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Original Research Article

Clinical Evaluation of Intravitreal Triamcinolone Acetonide in Diabetic Macular Oedema

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Abstract: The study was carried out to evaluate prospectively the efficacy and safety of intravitreal Triamcinolone acetonide (IVTA) injection in Diabetic Macular Oedema (DME). Patient who were diagnosed to have DME were enrolled in the study after obtaining written informed consent and fulfilling the inclusion criteria. They were then subjected to comprehensive eye examination followed by recording of best corrected visual acuity (BCVA) with Snellen chart and obtaining coloured fundus photography and fundus Fluorescein Angiography (FFA) before treatment. Triamcinolone was injected in each eye of Test group. BCVA assessment, coloured fundus photo recording and FFA were performed at 1st and 3rd post IVTA month's follow up visit. Intraocular pressure (10P) was measured at every follow up. 100 eyes of 90 patients were selected. 50 eyes randomized to receive active treatment (Test Group) and rest 50 eyes of another 50 patients were put on to strict metabolic control (Control Group) Significant improvement was noticed in visual acuity, in coloured fundus picture and also in FFA in test eye group both at 1 month and at 3 months follow up. 10P rise was seen in only 10% of test eyes. This IVTA is a premising, effective and relatively safe therapeutic mode of treatment for DME and it was observed to have definite potential in improving visual acuity in short terms. The side effects are also transient. Further ongoing work on IVTA would pave the way for finding more effective regime for managing DME.
Keywords: Diabetic macular odema, Intravitreal Trimcinolone Acetonide, Best corrected visual acuity, coloured fundus picture, Fundus Fluorescein Angiography, Intraocular pressure

INTRODUCTION:

Diabetic mellitus, usually referred as 'diabetes' has been known to mankind since ancient times. Diabetes means "flowing through" and mellitus means "Sweet as honey". It is a metabolic disorder with multiple organ involvement due to lack, or impaired efficacy of endogenous insulin [1].

Approximately 285 million people worldwide (6.6%) in the 20-79 years of age group have diabetes in 2010 and by 2030, 438 million people (7.8%) of the adult is expected to have diabetes [2].

There are approximately 93 million people with Diabetic Retinopathy (DR), 17 million with proliferative DR, 21 million with Diabetic macular oedema. Longer the diabetes duration and poor glycaemic and B.P. control are strongly associated with DR [3]. The Wisconsin Epidemiologic study of Diabetic Retinopathy estimated that after 15 years of known Diabetes, the prevalence of Diabetic Macular oedema is 20% in patients with type 1 Diabetes, 25% in patients with type 2 diabetes who are taking insulin and 14% in patients with type 2 Diabetes who do not take insulin [4].

As regards pathogenesis, DME is characterized by accumulation of extracellular fluid in Henle's layer and inner nuclear layer of the retina and the most important mechanism involved is the breakdown of the blood retinal barrier [5].

Triamcinolone (9-fluoro 16-hydroxy prednisolone) have been shown to inhibit Vascular endothelial growth factor (VEGF) and other cytokines and growth factors, thereby regulating endothelial cell

tight junctions. In addition, they inhibit prostaglandin and leukotriene synthesis, which results in a local reduction of inflammatory mediators. The resultant anti-inflammatory effect contributes to the reduction of oedema. Besides increased diffusion by modulation of calcium channel could account for the efficacy of the corticosteroid in reducing macular oelama [6].

Considering the vast prevalence of DME among diabetic population and causing loss of Central vision and since laser photocoagulation and para plana vitrectomy are associated with significant side effects and complications and laser photocoagulation usually does not improve vision [7] intravitreal Triamcinolone injection constitutes a newer, less destructive modality with definite improvement of visual activity and reduction in oedema in the management of DME.

Aim of the Study:

The study was done to evaluate prospectively the efficacy and safety of intravitreal injection of Triamcinolone acetonide 4mg (IVTA) in Diabetic Macular Oedema as a newer treatment modality for the benefit of the disease sufferers. We also assessed and compared the pre-treatment visual acuity, colour fundus photo and fundus fluorescein angiography with post injection status in respect of visual acuity, colour fundus photography and fundus fluorescein angiography (FFA).

