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Intravitreal Triamcinolone Acetonide in Diabetic Macular Edema

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Abstract: ***Diabetic retinopathy (DR) is the most common microvascular complication of diabetes. The most common cause of vision loss in diabetic retinopathy is diabetic macular edema. Intravitreal injection of corticosteroids (triamcinolone acetonide), constitutes a newer, less destructive treatment modality in the management of diabetic macular edema. Intravitreal triamcinolone acetonide is a favourable and promising therapeutic tool in managing diffuse diabetic macular oedema for certain duration of time with minimal transient side effect.***

Keywords: Diabetic macular edema, OCT, intravitreal triamcinolone acetonide

1. 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] Diabetic retinopathy (DR) is the most common microvascular complication of diabetes.[2] The most common cause of vision loss in diabetic retinopathy is diabetic macular edema. The Wisconsin Epidemiologic Study of Diabetic retinopathy (WESDR)[3] documented the prevalence of macular edema in 11% overall among patients with diabetes.

The optical coherence tomography (OCT) is a modality that helps in the objective assessment of diabetic macular edema. Moreover, OCT is found to be useful in the morphological description of diabetic macular edema. As regards with 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.[4]

Intravitreal injection of corticosteroids (triamcinolone acetonide), constitutes a newer, less destructive treatment modality in the management of diabetic macular edema.

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[5] and is in part 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. 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 edema.[6] Increased diffusion by modulation of calcium channels[7] could also account for the efficacy of the corticosteroids in reducing macular edema.

As the eye comprises only 0.01% of the whole body volume, the best way to achieve optimal concentration of a drug in the eye would be a direct application to its site of action.

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.

2. Materials and Methods

This hospital based, prospective, interventional study was conducted in the Regional Institute Of Ophthalmology, Gauhati Medical College and Hospital, during the period of July 2017 to July 2018. The patients were selected from the outdoor as well as indoor of Regional Institute Of Ophthalmology,Guwahati. A total of 35 eyes of 20 patients were included in the study. Informed consent was obtained from each patient after explaining them the procedure of the study design.

Inclusion criteria included patients with age > 18years, type 1 or 2 Diabetes Mellitus, diabetic Macular Edema affecting the fovea in one or both the eyes, retinal thickness of > 250 microns in central 1mm subfield macula on stratus domain OCT, intraocular pressure < 22mmHg and women of child bearing potential must have a negative pregnancy test at the screening visit.

Exclusion criteria included patients known allergy to agents used in the study,women who are pregnant, nursing or planning a pregnancy, loss of vision or macular edema due to other causes(eg. ARMD, myopic macular degeneration, retinal vein occlusion), history of any treatment for diabetic retinopathy at any time within 3 months of starting the standardized regimen, uncontrolled glaucoma, use of systemic steroids and/or systemic anti-VEGF, recent history of arterial thromboembolic event, and poorly controlled hypertension and any history of chronic renal failure requiring dialysis or renal transplant.

A thorough and complete history was taken and detailed systemic examination was done. Ocular examination was done very meticulously in every patient which included Visual acuity-with LogMar equivalent of standard Snellen`s chart and Snellen`s near vision chart for both eyes,intraocular pressure was recorded, detailed slit lamp examination was done, detailed posterior segment examination was carried out with direct ophthalmoscopy , slit lamp biomicroscopy with 90 D lens for posterior pole and vitreous examination and indirect ophthalmoscopy for peripheral retinal examination.

Colour fundus photography and OCT was obtained at pretreatment, at 1st month, 3rd month and 6th month of post treatment visit.

All patients were informed of the procedure, the possible complications and informed consent was obtained. A commercially available Triamcinolone (4mg/0.1ml) was prepared for each patient. One day prior to the injection, topical antibiotic eye drop (moxifloxacin) was started in the planned eye. Adequate papillary dilatation was done. Povidine iodine(10%) painting was done. Following this , a sterile eyedrape was applied and the eyelids were separated with a wire speculum. Topical anesthetic drop (lignocaine 4 %) was instilled and 5% povidine iodine solution was instilled into the conjunctival sac then washed off. 0.1 ml (4mg) of Triamcinolone was drawn in a 1 cc syringe and fitted with 27 g needle. The injection site was usually the superotemporal quadrant and injected 3.5 mm and 4 mm from limbus in pseudophakic and phakic eyes respectively. After injection, the needle was removed simultaneously with the application of a cotton tipped applicator (dipped with 1 drop of betadine and 1 drop of topical antibiotic eye drop) over its entry site to prevent regurgitation of the inject material. Pad and bandaging was done for 24 hours. All patients were given tab acetazolamide 250mg half tablet 2 times a day, tab pantaprazole 40mg before food, tab diclonac 50 mg after food for the same day. Dressing was done next day with topical antibiotic eye drop. IOP was checked and pupils dilated to look for any anterior or posterior segment inflammation. Patients were instructed topical antibiotic (Moxifloxacin) eye drop 1 hourly for 1 day followed by 6 times daily for 2 weeks.

