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ORIGINAL ARTICLE

INTRAVITREAL TRIAMCINOLONE IN DIABETIC MACULAR EDEMA:A COMPARATIVE STUDY OF 1MG AND 4MG DOSES

Sikander A. K. Lodhi[1], Sudhakar Reddy[2], Santosh Devulapally[3]

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ABSTRACT: Macular edema is a frequent manifestation of diabetic retinopathy and animportant cause of visual disturbance in diabetic patients. **AIM:** To compare the efficacy and safety of 1mg and 4mg intravitreal triamcinolone acetonide (IVTA) in the management of diabetic macular edema. **SETTING:** Sarojini Devi Eye Hospital, Hyderabad. **MATERIAL AND METHODS:** 42 eyes of 42 patients with diabetic macular edema were randomly assigned toreceive either 1-mg or 4-mg dose of Intravitreal triamcinolone acetonide (IVTA). Each patient underwent a complete comprehensive eye examination at baseline andat each visit.Fundus fluorescein angiography and optical coherence angiographywas done at baseline and at 1, 3 and 6 months.BCVA, lens status, IOP wererecorded at each follow up visit. Each patient's BCVA was measured in snellen's lines and converted into logarithm of minimum angle of resolution (log MAR) scale for analysis. **STATISTICAL ANALYSIS USED:** The data were statistically evaluated using the Wilcoxon signedrank test, Mann-Whitney test and t tests wherever applicable. A p value of lessthan.05 was considered significant. **RESULTS:** There was no statistically significant difference in the mean foveal thickness measurement at baseline (p=.723) or at 3rd month (p=.878) between the sub-groups. BCVA significantly improved from baseline to subsequent visits in both the groups, but there was no statistically significant difference observed in the mean baseline BCVA between the two sub-groups (p=.754). There was no statistically significant difference observed in IOP between the two sub-groups at any follow up visit. **CONCLUSIONS:** The results of our study suggest that 1-mg dose of IVTA is as effective as 4-mgdose of IVTA in improving the functional and anatomical outcome in macularedema associated with diabetic retinopathy.

KEYWORDS: Triamcinolone, Macular edema, Diabetic retinopathy, Intraocularpressure.

INTRODUCTION: Diabetic retinopathy is an important cause of macular edema causingserious visual impairmentin young- to middle-agedadults.[1] The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a population-based study in southern Wisconsin, estimated that after 20 years of known diabetes, the prevalence of diabetic macular edema (DME) was approximately 28% in both type 1 and type 2 diabetes.[1] Laser treatment remains gold standard in the management ofdiabetic retinopathy, but isassociated with side effects.[2] Despite itsproven effect, recoveryofvision is difficult with lasertreatment. The use of intravitreal pharmacotherapeutic agents have increased recently to treat diabetic macular edema. Steroids (triamcinolone acetonide and steroid slow release implants) and anti-vascular endothelial growth factors (Anti VeGF) use has increased enormously in treating diabetic macular edema.[3] Intravitreal triamcinolone acetonide, asuspension, is effective for three months in a non-vitretomized eye, so repeated injections may benecessary.[4] It can cause significant side effects, like rise in intraocular pressure and progressionof Nuclear sclerosis.[5,6] To overcome these side effects, a dose of 1mg/0.1ml can be tried andcompared with the usual 4mg/0.1ml for

safety and effectivity. It was anticipated that the 1-mg dose would have a lower risk of steroid-related adverse events.

Primary Objectives: To compare the best corrected visual acuity (BCVA) scores between 1-mg and 4-mg doses of IVTA injections. Secondary objectives: Comparison of steroid related complication rates as evaluated byintraocular pressure (IOP) measurements and cataract progression.

MATERIAL AND MEHODS: This study was a prospective comparative interventional study conducted on patients attending the Retina department of Sarojini Devi Eye Hospital, Hyderabad from December 2010 to May 2012. 42 eyes of 42 patients with diabetic macular edema were randomly assigned to receive either 1-mg or 4-mg dose of Intravitreal triamcinolone acetonide (IVTA). Diagnosis, prognosis, various treatment options and possible complications were explained to thepatients and their informed consent taken before enrolment.