MATERIALS AND METHODS:

This case controlled cross sectional study included 100 eyes of 90 patients who were diagnosed as Diabetic Macular oedema attending the outpatient department of Ophthalmology, at Assam Medical College, Dibrugarh. The age of patients ranged from 30 – 8o years. The study was conducted from during Sept., 2009 to August, 2010. Both Proliferative Diabetic Retinopathy (PDR) and Non Proliferative Diabetic Retinopathy (NPDR) patients were included. 50 eyes randomized to receive active treatment (Test group) and remaining 50 eyes of another 50 patients were put on to strict metabolic control only (Control group).

Inclusion criteria included all patients with severe (involving central fovea) diabetic macular oedema, diffuse or focal, having best corrected visual acuity (BCVA) in the affected eye (s) of 6/18- to <3/60/ worse and those with DME previously treated with laser photocoagulation. Patients were deemed to be enrolled in the study after they had given written informed consent and fulfilled the above inclusion criteria.

Exclusion criteria included patients with sign of vitreous macular tractions, patients with ≥ 1 mm diameter of macular capillary closer on FFA, uncontrolled glaucoma, family history of Primary Open angle Glaucoma (POAG), macular oedema due to central/Branch Retinal Vein occlusion (CRVO/BRVO), poorly controlled D.M. & hypertension, patients with hazy media, those failed to give written consent and one eyed patients.

All patients received a complete eye examination inclusive of best corrected visual acuity, Applanation tonometry, slit lamp examination, lens states evaluation, indirect ophthalmoscopy and slit lamp biomicroscopy of the posterior pole with 90D lens. BCVA was performed using Snellen chart, colour fundus photography and FFA was obtained at pretreatment, at 1st month and 3rd month of post treatment visit.

With meticulous aseptic precaution in the operation room and after putting the eye speculum, 0.5% Proparacaine hydrochloride drops as topical anesthesia was applied. Triamcinolone acetonide in a single use bottle (40mg/ml, 1ml bottle) was drawn in a 1cc tuberculin syringe after clearing the top of the bottle with an alcohol wipe; a separate 26 gauge needle is placed on the syringe, which was then inverted to remove the bubbles. The excess triamcinolone is discarded till 0.1 ml (4mg) remains in the syringe. The site of injection was inferotemporal quadrant to avoid drug deposition in front of visual axis. The site was given 3mm from limbus (in aphakic and pseudophakic patients) and 3.5mm in phakic patients. Using a single, purposeful continuous maneuver, the drug is injected into the eye. The needle was removed simultaneously with the cotton tipped applicator's application to prevent regurgitation of drug. A drop of topical antibiotic solution was administered and the eye is patched. A course of topical antibiotic eye drop (Moxifloxacin) was given for a week.

The initial follow up visit were at 1st day, 7th day of post injection. Thereafter they were followed up on 1st and 3rd post IVTA month. BCVA, colour fundus photo and FFA were performed at 1st and 3rd post IVTA month follow up visit. Potential steroid induced injection related complications were also observed. Intra Ocular Pressure (IOP) was measured at every follow up. 2 line improvements in Snellen chart, 50% regression of existing macular oedema and hard exudates and 50% regression of diffuse leakage in FFA were considered a significant improvement.

PHOTOS ON IVTA PROCEDURE

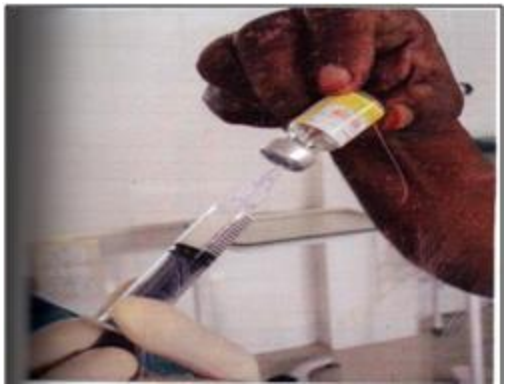


Photo-1: Triamcinolone Acitonide Preparation

Photo- 2: Injection Procedure

OBSERVATION AND RESULTS:

The study population consisted of 100 eyes of 90 patients aged between 30 to 80 years at Assam medical College Hospital, Dibrugarh who were selected to evaluate the efficacy of IVTA among test and control group having DME. Side by side their demographic variations were also observed.