The following study parameters were evaluated 1 month, 3 months and 6 months after the proposed procedure: visual acuity, central macular thickness as measured by OCT, incidence of any side effects such as rise in intraocular pressure (IOP), inflammation or endophthalmitis, any systemic side effect such as rise in BP or any thromboembolic effect.

The data were presented as the mean ± standard deviation. Statistical differences between pre and post clinical data were were assessed using one-way ANOVA test within the group. . A p-value of less than 0.05 was considered to be statistically significant.

3. Results and Observations

The study enrolled 25 subjects, of which 20 patients lost to follow up. Thus, a total number of 35 eyes of 20 subjects were included in the study.

The age at presentation varied from 45-74 years and and most of the patients (50%) belonged to the age group 51-60 years.
The mean age of presentation was 56.85 years with SD of 7.66 years.

Table 1: Age at Presentation of the Patients

Age (in Range) in Years	Frequency	Percentage (%)
<30	0	
31-40	0	
41-50	4	20
51-60	10	50
61-70	5	25
71-80	1	5
TOTAL	20	100
MEAN±SD	56.85±7.66	
MEDIAN	55	
RANGE OF AGE	45-74	

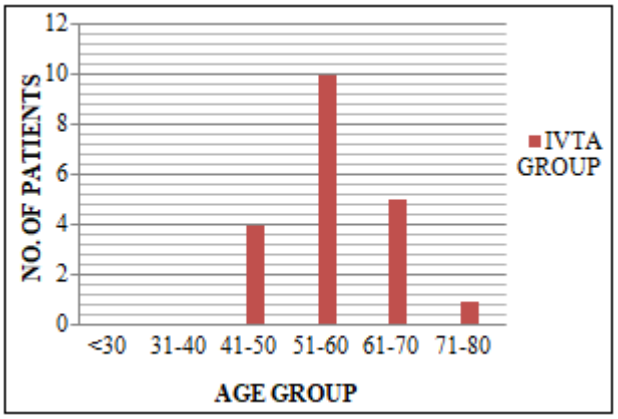

Figure 1: Bar Diagram Showing Age at Presentation

Out of 20 patients, 13 (65%) were males and 7 (35%) were females.

In the present study, the duration of diabetes mellitus in the patients, ranged from 5 years to 22 years. Among 20 patients, 10 (50%) had diabetes mellitus for 11-20 years, 9 patients (45%) had diabetes for less than 10 years and only one patient (5%) had diabetes for more than 20 years. Mean duration of diabetes was found to be 11.9±4.11 years and median duration was found to be 11 years.

Table 2: Duration of Diabetes in Both Groups

Duration of DM (in years)	No. of Patients	Percentage
<10 Years	9	45
11-20 Years	10	50
>20 Years	1	5
Total	20	100
Mean±SD	11.9±4.11	
Median	11	
Range	5-22 Years	

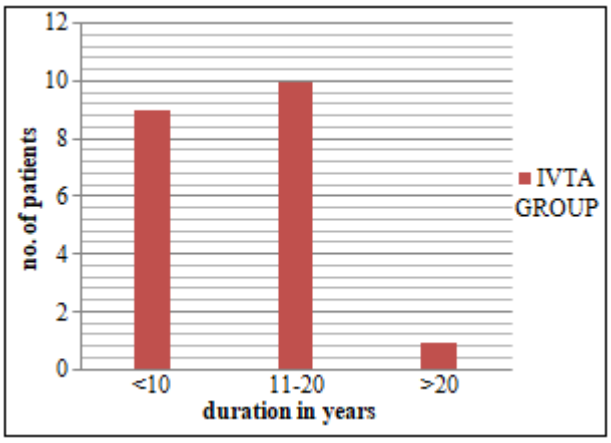

Figure 2: Bar Diagram Showing No. of Patients in Relation To Duration of Diabetes Mellitus

Out of 35 eyes, 94.29% of eyes were associated with NPDR and 5.71% were associated with PDR. It shows that most of the patients, whose loss of vision was due to DME, were in NPDR stage. Among NPDR stage, out of 35 eyes, maximum number of eyes (19) associated with DME had moderate NPDR which was found in 54.28%. The rest 12 eyes (34.28%) were in severe NPDR stage, and 2 eyes were in very severe NPDR stage.

