of Ophthalmology ,Gauhati Medical College during the period of July 2017 to June 2018. This study is a hospital based, prospective, and interventional study.

Selection of cases

The patients were selected from the outdoor as well as indoor patients of Regional institute of Ophthalmology,Guwahati. A total of 49 eyes of 30 patients were treated with intravitreal bevacizumab(IVB) at 6 weeks interval and then following 2nd injection the eyes are followed up at 1 month,3 month and 6 month for improvement of Best Corrected Visual Acuity(BCVA).

Inclusion criteria

a) Age> 18 years, sex- all.
b) Type 1 or 2 diabetes Mellitus.
c) Diabetic Macular Edema affecting the fovea in one or both the eyes.
d) Retinal thickness of > 250 microns in central 1mm subfield macula on stratus domain OCT
e) Intraocular pressure <22mm of Hg.
f) Women of child bearing potential must have a negative pregnancy test at the screening visit.

Exclusion criteria

a) Known allergy to the agents used in the study
b) Women who are pregnant, nursing or planning a pregnancy.
c) Loss of vision or macular edema due to other causes (eg. ARMD, myopic macular degeneration ,retinal venous occlusion).
d) History of treatment of DR within 3 months of starting the treatment.
e) Uncontrolled glaucoma
f) Use of systemic or intravitreal steroids within last 6 months as well as systemic anti-VEGF.
g) Recent history of arterial thromboembolic event and poorly controlled hypertension.
h) History of chronic renal failure requiring dialysis or renal transplant.

A complete history is taken regarding the age, sex, details complaints, duration of diabetes, any treatment history and any associated disorders. Detailed systemic examination is done along with routine blood investigations (complete blood count,HbA1c, FBS,PPBS,Fasting lipid profile, ECG.

Patients are then taken for ocular examinations-

1) Visual acuity-both near and distant vision is recorded along with the pin hole vision using the LogMAR equivalent of the Snellen's chart.
2) Intraocular pressure-was recorded using applanation tonometer in both eyes.
3) Detailed slit lamp examination was done to note any anterior segment pathology
4) The pupils were dilated using Tropicamide 0.8% and phenylephrine 5% and detailed posterior segment examination was done by direct ophthalmoscopy, slitlamp biomicroscopy using 90D lens, Indirect ophthalmoscopy and fundus photography. OCT imaging was performed using stratus OCT machine model 3000(Carl Zeiss Meditec Inc. with software version 4.0.Fundus fluorescein angiography(FFA) was done using the Zeiss visucam fundus photograph camera by receiving informed consent.

Operative procedure of intravitreal bevacizumab:

1) Prior informed consent is taken regarding the procedure, complications
2) Bevacizumab(1.25mg Avastin;Hoff and Roche Ltd, Basel, Switzerland) was used
3) Topical antibiotics(Moxifloxacin) was started one day prior to the procedure
4) Following adequate pupillary dilatation Povidone Iodine(10%) painting was done
5) After proper antiseptic draping topical anaesthetic drop(lignocaine 4%) was instilled and then 5% povidone iodine is instilled into the conjunctival sac
6) 0.05mi(1.25mg/ml) of bevacizumab was drawn in a 1cc syringe and then fitted with 26G needle. The injection is given 3.5mm and 4mm from limbus in pseudophakic and phakic eyes in the superotemporal region
7) The needle is then removed after the bevacizumab is pushed and then a cotton tipped applicator dipped in 1 drop of betadine and topical antibiotic is used to prevent the regurgitation of the injected material
8) Pad and bandage is then done for 24 hours
9) All patients were given tab acetazolamide 250mg twice a day, tab pantoprazole, tab diclofenac
10) Dressing was done the very next day with topical antibiotic, Intraocular pressure was measured, visual acuity was also measured .Patients were then instructed to use moxifloxacin 1 hourly for day 1 the 6 times daily for 2 weeks.
11) 6 weeks after injection re injection was performed in a similar way

Post-operative Evaluation:

The patient is then followed up every 1,3,6 months and then looked for the visual acuity, pin hole and central macular thickening by OCT. The patients were also checked for hypertension or any recent thrombotic effect.

RESULTS AND OBSERVATIONS:

The study is a prospective, interventional study done in regional institute of Ophthalmology from July 2017 to June 2018.The study was done on 49 eyes of 30 patients.

