ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 06 | June - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A COMPARATIVE STUDY ON THE COMPLICATIONS OF INTRAVITREAL INJECTION OF BEVACIZUMAB, RANIBIZUMAB AND TRIAMCINOLONE ACETATE IN THE TREATMENT OF DIFFUSE DIABETIC MACULAR EDEMA IN A TERTIARY CARE HOSPITAL

Ophthalomology

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ABSTRACT

Purpose: To compare the various complications of intravitreal anti-VEGF Bevacizumab, Ranibizumab and 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:** 90 eyes of 80 patients were selected for the study. Patients were randomly selected for each group of intravitreal bevacizumab and intravitreal triamcinolone and intravitreal ranibizumab. 3 injections of intravitreal bevacizumab and intravitreal triamcinolone and intravitreal ranibizumab is given at 6 weeks and 12 weeks interval respectively and the patients were followed up at 1,3 and 6 months from last injection. The patients were evaluated for their complications immediate post injection and in the subsequent visits. **Results:** the age of presentation varied from 40 to 70 years and most of the patients belonged to the age group of 51 to 60 years. Of the total 80 patients, 30 patients were given intravitreal bevacizumab and 30 were given intravitreal triamcinolone and 20 patients were given intravitreal ranibizumab. Most of the patients in both the groups had subconjunctival hemorrhage as the most presenting complication. 8.57 % patients in intravitreal triamcinolone had presented with cataract as late complications and intravitreal bevacizumab group it was 2.04%. Intravitreal triamcinolone patients presented with raised intraocular pressure with 8.57 % whereas the intravitreal bevacizumab group had 2.04 %. **Conclusion:** DDME considered one of the most important causes of central visual loss in patients of diabetes mellitus. Intravitreal injections had a very important role in improving the wellbeing of DR patients but as the procedure is an invasive one there is always a chance of complication. Most important and dreaded complication being endophthalmitis, retinal detachment but there might be some minor complications like sub conjunctival hemorrhage. Besides intravitreal triamcinolone is a steroid so it also comes with steroid related complications that needs to be addressed.

KEYWORDS

INTRODUCTION

The term diabetes mellitus (DM) describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbance 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 breakdown of blood retinal barrier mainly in the retinal pigment epithelium and retinal endothelium junction mainly mediated by loss of tight junction proteins[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 bio microscopy. Fluorescein angiography is also a very important tool both in diagnosis 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, thereby regulating endothelial cell tight junctions as well as they inhibit prostaglandins and leukotrienes synthesis, which results in a local reduction of inflammatory mediators which in turn results in reduction of edema[7]. Triamcinolone acetate 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, 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 maybe performed as outpatient in office procedures or in patient operating room procedures.

Ranibizumab was the first approved anti VEGF agent that revolutionized DME treatment. It is a recombinant humanized monoclonal antibody and VEG-A antagonist used for the treatment of macular edema after retinal vein occlusion, ARMD and diabetic macular edema. it may constitute a significant treatment modality in the management of other diabetic vision threatening complications including proliferative diabetic retinopathy.

AIM OF THE STUDY

The main aim of the study is to compare the various complications of intravitreal injection of Bevacizumab, Ranibizumab and 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 have a very important role in reducing the thickness of diabetic macular edema as in intra injection there is direct drug delivery it is most effective way of tacking the disease. But as the procedure is an invasive one it is more prone to complications.

Haritloglou C et al (2006)[8] has evaluated the efficacy of bevacizumab for treating DDME in 51 patients by 2 intravitreal injections and followed up at 6,12 weeks period. Sagamoto et al (2002) 4 mg in 0.1 ml of triamcinolone is more popular but the 1mg version is mostly used and the 4mg is used for reinjection as higher doses of steroids leads to glaucoma, cataract, endophthalmitis and pseudoendolphthalmitis.

MATERIALS AND METHODS

The present study was conducted in the Regional Institute of Ophthalmology, Gauhati Medical College during the period of this study is a hospital based, prospective, interventional study.

Selection Of Cases

90 patients with 80 diseased eyes were selected from the outdoor as well as indoor patients of Regional Institute of ophthalmology, Guwahati. 45 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, 6 months and 25 eyes of 30 patients were given intravitreal triamcinolone (IVTA) with reinjections performed after 12 weeks interval. 20 eyes of 20 patients were treated with intravitreal ranibizumab with reinjections performed at 6 weeks interval.

Inclusion Criteria

1. Age >18 years, sex – all
2. Type 1 or 2 diabetes mellites
3. Diabetic macular edema affecting fovea in one or both the eyes.
4. Retinal thickness of >250 microns in central 1mm subfield macula
5. Intraocular pressure <22 mm Hg
6. Women with a negative pregnancy test

Exclusion Criteria

1. Known allergy to the agents used in the study
2. Women who are pregnant, nursing or planning pregnancy
3. Loss of vision or macular edema due to other causes (e.g., ARMD)
4. History of treatment of DR within 3 months of starting the treatment.
5. Uncontrolled glaucoma
6. Use of systemic or intravitreal steroids and anti-VEGF within last 6 months
7. Recent history of arterial thromboembolic event and poorly controlled hypertension.
8. History of chronic renal failure

A complete history and detailed systemic examination are done along with routine blood investigations.

