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# A STUDY TO COMPARE THE VARIOUS COMPLICATIONS OF INTRAVITREAL ANTI-VEGF AND INTRAVITREAL TRIAMCINOLONE ACETATE IN PATIENTS WITH DIFFUSE DIABETIC MACULAR EDEMA

Medicine

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## ABSTRACT

**PURPOSE:** To compare the various complications of intravitreal anti-VEGF and intravitreal triamcinolone acetate in patients presenting with diffuse diabetic macular edema and thus play a role in reducing such complications. **DESIGN:** prospective, interventional **MATERIALS AND METHODS:** 84 eyes of 50 patients were selected for the study. Patients were randomly selected for each group of intravitreal bevacizumab and intravitreal triamcinolone acetate.2 injections of intravitreal bevacizumab and intravitreal triamcinolone acetate is given at 6 weeks and 12 weeks interval respectively and the patients were followed up at 1,3 and 6 months period from the last injection. The patients were evaluated for their complications, immediate post injection and then is subsequent visits. **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. Of the total 50 patients,30 patients were given intravitreal bevacizumab and rest 20 patients received intravitreal triamcinolone. Most of the patients in both the groups had subconjunctival haemorrhage as the most presenting complications.8.57% patients in intravitreal triamcinolone had presented with cataract as late complications and in intravitreal bavacizumab group it was 2.04%.Intravitreal triamcinolone patients also presented with raised intra ocular pressure with 8.57% where as the intravitreal bevacizumab group had 2.04%. **CONCLUSION:** DDME is considered as one of the most important cause of central visual loss in patients of diabetes mellitus. Intravitreal injections has a very important role in improving the wellbeing of DR patients. But as the procedure is a invasive one there is always a chance of complications. Most important and dreaded complications being endophthalmitis,retinal detachments but there might be some minor complications like subconjunctival haemorrhage.Besides intravitreal triamcinolone is a steroid so it also comes with seroid related complications that needs to be addressed.

## KEYWORDS

Diffuse Diabetic Macular Edema, Intravitreal Bevacizumab, Intravitreal Triamcinolone,

### 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 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].

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].

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.

The rationale for the use of corticosteroids in the treatment of diabetic macular edema follows from the observation that the breakdown of the blood retinal barrier leads to the edema[6] and in parts mediated by Vascular Endothelial growth factor(VEGF).Corticosteroids have been shown to inhibit VEGF and other cytokines and growth factors, there by regulating endothelial cell tight junctions as well as they inhibit prostaglandin and leukotriene synthesis, which results in a local reduction of inflammatory mediators which in turn results in reduction of edema[7].Triamcinolone acetonide is a potent, relatively insoluble steroid that has been used for treatment of ocular inflammation. Intravitreal use of the drug leads to local effectiveness of the drug thus leading to better management. Many of the complications associated with intravitreal treatment for diabetic eye complications are related to the injection procedure itself, including serious adverse events such as endophthalmitis, retinal tears or detachment, and vitreous hemorrhage. Of these, endophthalmitis is of particular concern in diabetic patients given their known increased susceptibility to infection. It has been suggested that patients with diabetes have an increased tendency to develop endophthalmitis after cataract surgery. Intravitreal injections may be performed as outpatient in-office procedures or inpatient operatingroom procedures.

### AIM OF THE STUDY:

The main aim of the study is to compare the various complications of intravitreal anti-vegf and intravitreal triamcinolone acetate in patients with diffuse diabetic macular edema.

### 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. Intravitreal injections has a very important role in reducing the thickness of diabetic macular edema. As in intravitreal injection there is direct drug delivery it is most effective way of tackling the disease. But as the procedure is an invasive one it is more prone to complications.

Haritoglou C et al.(2006)[8], 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. Sagamoto et al.(2002)[9]4mgin 0.1 ml of triamcinolone is more popular but the 1mg version is mostly used and the 4mg one is kept for reinjections as higher doses of steroids results in glaucoma, cataract, endophthalmitis, and pseudoendophthalmitis.

### 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*

50 patients with 84 diseased eyes were selected from the outdoor as well as indoor patients of Regional institute of Ophthalmology,Guwahati.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 1,3 and 6 months and 35 eyes of 20 patients were given intravitreal triamcinolone(IVTA) with re injections performed after 12 weeks interval.

**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
e) Intraocular pressure <22mm of Hg.
f) Women with a negative pregnancy test.

**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 etc.)
d) History of treatment of DR within 3 months of starting the treatment.
e) Uncontrolled glaucoma
f) Use of systemic or intravitreal steroids and anti-VEGF within last 6 months
g) Recent history of arterial thromboembolic event and poorly controlled hypertension.
h) History of chronic renal failure

A complete history and detailed systemic examinations is done along with routine blood investigations.