All the patients taken for study were diagnosed cases of T2DM having Non Proliferative Diabetic Retinopathy (NPDR) or Proliferative Diabetic Retinopathy(PDR) with Diffuse Diabetic Macular Edema(DDME) which was diagnosed by slitlamp biomicroscopy using 90D lens and OCT and by doing the visual acuity(VD) and pinhole.

Age of presentation

The age of presentation varied from 40-78 years and most of the patients(43.33%) belonged to the age group of 51-60 years with the mean age of presentation 56.4 years

TABLE 1: AGE AT PRESENTATION OF THE PATIENTS

AGE(IN RANGE IN YEARS)	FREQUENCY	PERCENTAGE(%)
<30	0	0
31-40	2	6.66
41-50	5	16.66
51-60	13	43.33
61-70	8	26.66
71-80	2	6.66
TOTAL	30	100
MEAN±SD	56.4±8.87	
MEDIAN	56	
RANGE OF AGE	40-78	

Sex distribution

30 patients that were included in the study had 19(63.33%) males and 11(36.66%) females which signify that males were more affected by the disease than females.

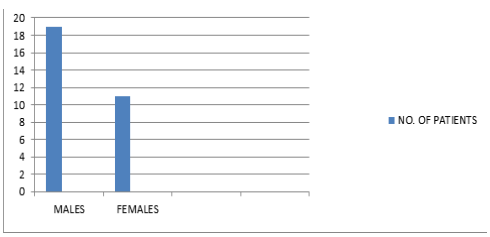

FIGURE 1: BAR DIAGRAM SHOWING THE SEX DISTRIBUTION OF THE PATIENTS

Duration of diabetes

In the study maximum number of cases (56.66%) had DR features who have DM for more than 10 years and the mean duration of diabetes was found to be 12.07 years.

TABLE 2: DURATION OF DIABETES

DURATION OF DIABETES(IN YEARS)	NO. OF PATIENTS	PERCENTAGE(%)
<10	12	40
11-20	17	56.66
>20	1	3.33
TOTAL	30	100
MEAN±SD	12.07±6.30	
MEDIAN	14	
RANGE	2-27	

Grades of retinopathy

95.92% of eyes were associated with NPDR where as 4.08% had PDR. Most of the patients having difficulty of vision had DDME in mod NPDR group.

TABLE 3: GRADES OF RETINOPATHY

TYPE OF RETINOPATHY	NO. OF EYES	PERCENTAGE(%)
MILD NPDR	1	2.04
MODERATE NPDR	26	53.06
SEVERE NPDR	18	36.73
VERY SEVERE NPDR	2	4.08
EARLY PDR	2	4.08
HIGH RISK PDR	0	0
TOTAL	49	100

From the above table, maximum number of eyes (26) had moderate NPDR which was found in 53.06% of eyes at the time of presentation. The rest 18 eyes(36.73%) were having severe NPDR,2 eyes(4.08%) were in very severe NPDR and early PDR groups respectively and 1 eye(2.04%) was associated with mild NPDR group.

Baseline VA at presentation

In the study it was found that most of the patients had visual acuity(VA) between >0.3- 0.6 group(21 eyes;42.86%) of logMAR equivalent of snellen's chart followed by >0.6-1 group(20 eyes;40.82%),>1 group(7 eyes;14.28%) and 0-0.3 group(1 eye;2.04%)

TABLE 4: BASELINE VISUALAQUITY AT PRESENTATION

VA(logMAR EQUIVALENT OF SNELLEN'S CHART)	NO. OF EYES	PERCENTAGE(%)
0-0.3	1	2.04
>0.3-0.6	21	42.86
>0.6-1	20	40.82
>1	7	14.28
TOTAL	49	100

LogMAR visual acuity(Snellen's equivalent) in at 1 month,3 months and 6 months

In our study we found that the improvement of BCVA was significant throughout 6 month follow up following 2 injections of bevacizumab with maximum improvement at 3 months. At 1 month, visual acuity improved to logMAR (0.486±0.204) and at 3 months visual acuity was found to be improved to logMAR (0.345±0.155) which were statistically significant($p<0.001$).