Patients are then taken for ocular examination as per protocol like visual acuity. Intraocular pressure measurement, detailed slit lamp examination, dilated fundoscopy, slit lamp bio microscopy, fluorescein angiography (FFA), OCT etc.

Operative Procedure Of Intravitreal Injections

1. Prior informed consent is taken.
2. Bevacizumab and triamcinolone and ranibizumab were used.
3. Topical antibiotics (Moxifloxacin) was started one day prior to the procedure.
4. Povidone iodine painting (10%) was done
5. After proper antiseptic draping, topical anesthetic drop (lignocaine 4%) was instilled and then 5% povidone iodine is instilled into the conjunctival sac.
6. 0.05 ml (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 pseudo phakic and phakic eyes in the supero-temporal 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 are then done for 24 hours
9. All patients were given tab acetazolamide 250 mg twice daily, tab pantoprazole, tab diclofenac
10. Dressing was done next day with topical antibiotic, IOP, visual acuity was measures and any signs of injury to the eye was found outpatients were then instructed to use moxifloxacin 1 hourly for 1 day, 6 times daily for 2 weeks
11. 6 weeks after injection, reinjection was performed in a similar way.

RESULTS AND OBSERVATIONS

THE study is a prospective interventional study done in regional institute of ophthalmology from July 2018 to June 2019.The study was done on 90 eyes of 80 patients.

All the patients taken for study were diagnosed cases of T2DM having Non proliferative diabetic retinopathy (NPDR) or Proliferative Diabetic Retinopathy (PDR) with DDME which was diagnosed by slit lamp bio microscopy 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 to 78 years and most of the patients (43.44%) were of age group 51 to 60 years with the mean age of 56.4 years. In IVTA, age of presentation was from 45 to 74 years and in this 46.66% were from 51 to 60 years with mean age 56.85%. in intravitreal ranibizumab, the age group is between 42 to 75 years and most of the patients were of age group 45 to 60 years. In IVR, age group is between 42 to 75 years and most of the patients were in age group 51 to 60 years with mean age 51.6 years.

Table 1: Age At Presentation Of The Patients

Age (in range) in years	Ivb Group		IVTA		Ranibizumab	
	Frequency	Percentage%	Group Frequency	Percentage%	Frequency	Percentage %
<30	0		0		0	0
31-40	2	6.66	0	0	0	0
41-50	5	16.66	6	20.0	5	25
51-60	13	43.33	14	46.66	10	50
61-70	8	26.66	9	30.0	5	25
71-80	2	6.66	1	3.33	1	5
TOTAL	30	100	30	100	20	100
MEAN	56.4		56.85			
Median	56		55			
Range Of Age	40-78		45-74		42-75	

Sex Distribution

30 patients of IVB group, were males 19 (63.33%) and 11(36.66%) were females which signify that males were more affected by the disease than females. Among IVTA, out of 30 patients, 20(66.66%) were males and rest 10 (33.33%) were females. Among IVR, 13 patients (65%) were males and 7(35%) were females.

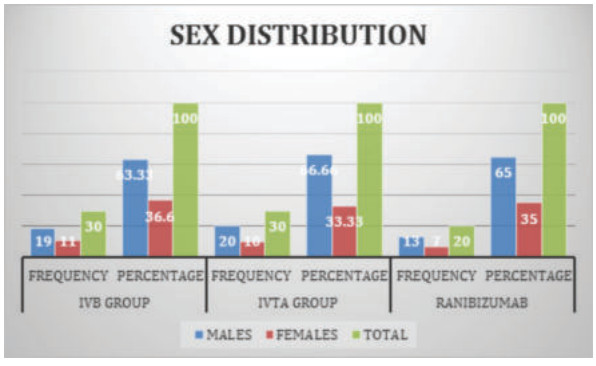

Figure 1: Showing Sex Distribution Of The Patients

Duration Of Diabetes

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

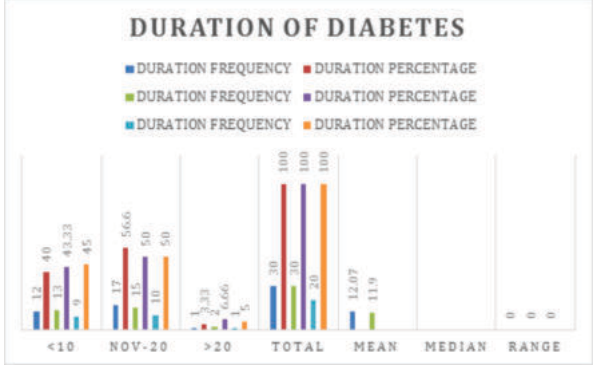

Figure 2: Graph Showing Duration Of Diabetes

Ocular Complications

3 out of 45 eyes had sub conjunctival hemorrhage in IVB group 1 out of 25 eyes in IVTA group which resolved completely in 2 weeks.