The incidence of DME was seen to the maximum in the age group 51-60 years, 52.5% and 50% in test and control group respectively. The second highest incidence was seen in between 41-50 years, 25% and 24% in test and control group respectively. The lowest incidence was observed in the younger age between 31-40 years where only Test-group having 25% and no patients in control group. With increase in age, the incidence of DME was found to increase (Table-1) and (fig-1).

Table 1: Incidence of Age Distribution among Patients Having DME

Age Group In years	Test Group (40 Patients)		Control Group (50 patients)	
	No	%	No	%
30-40	1	2.5	0	0.1
41-50	10	25	12	24
51-60	21	52.5	25	50
61-70	5	12.5	8	16
71-80	3	7.5	5	10
Total	40	100	50	100

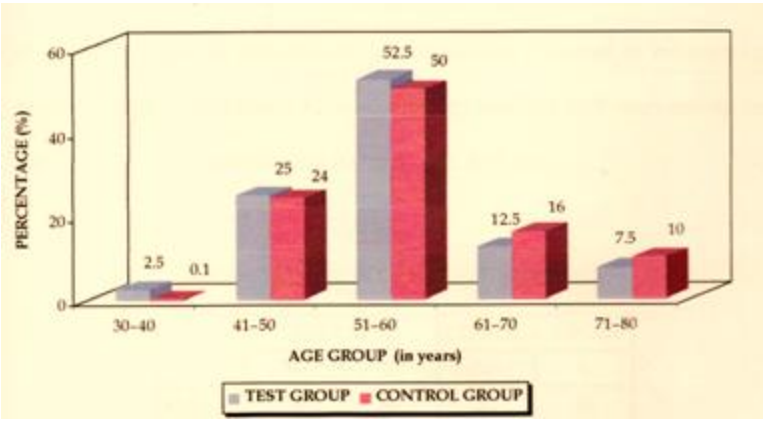


Fig-1: Incidence of Age Distribution among Patients Having DME

Among test group 24 were male and 16 were female whereas 27 were male and 23 were female in control group. Male accounted for 60% and 54% in test and control group respectively whereas female accounted for 40% and 46% in test and control group respectively. So, incidence of DME in relations to gender was almost comparable.

The maximum number of DME cases was found between 11 to 15 years duration of diabetes, (15 and 19 cases) 37.5% and 38% in test and control group

respectively. Patients with > 15 years duration of Diabetes accounted for (9 and 11 cases) 22.5% and 22% in test and control group respectively. Lowest numbers of cases were found with 1-5 years duration. As such maximum number of DME was noticed with duration of 11-15 years of Diabetes and incidence of DME increase with duration of Diabetes. (Table -2) and (fig-2)

Table 2: Duration of Diabetes Mellitus with DME

Duration of DM (in years)	Test Group		Control group	
	No	%	No	%
1-5	6	15	7	14
6-10	10	25	13	26
1-15	15	37.5	19	38
>15	9	22.5	11	22