TABLE 5: SHOWING logMAR VISUAL AQUITY(SNELLEN'S EQUIVALENT) AT 1 MONTH,3 MONTHS AND AT 6 MONTHS

	BASELINE	AT 1 MONTH	AT 3 MONTHS	AT 6 MONTHS
MEAN	0.698	0.486 (P<0.001)	0.345 (P<0.001)	0.367 (P<0.001)
SD	0.305	0.204	0.155	0.127
MEDIAN	0.600	0.500	0.300	0.374
LOWER CONFIDENCE LIMIT	0.610	0.427	0.300	0.330
UPPER CONFIDENCE LIMIT	0.786	0.544	0.389	0.403

DISCUSSION

Age distribution

In the present study we have taken 30 patients and all were diagnosed with macular edema with age more than 18 years. All the patients belonged to the age group of 40-78 years with a maximum of 13 patients (43.66%) in 51-60 years group. In our study largest numbers of patients with DDME were within the age group of 51-60 years with the mean age of presentation 56±8.87 years. Most of the studies show an increase in prevalence of DDME with increasing age of the patient. The Wisconsin Epidemiologic Study of Diabetic Retinopathy(WESDR) Klein et al. (1984),8 had found the age of presentation of DDME as 35±11.3 years in type 1 DM and 64.9 years in type 2 DM. Azad R et al. (2012),9 and Kriechbaum K et al (2014),10 found the mean age of patients with DDME as 53.7±5.9 years and 59±11 years respectively which correlates with the mean age of patients in our study.

Sex distribution

Our study had 30 patients of which 19(63.33%) were males and rest 11(36.66%) were females which corresponds to the study conducted by Raman R et al. (2009)11 and Chakrabarti M et al.(2013)12 which had found higher males prevalence 21.1% and a M/F ratio of 2:1 respectively.

Duration

In the present study the duration of DM ranged from 2-27 years ,of which most of the patients had DM for 11-20 years(17;56.66%) and the mean duration of diabetes was found out to be 12.07±6.30)years and median being 14 years which corrosponds to the study conducted by Klien et al.(1984),8 and Chakrabarty M et al. (2013)12 who found that less than 5 years of DM had 0% DDME and with more than 20 years had 29% of the disease in the former study and the later study concluded that the mean age of DDME was 13.5 years of DM.

Severity of diabetic retinopathy

95.92% of eyes who received IVB had NPDR and 4.08% had PDR which shows that most of the patients with loss of vision due to DDME had NPDR. Among the patients maximum of 26 eyes(53.06%) had moderate NPDR,18 eyes(36.73%) had severe NPDR,2 eyes had very severe and 1 eye had mild NPDR which corresponds to the study conducted by Ghasemzadeh et al. (2012)13 who found that 75.9% had NPDR and 24.1% had PDR.

logMAR visual acuity (Snellen's equivalent) in at 1 month,3 months and 6 months In our study we found that improvement of BCVA was significant throughout 6 month follow up with maximum improvement seen at 3 months.AT 1 month visual acuity improved to logMAR (0.486±0.204) and at 3 months improved to logMAR(0.345±0.155) which was statistically significant($p<0.001$) with baseline improvement from logMAR (0.698±0.305) to logMAR(0.367±0.127) AT 6 months Kumar A et al.(2007),7 showed statistically significant changes in VA(baseline logMAR= 1.338±0.455) at 3 months after IVB which improved to a mean of logMAR(1.094±0.254) a difference of from baseline that is highly significant($p<0.008$).At 6 month the second injection VA was logMAR(1.124±0.219).

Arevalo et al. (2007), found that by 1 month, mean BCVA improved from 0.87 to 0.6, a difference that was statistically significant($p<0.001$).At 3 and 6 months follow up, mean BCVA of 0.6 did not differ statistically($p=0.775$ and $p=0.688$ respectively) from BCVA of 1 month follow up.

From the above comparison it is evident that our study has a correlation with the above mentioned studies and is also statistically significant.

CONCLUSION:

DDME is considered as one of the most important cause of central visual loss in patients of diabetes mellitus more so if the duration of the disease is more(>20 years) which is very well established in our study and also in many other previous studies and so has a very strong correlation. In our study we found that Intravitreal bevacizumab has a very important role in improving the visual acuity of the patients which is the sole important symptom which the patient experience so it adds on in the wellbeing of the patient and also help the ophthalmologists to

see the progress of the therapy. In our study it was found that improvement of vision started to appear even after single injection and after the 2 nd injection it had an added improvement. There was a constant improvement of visual acuity in the patients at 1month,3 months and at 6 months follow up with maximum difference from baseline at 3 months and the least from 3 month to 6 month. Thus it can be concluded that detection of visual acuity is a very import and easy tool to detect as well as to see the improvement in symptoms in patients of Diffuse Diabetic Macular Edema(DDME).

FINANCIAL SUPPORT AND PARTNERSHIP:
Nil

CONFLICTS OF INTEREST:
There are no conflicts of interest.

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