With respect to change in visual acuity, we found that improvement in BCVA was significant throughout 6 month follow up with maximum improvement seen at 3 months. At 1 month, visual acuity improved to logMAR (0.498±0.198) and at 3 months improved to logMAR (0.346±0.158) which were statistically significant ($p<0.001$). Baseline visual acuity improved from logMAR (0.698±0.223) to logMAR (0.440±0.137) at 6 months which was also statistically significant ($p<0.001$).

Table 3: Showing Logmar Visual Acuity (Snellen`S Equivalent) at 1 Month, 3 Months and 6 Months

	Baseline	At 1 Month	At 3 Months	At 6 Months
Mean	0.698	0.498 (P<0.001)	0.346 (p<0.001)	0.440 (p<0.001)
SD	0.223	0.198	0.158	0.137
Median	0.600	0.480	0.300	0.438
Lower Confidence Limit	0.621	0.430	0.292	0.393
Upper Confidence Limit	0.774	0.556	0.401	0.488

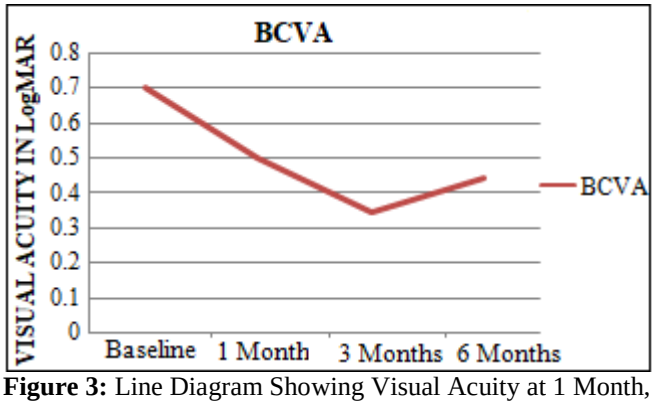

Figure 3: Line Diagram Showing Visual Acuity at 1 Month, 3 Months and 6 Months

With respect to change in central macular thickness (CMT), we found that baseline mean central macular thickness decreased considerably throughout the study period from 389.94±68.20µm to 310.11±39.80µm and the maximum decrease was seen at 3 months to 265.69±41.48µm.The mean decrease in CMT throughout the 6 month follow up was statistically significant ($p<0.001$).

Table 4: Mean Central Macular Thickness at Baseline, 1 Month, 3 Months and 6 Months

	Baseline	At 1 Month	At 3 Months	At 6 Months
Mean	389.94	326.06 (P<0.001)	265.69 (P<0.001)	310.11 (P<0.001)
SD	68.20	41.37	41.48	39.80
Median	384	315	261	310
Lower Confidence Limit	366.51	311.84	251.43	309.35
Upper Confidence Limit	413.37	340.27	279.94	310.88

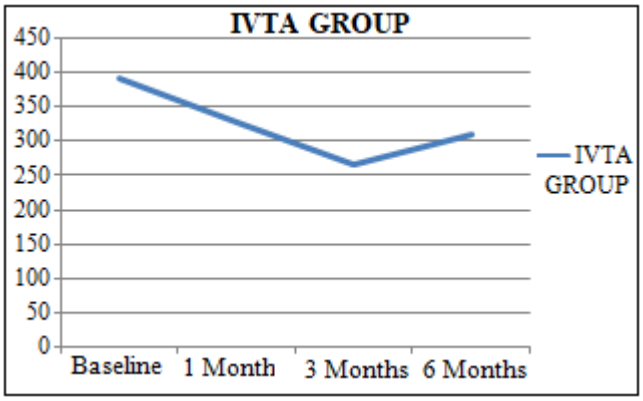

Figure 4: Line Diagram Showing Central Maculr Thickness at Baseline, 1 Month, 3 Months and 6 Months

2 out of 35 eyes had sub conjunctival haemorrhage, which resolved completely within 2 weeks. At 1 month follow up, 3 out of 35 eyes in the IVTA group had raised IOP. Whereas, at 3 months follow up, further 2 eyes had raised IOP in the IVTA group which was managed conservatively. 3 patients had developed cataract at 6 months follow up.