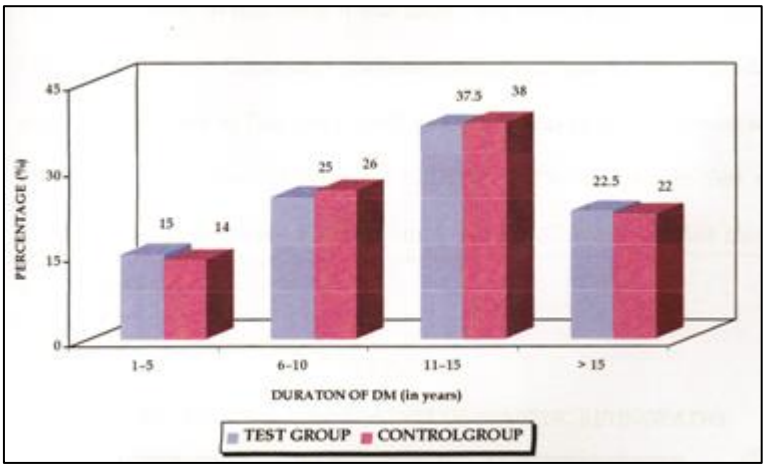


Fig-2: Duration of Diabetes Mellitus with DME

The maximum number of cases belonged to Non Proliferative Diabetic Retinopathy group (NPDR) (27 and 33 cases), 67.5% and 66% in test and control groups respectively while the number of cases of proliferative Diabetic Retinopathy (PDR) were (13and 17 cases) 32.5% and 34% in test and control group respectively showing of more incidence in NDPR group.

Going to changes in visual acuity at the end of 1 month of IVTA injection, 37 eyes (74%) out of 50 test eyes showed significant improvement whereas in control eyes only 10 eyes (20%) out of 50 control eye showed significant improvement. Also in test group, 10 eyes remained static and 6 eyes deteriorated after IVTA (Fig.-3). At end of 3 months, 33 eyes of test group (66%) retained improved visual acuity while 7 eyes of control group (14%) retained improved vision. The difference of improvement among the test and control group at the end of 1 month and 3 months were evaluated by 'Z' test which showed the improvement were statistically significant ($P<0.001$) among the test eyes as compared to control eyes. (Fig-3) and (Fig-4).

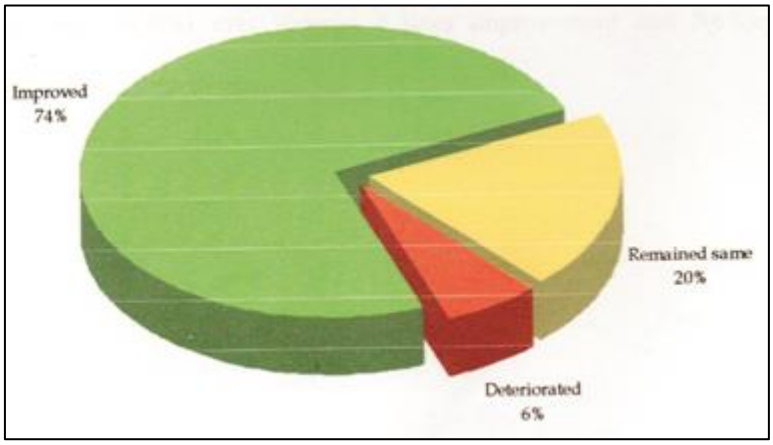


Fig-3: Changes of visual activity among test eyes

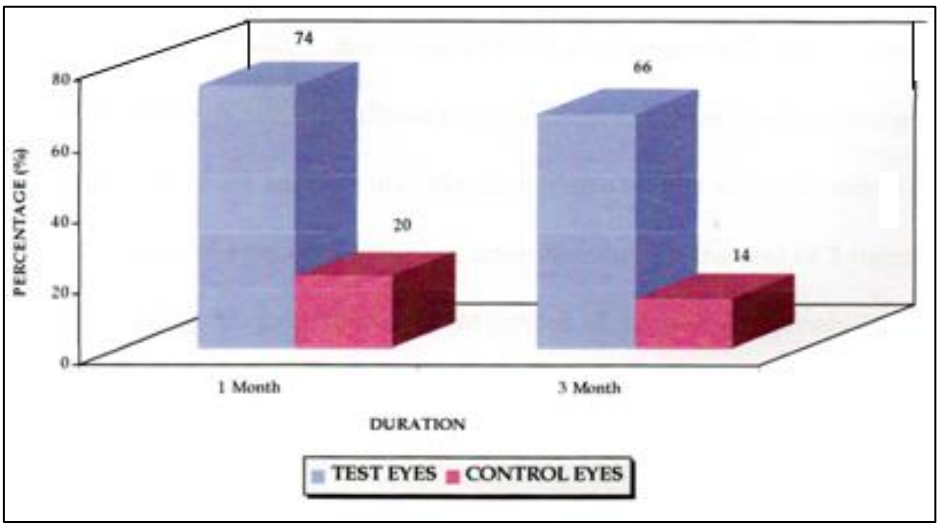


Fig-4: Comparative evaluation of improvement of visual activity among test and control eyes at the end of 1st and 3rd Post IVTA month