Patients are then taken for ocular examinations as per protocol like visual aquity,intra ocular pressure measurement,detailed slit lamp examination,dilated fundoscopy,slitlamp biomicroscopy,fluorescein angiography(FFA),OCT etc.

**Operative procedure of intravitreal injections:**

1) Prior informed consent is taken.
2) Bevacizumab(1.25mg Avastin;Hoff and Roche Ltd,Basel,Switzerland) and triamcinolone(inj Tricort 40mg/1 ml,Cadila Pharmaceuticals,Ahmedabad,India) was used.
3) Topical antibiotics(Moxifloxacin) was started one day prior to the procedure
4) 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) A cotton tipped applicator dipped in 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 next day with topical antibiotic. IOP, visual acuity was measured and any signs of injury to the eye was found out .Patients were then instructed to use moxifloxacin 1 hourly for day 1,6 times daily for 2 weeks.
11) 6 weeks after injection re injection was performed in a similar way

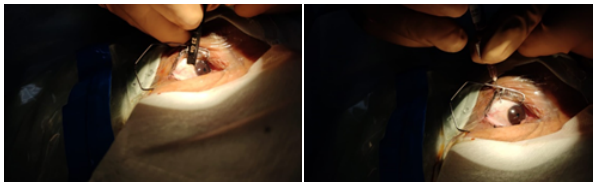

**Fig a: Measurement of injection site** **Fig b: injection is being given**

**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 84 eyes of 50 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 in IVB varied from 40-78 years and most of the patients(43.33%) were of age group 51-60 years with the mean age of 56.4 years. In IVTA group age of presentation was from 45-74 years and in this 50% were from 51-60 years with mean age of 56.85%.

**TABLE 1: AGE AT PRESENTATION OF THE PATIENTS**

| Age(in Range) In Years | IVB Group | | IVTA Group | |
|---|---|---|---|---|
| | Frequency | Precentage % | Frequency | Percentage % |
| <30 | 0 | | 0 | |
| 31-40 | 2 | 6.66 | 0 | |
| 41-50 | 5 | 16.66 | 4 | 20 |
| 51-60 | 13 | 43.33 | 10 | 50 |
| 61-70 | 8 | 26.66 | 5 | 25 |
| 71-80 | 2 | 6.66 | 1 | 5 |
| TOTAL | 30 | 100 | 20 | 100 |
| MEAN | 56.4 | | 56.85 | |
| MEDIAN | 56 | | 55 | |
| RANGE OF AGE | 40-78 | | 45-74 | |

**Sex distribution**

30 patients of IVB group ,were males 19(63.33%) and 11(36.66%) females which signify that males were more affected by the disease than females. Among IVTA group, out of 20 patients ,13(65%) were male and rest 7(35%) were female.

**TABLE 2: TABLE SHOWING THE SEX DISTRIBUTION OF THE PATIENTS**

| Sex | IVB Group | | IVTA Group | |
|---|---|---|---|---|
| | Frequency | Percentage % | Frequency | Precentage % |
| Males | 19 | 63.33 | 13 | 65 |
| Females | 11 | 36.66 | 7 | 35 |
| Total | 30 | 100 | 20 | 100 |

**Duration of diabetes**

In the study maximum number of cases of IVB group(56.66%) had DR features with DM>10 years and In IVTA group 50% had developed retinopathy after 10 years of the disease.

**TABLE 3: DURATION OF DIABETES**

| Duration Of DM(in Years) | IVB Group | | IVTA Group | |
|---|---|---|---|---|
| | No. Of Patients | Percentage % | No. Of Patients | Percentage |
| <10 | 12 | 40 | 9 | 45 |
| 11-20 | 17 | 56.66 | 10 | 50 |
| >20 | 1 | 3.33 | 1 | 5 |
| TOTAL | 30 | 100 | 20 | 100 |
| MEAN | 12.07 | | 11.9 | |
| MEDIAN | 14 | | 11 | |
| RANGE | 2-27 YEARS | | 5-22 YEARS | |

**Ocular complications**

3 out of 49 eyes had subconjunctival haemorrhage in IVB group 2 out of 35 eyes in IVTA group which resolved completely within 2 weeks.

At 1 month follow up, 3 out of 35 eyes in IVTA group had raised IOP where as in IVB group there was none.

At 3 months follow up,2 eyes had raised IOP in IVTA group while in IVB group there was only 1 eye.