4. Discussion

Corticosteroids also may work through multiple mechanisms of action. They are known to reduce vascular permeability, reduce blood–retinal barrier breakdown, down-regulate VEGF production, and inhibit some matrix metalloproteinase. Some studies have evaluated this drug effect in DME.[8,9]

Penfold et al a(1995),[10] in a pilot study demonstrated that triamcinolone acetonide; a longer acting corticosteroid was well tolerated in patients with exudative ARMD. From that time onwards, intravitreal triamcinolone acetonide as an ophthalmic tool is gaining rapid popularity and acceptability among physicians in treating conditions such as macular edema.

The human study done by **Beer et al. (2003),**[11] concluded that the mean elimination for nonvitrectomised eyes was 18.6 days while for vitrectomised eyes was only 3.2 days.

Given the calculated half- life, a single 4 mg intravitreal injection of triamcinolone could be expected to last approximately three months in a non vitrectomised eye. Thus it appears that there is dose dependant retention in the vitreous cavity with higher doses being retained for longer periods. Therapeutic levels appear to be present in the vitreous for about three months.

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) VA was noted in the 3rd month post IVTA. However, the effect on improving VA blunted somewhat at 6 months follow up.

Jonas JB et al (2003),[12] found mean ± SD visual acuity improved significantly (P<.001) from 0.12 ± 0.08 at baseline of the study to a maximum of 0.19 ± 0.14 during the follow-up period. Improvement in visual acuity was statistically significant at the examinations performed 6 weeks (P = .003), 10 weeks (P = .01), 5 months (P = .03), and 6 months (P = .02) after the injection.

In a study by Gibran SK et al (2006),[13] Preoperative VA (LogMar) (mean±SD) was 0.905±0.23. At 1 month postoperatively, VA (mean±SD) improved from 0.905±0.23 to 0.605±0.28 (P<0.001). At 3 month postoperatively, VA (mean±SD) was 0.555±0.29 (P<0.001) and at 6 months postoperatively, VA (mean±SD) was 0.730±0.30 (P<0.04). Thus the improvement in visual acuity was statistically significant.

Change in central macular thickness was also significant throughout the study period with maximum improvement seen at 3rd month. However, the effect on reducing central macular thickness blunted somewhat at 6 months follow up.

Massin P et al (2004),[9] reported that before injection, CMT was 509.6±143.5 µm (mean ± standard deviation [SD]) in injected eyes, versus 474.4±82.6 µm in control eyes. Four weeks after injection, it was 207.3±44.2 µm in injected eyes and 506.7±122.4 µm in control eyes (P<0.001, bilateral Wilcoxon test for paired samples), and after 12 weeks, 207±96.7 µm and 469.3±117.6 µm, respectively (P = 0.005). The difference between the CMTs of injected and control eyes was no longer significant at 24 weeks because of the recurrence of macular edema in 5 of 12 injected eyes. This study concluded that intravitreal injection of triamcinolone effectively reduces macular thickening due to diffuse diabetic macular edema, at least in the short term.

In a study by GibranSK et al (2006),[13] at 1 month postoperatively, OCT macular thickness (mean±SD) decreased from 418.7±104.2 μm at baseline to 276.9±72.6 μm (P<0.0001). At 3 month postoperatively, OCT macular thickness (mean±SD) was 250.6±53.1 μm (P<0.001) and at 6 month postoperatively, OCT macular thickness (mean±SD) was 308.8±87.3 μm (P<0.01). This study further reported that at 6 months post IVTA injection, VA showed a tendency to decline and this was associated with an increase in central macular thickness on OCT. These findings support the short-term effectiveness of IVTA use.

The main side effects we noticed was IOP elevation which occurred in 5 out of 35 eyes at interval after IVTA which was controlled with antiglaucoma drugs. Jonas JB et al.(2003),[12] reported rise in IOP in about 34.6% of eyes which normalized at 5th month follow up. However Jonas JB used 25 mg as dose of intravitreal triamcinolone injection. No systemic side effects has been encountered in our study.

It is further said that IVTA of 4mg appears to be an effective and relatively safe therapeutic method for diffuse DME which co-relates with our study.[14]

5. Conclusion

Intravitreal 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 reducing the central macular thickness. IVTA is a favourable and promising therapeutic tool in managing diffuse diabetic macular oedema for certain duration of time with minimal transient side effect. However, studies with longer follow up period is needed to evaluate the safety profile and efficacy of IVTA in the treatment of diabetic macular edema.

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