As per snellen chart, 37 test eyes (74%) showing improvement of vision at the end of 1st month, 24 eyes (48%) showed 2 line improvement, 10 (20%) eyes showed 3line improvement and 3 (6%) eyes showed > 3 line improvement.

In colour fundus photograph, significant improvement seen in 35 Test eyes out of 50 (70%) while only 12 control eyes (24%) showed improvement at the end of 1st month. At the end of 3rd month, 30 test eyes (60%) retained improvement is fundus picture while only 7 control eyes maintained improved fundus picture. These fundus changes among the two groups were evaluated by 'Z' test which proved that improvement among test eyes were statistically significant (P<0.001) (Fig-5)

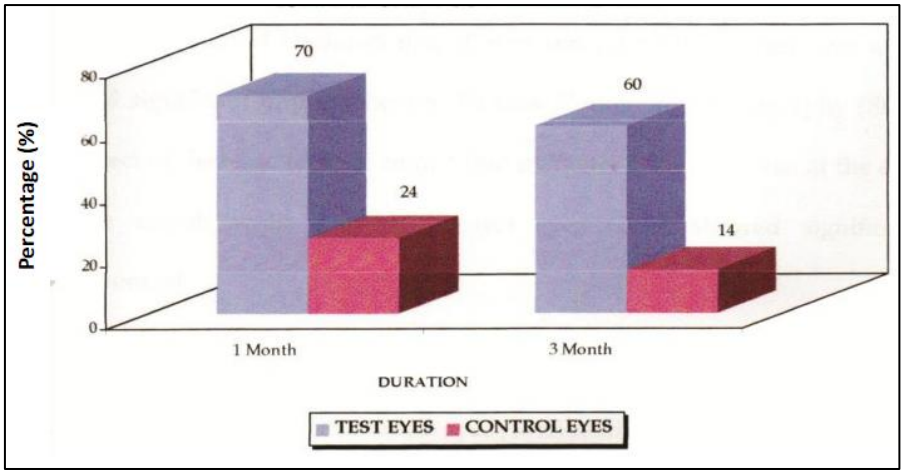


Fig-5: Comparative evaluation of improvement in colour fundus photo among test and control eyes at the end of 1st and 3rd Post IVTA month

As regards Fundus Fluorescein Angiography (FFA), it showed significant improvement in respect of decrease leakage from 1 disc diameter area round fovea centralis in 40 test eyes (80%) and control eyes (20%) at the end of 1st month. While at the end of 3rd month, 34 test eyes (68%) and 8 control eyes (16%) retained improvement. These improvements in FFA were evaluated by 'Z' test showed that improvement was statistically significant (P< 0.001) among test eyes. (Fig-6)