Inclusion Criteria: Macular edema due to retinal vein occlusion and diabetic retinopathy BCVA worse than 6/12 Macular edema diagnosed by slit lamp bio microscopy FFA showing evidence of leakage Foveal thickness of >200μ on OCT.

Exclusion Criteria: Macular edema due to other causes Significant cataract estimated to have reduced visual acuity Any form of treatment (Intravitreal or peribulbar steroids, lasers) 4 months prior to injection Any retinal photocoagulation for DME or panretinal photocoagulation in the prior 4 months. Prior parsplanavitrectomy Cataract surgery or YAG capsulotomy 4 months prior to injections Any vitreo-macular traction on OCT Patients with thin sclera Glaucoma, Ocular hypertension, Psuedoexfoliation Aphakia Each patient underwent complete comprehensive ocular examination, including best corrected visual acuity (BCVA), slit lamp examination of anterior segment and posterior segment (Using90D lens), Indirect ophthalmoscopy and Goldmann applanation tonometry at baseline and ateach visit. FFA and OCT was done at baseline, 1 month, 3 months and 6 months whenever possible. Each patient's BCVA was measured in snellen's lines and converted into logarithm ofminimum angle of resolution (log MAR) scale for analysis. All the patients were investigated for blood and urine sugars, Glycated Hb, Hb%, Serum lipids, anaemia, Serum creatinine and blood urea. Patients with abnormal parameters and with hypertension were referred to the physician for the control of systemic factors before giving intravitreal injection. All the study eyes received topical Gatiflox eye drops one day before and on the day of injections. For the intravitreal injection, after instilling topical anaesthetic drops, asepsis was achieved by surface preparation of eye including the lashes using 2-3 drops of 5%povidineiodine.

Then 0.1ml (either 1-mg or 4-mg) of triamcinolone acetonide was slowly injected using 1 ml syringe through pars plana in the inferotemporal quadrant 3.5mm posterior to limbus in psuedophakic eyes and 4mm posterior to limbus in phakic eyes keeping the tip ofthe needle in view throughout the procedure. A preservative-free formulation of triamcinolone was used in this study in an effort to avoid the post injection intraocular inflammation. The patients were reviewed the next day and proper placement of the drug confirmed. Patients were instructed to use topical Gatiflox eye drops 4 times a day for 1 week after the injection. Patients were re-examined at 1 day, 1 week, 1 month, 3 months, and 6 months after the injection. The minimum period of follow up was 6 months. The data thus collected was subjected to statistical analysis. Snellen's VA was converted to the

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logarithm of the minimum angle of resolution (log MAR) and averaged for the purpose of statistical analysis. Statistical analysis was performed using commercial statistical software (IBM SPSS for Windows, version 20). The data were statistically evaluated using the Wilcoxon signed rank test, Mann-Whitney test and t tests wherever applicable. A p value of less than 0.05as considered significant.

RESULTS AND OBSERVATIONS: Out of the total 42 patients, 1 patient receiving 1-mg of IVTA and 1 patient receiving 4-mg of IVTA were lost to follow up. Forty patients completed 6 months follow up. Therefore 40 eyes of40 patients with a minimum follow up period of 6 months were included for analysis. Variables including age, gender, BCVA, lens status, IOP were recorded at baseline. BCVA, lens status, IOP were recorded at each follow up visit. FFA was done at baseline, one, third and sixth months post injection. The data after statistical evaluation were presented as Mean ± SD.