In IVB group,at 6 months followup 1 patients developed cataract, while in the IVTA group, 3 had developed cataract.

No other complications were reported in either group in the study period.

**Table 4: OCULAR COMPLICATIONS AMONG BOTH THE GROUPS.**

| | AT 1 WEEK | | AT 1 MONTH | | AT 3 MONTHS | | AT 6 MONTHS | | PERCENTAGE% | |
|---|---|---|---|---|---|---|---|---|---|---|
| | IVB | IVTA | IVB | IVTA | IVB | IVTA | IVB | IVTA | IVB | IVTA |
| RAISED IOP | 0 | 0 | 0 | 3 | 1 | 2 | 0 | 0 | 2.04 | 8.57 |
| SUB CONJUNCTIVAL HAEMORRHAGE | 3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 6.12 | 5.71 |
| ENDOPHTHALMITIS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| CATARACT | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 | 2.04 | 8.57 |
| UVEITIS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| MACULAR HOLE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |
| TRACTIONAL RETINAL DETACHMENT | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | |

**Systemic complications**

At 1 month follow up,2 out of 30 patients in IVB group and 1 out of 20 patients in IVTA group had rise in blood pressure. All 3 were previous hypertensive.1 out of the 2 patients in IVB group had raised systemic blood pressure even at 3 months follow up, however at 6 months follow up, the blood pressure was controlled.

**Table 5: SYSTEMIC COMPLICATIONS AMONG BOTH GROUPS.**

| | AT 1 WEEK | | AT 1 MONTH | | AT 3 MONTHS | | AT 6 MONTHS | |
|---|---|---|---|---|---|---|---|---|
| | IVB | IVTA | IVB | IVTA | IVB | IVTA | IVB | IVTA |
| RISE IN IOP | 0 | 0 | 2(6.66%) | 1(5%) | 1(3.33%) | 0 | 0 | 0 |
| MYOCARDIAL INFRACTION | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| THROMBOEMBOLISM | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## DISCUSSION

**Age distribution**

In the present study we have taken 50 patients with 30 patients under IVB group and 20 patients under IVTA group and all were diagnosed with macular edema with age more than 18 years. Under IVB group, all belonged to the age group of 40-78 years with a maximum of 13 patients (43.66%) in 51-60 years group where as in IVTA group 45-74 years age group patients were mostly included in the study. 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)*,[10] 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)*,[11] and *Kriechbaum K et al (2014),*[12] 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**

In our study, among IVB group, out of 30 patients ,19(63.33%) were males and 11(36.66%) were females and among IVTA group, out of 20 patients, 13(65%) were males and 7(35%) were females which corresponds to the study conducted by Raman R et al. (2009)[13] and Chakrabarti M et al.(2013)[14] 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 in IVB group and 5-22 years in IVTA group ,of which most of the patients in IVB group had DM for 11-20 years(17;56.66%) where as in IVTA group most of the patients with DM had duration of 10 years(50%) which corresponds to the study conducted by Klien et al.(1984),[10] and Chakrabarty M et al. (2013)[14] 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.

In our study ,we found that in the IVB group ,3 out of 49 eyes had sub conjunctival haemorrhage whereas in the IVTA group it was 2 out of 35 eyes which corresponds with the study conducted by Ladas ID et al. (2009)[15] which said that sub conjunctival haemorrhage occurs in 10% of patients after injections.

At 1 month follow up, 3 out of 35 eyes in IVTA group had raised IOP. At 3 months follow up it was seen that 2 eyes had raised IOP in IVTA group while only 1 eye had raised IOP in IVB group.1 patients developed cataract in IVB group and 3 in IVTA group at 6 months follow up which corresponds with the study conducted by Forte R et al.(2010 )[16] and Shahin M et al.(2010)[17] who found rise in IOP after IVTA in 10.4% and 16.7% respectively.

Among the systemic complications , we found that at 1 month follow up, 2 out of 30 patients in the IVB group and 1 out of 20 patients in the IVTA group had raised blood pressure.1 out of the 2 patients in the IVB group had raised BP even at 3 months.

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 injections are relatively safe method of reducing the burden of DR as it has very less complications. IVB is more safer as compared to IVTA as the latter had a complication of raised IOP.IVTA receiving patients also encounter with early cataract as compared to the IVB group. Sub conjunctival haemorrhage is common in both the case and it resolves on its own. Prolonged hypertension is also a matter of concern in IVB group which needs to be dealt accordingly. Finally it can be concluded intravitreal injections may come with complications but their benefits cannot be ignored in patients with diabetic retinopathy.

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Nil

## CONFLICTS OF INTEREST:

There are no conflicts of interest.

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