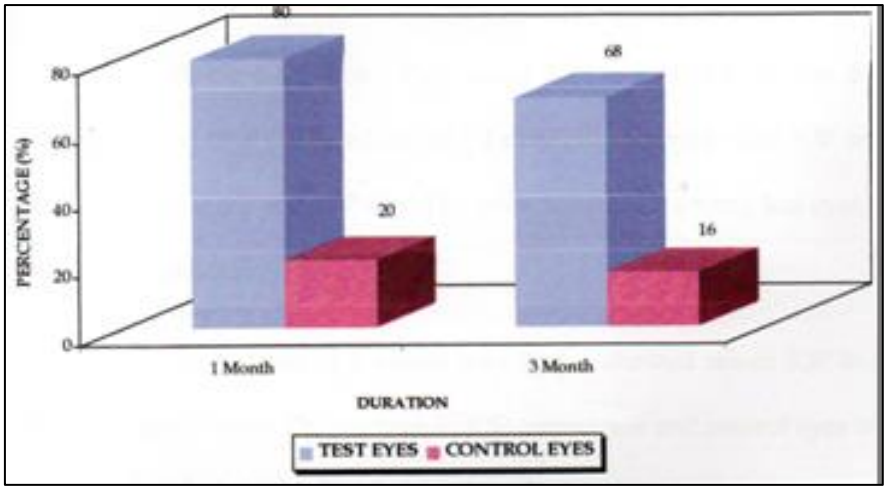
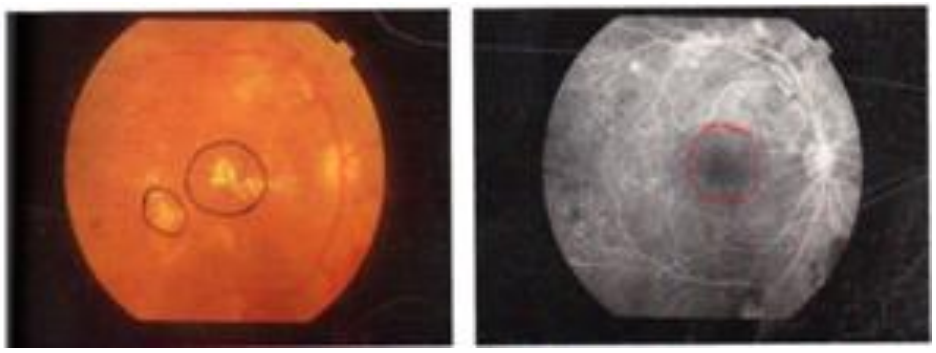


Fig-6: Comparative evaluation of changes in FFA among test and control eyes at the end of 1st and 3rd Post IVTA month

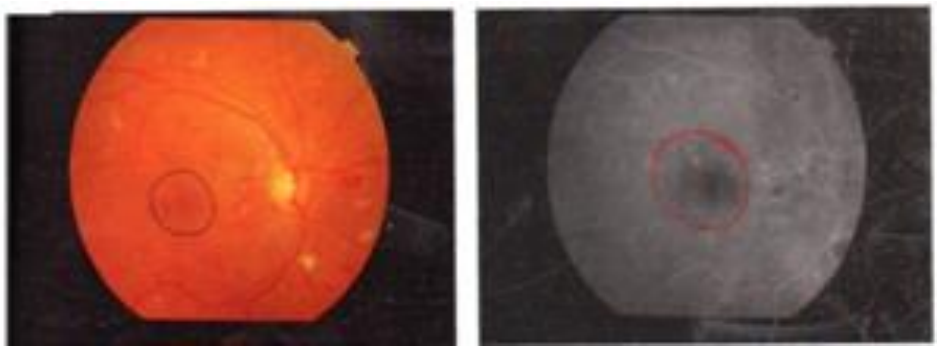
Lastly raised IOP after IVTA was noticed in 5 test eyes (10%) and only 2 control eyes showed IOP rise at the end of 7th day which were controlled with medication. At the end of 1st month only 2 eyes showed 10P rise in both test and control group while none of the eyes of either group had IOP rise at end of 3rd month.

PHOTOGRAPH



Colour Fundus Photo FFA Picture

Photo-3: Pre IVTA



Colour Fundus Photo FFA Picture

Photo-4: Post IVTA (After 1 Month)

DISCUSSION:

The application of intravitreal steroid was first introduced by Machemer *et al.;* [8] for the treatment of Proliferative Vitreoretinopathy. Mc. Cuen *et al.;* [9] demonstreated in an experimental rabbit the lack of ocular toxicity of intravitreal Tniamcinolane acetonide. The use of steroids in DME is linked to their capacity to inhibit the initial arachidonic acid cascade, to determine a down regulation of the cytokines and to attenuate the tearing of hemotoretinal barrier.

Our prospective controlled study demonstrate the efficacy of one intravitreal injection of Triamcinolone acetonide in main aim to improve visual acuity along with changes in the fundus picture and in reducing diffuse leakage in FFA due to diffuse diabetic macular aedema, at least in the short term. This corroborates the result published by Martidis *et al.;* [10] after one intravitreval injection of 4 mg. Triamcinolone for DME and Jones *et al.;* [8] after 25 mg of TA [11].