At 1 month follow up, 2 out of 25 patients had raised IOP, in IVB group there was none. In IVR group, there was 1 patient with raised IOP.

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

At 6months follow up, IVB had 1 cataract while in IVTA group there was 2 patients developed cataract.

No other complications were noticed in the groups during the study period.

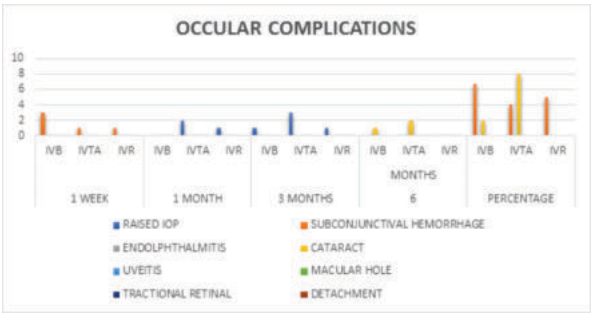

Figure 3: Graph Showing Ocular Complications Among Both The Groups

Systemic Complications

At 1 month follow up, 2 out of 30 patients in IVB group and 2 out of 30 patients in IVTA group had rise in blood pressure. 1 out of 20 patients had increase in blood pressure in IVR group. All 5 were previously hypertensive. 1 out of 2 patients in IVB group had raised blood pressure even after 3 months follow up, however at 6 months follow up, blood pressure was controlled.

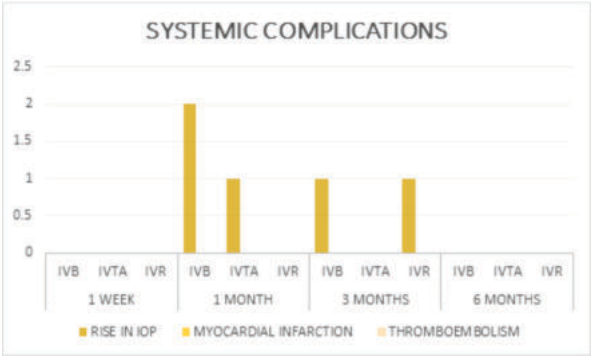

Figure 5: Graph Showing Systemic Complications Among Both Groups

DISCUSSION

Age Distribution

In the present study, we have taken 90 patients with 30 patients under IVB group and 30 patients under IVTA group and 20 patients under IVR group all were diagnosed with macular edema with age more than 18 years. Under IVB group, all belonged to the age group 40-78 years with maximum of 13 patients in 51 to 60 years group whereas in IVTA group 45 to 74 years patients were included mostly. In IVR group, age is between 42 to 75 years and 50% patients belonged to 51 to 60 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)[1], 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 Kirshbaum 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 corelates with the mean age of patients in our study.

Sex Distribution

In our study, among IVB group, out of 30 patients, 19 were males and 11 were females and among IVTA group, out of 30 patients, 20 were males and 10 were females. In IVR group, 13 were males and 7 were females which corresponds to the study conducted by Raman R et al. (2009)[13], and Chakraborty m et al. (2013)[14] which had found higher males prevalence 21.1% and a M/F ratio 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%)whereas in IVTA group, most of the patients with DM had duration of 15 years (50%) and in IVR group, most of the patients had duration of diabetes from 11-20 years (50%) which corresponds to the study conducted by Klein et al. (1984)[1], and Chakraborty M et al.(2013)[13] 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.

In our study, we found that in the IVB group, 3 out of 45 eyes had subconjunctival hemorrhage whereas in the IVTA group, it was 1 out of 35 eyes and in IVR group, it was 1 out of 20 eyes which corresponds with the study conducted by Ladas ID et al (2009)[13] which said that subconjunctival hemorrhage occurs in 10 % of patients after injection. After 1 month follow up, 2 out of 35 eyes in IVTA group had raised IOP. 1 out of 20 eyes had raised IOP in the IVR group.

At 3 months follow up, 3 eyes had raised IOP in IVTA, group while only 1 eye had raised IOP in IVB group. Only 1 eye had raised IOP in the IVR group. 1 patient developed cataract in IVB group and 2 developed cataracts in IVTA group at 6 months. No patient developed cataract in IVR group follow up which corresponds with study conducted by Forte R et al.. (2010)[1] and Shahin M et al. (2010)[1] who found rise of 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 IVTA group had raised blood pressure. 1 out of 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 causes of central visual loss in patients of diabetes mellitus more so if the duration of the disease is more which is very well established in our study and in many other previous studies so has a strong correlation. In our study we found that intravitreal injections are a relatively safe method of reducing the burden of DR as it has very less complications. IVR is relatively safer than IVB and IVTA. IVB is relatively safer than IVTA since it has a lower risk of rise in IOP. IVTA patients also encounter with early cataract as compared to IVTA group. Sub conjunctival hemorrhage is common and is encountered in all the groups and 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 that intravitreal injections may come with complications but their benefits cannot be ignored in patients with diabetic retinopathy.

Financial Support And Partnership: Nil
Conflict Of Interest: There are no conflicts of interest.

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