The result of our study suggest that IVTA is an effective tool in the treatment of DME and our patients established that there is a definite improvement in visual acuity in diffuse DME. The most significant improvement in (Visual acuity) V/A was noted in the 1st month post IVTA, 37 test eyes out of 50 (74%) and 10 control eyes out of 50 (20%) which was retained in 33 test eyes (66%) and 7 control eyes (14%) at the end of 3rd post IVTA month. Besides, 10 eyes (20%) showed no changes and 3 eyes (67%) showed fall of vision. The results of this study are comparable with other studies including that of Jones JB *et al.;* [8] in 2004 [11], who evaluated outcome of IVTA in diffuse DME and concluded that IVTA resulted in visual improvement with no major side effects being observed. They enrolled 26 eyes of 20 patients and mean visual acuity improvement from 3+2.6 Snellen line at 2-6 months was observed. Sutter *et al.;* [12] who found a 55% visual improvement in Snellen chart or more at 3 months after 4mg IVTA. In our study, among 37 improved eyes, 24 showed 2 line improvements, 10 showed 3line and only 3 eyes showed > 3 line improvement.

Colour fundus picture and FFA in post injection period showed a significant improvement after IVTA, in which 35 test eyes (70%) at 1 month and 30 test eyes (60%) at 3 months showed improved fundus picture. Besides, 40 test eyes (80%) at 1 month and 34 test eyes (68%) at 3 months showed significant decrease in leakage. Ciardella AP *et al.;* [13] had rightly come up with similar type of results including re-absorption of hard exudates present in macular area over the follow up period. None of these studies experienced any major complication from IVTA injection. Our study also did not encounter any major complication and side effects.

The main side effects we noticed was IOP elevation which occurred in 5 test eyes (10%) at interval from 7 days to 4 weeks after IVTA which was controlled with Timolol. Previous studies on IVTA administration have reported IOP elevation to occur in 20-80% of patient [10, 11].

In our study, 4mg dose of IVTA was taken empirically as was the same as that injected in most pervious students [14, 10]. However, Jonas J.B. *et al.;* [8] in 2014 injected 25mg TA and reported a duration effect based on V/A of about 7-8 months after IVTA. Hence, further studies are required to define the optimal dose of IVTA.

It is further said that IVTA of 4mg appears to be an effective and relatively safe therapeutic method for diffuse DME [15] which co-relates with our study. IVTA is a promising therapeutic method in the eyes with DME without previous application of laser treatment [16]. Recent studies have even shown that IVTA has a positive effect on those forms of DME that are refractory to Retinal laser treatment [17]. Various studies including that of Masahiko Shimura *et al.;* [18] Liu Q1 *et al.;* [19] etc. demonstrated that Triamcinolone acetonide is more efficient is reducing DME and provided better and longer lasting visual improvement relative to Bevacizumab. Besides, a combination of IVTA and IV Bavacizumab is found to more effective than using IV bevacizumab alone in treating DME [20].

CONCLUSION:

Intravitrual Triamcinolone acetonide in the dose of 4mg appear to be very effective and relatively safe modality of treatment in reducing diffuse diabetic macular odema and seen to have definite potential is improving visual acuity and diabetic fundus picture. The optimum outcome is seen to be maximum at the end of 1st month after IVTA injection and improvement of visual acuity however sustained to a certain extent till the end of 3rd month. The fundus picture and fundus fluorescein angiography measures and compares the DME qualitatively is each follow up visit. IVTA is a favourable and promising therapeutic tool in managing diffuse diabetic macular oedema for certain duration of time with minimal transient side effect. Various current ongoing studies in large scale would definitely provide us more information in more detail about IVTA as first line of treatment, as a therapy for cases refractory to other modalities of treatment as well as an adjuvant/component in combined therapy in managing DME. Further, such work on IVTA will pave the way for finding out more effective and scientific regime and newer molecule in handling vast cases of Diabetic Macular Odema.

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