Gender	Number = 40	
	1-mg (N=20)	4mg (N=20)
Males	13	15
Females	7	5

Table 1: Gender Distribution

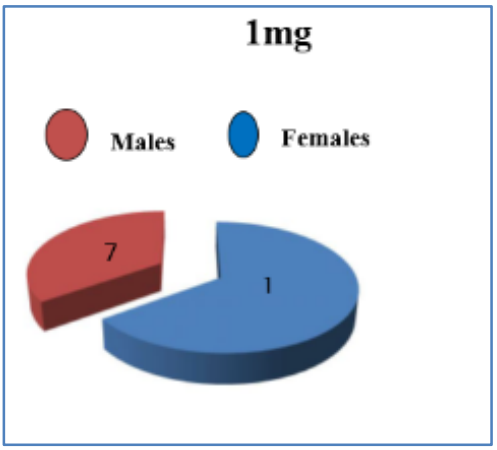

Figure 1

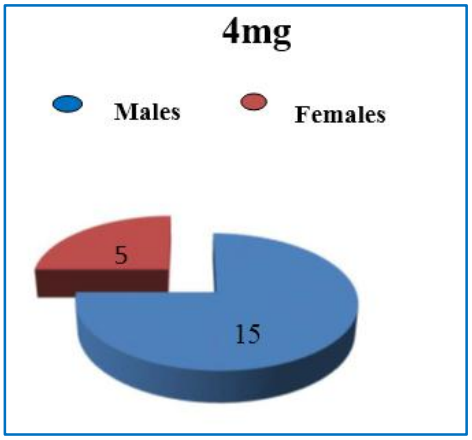

Figure 2

Age Distribution: The mean age was 56.1±7.26 in 1-mg sub-group and 54.4±11.00 in 4-mg sub-group.

Age	1mg (n=20)	4mg(n=20)
Mean+/-SD	56.1±7.26	54.4±11.00
Range	42-70	21-70

Table 2

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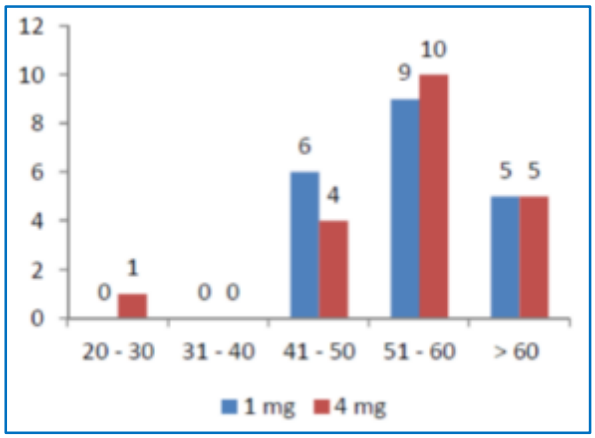

Figure 3

Type of Diabetic Retinopathy: Out of 20 eyes in 1-mg sub-group 10 eyes (50%) were diagnosed as PDR with CSME, 5 eyes (25%) as severe NPDR with CSME and 5 eyes (25%) as moderate NPDR with CSME. Out of20 eyes in 4-mg sub-group 7 eyes (35%) were diagnosed as PDR with CSME, 7 eyes (35%) assevere NPDR with CSME and 6 eyes (30%) as moderate NPDR with CSME.

Figure 4

Duration of Diabetes: The mean(±SD) duration of diabetes was 10.70±5.09 (Range 1-18) years in 1 mg sub-group and13.65±5.01 (Range 1-25) years in 4 mg sub-group.

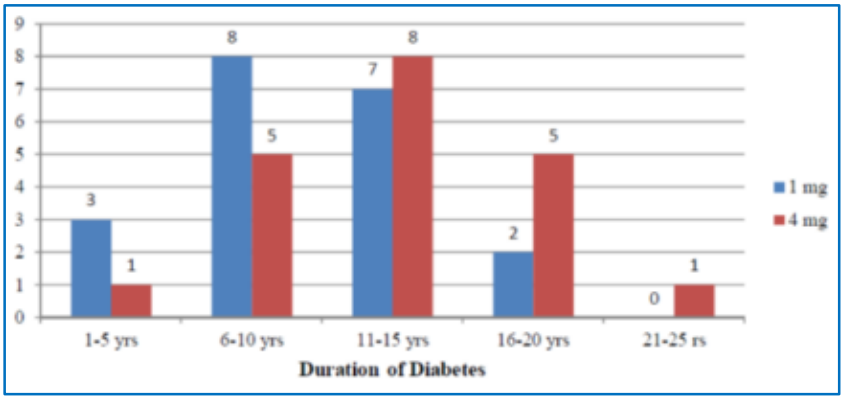

Figure 5

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Foveal Thickness: OCT could be obtained at baseline and at 3 months in 11 patents in 1-mg sub-group and 15patients in 4-mg sub-group. The mean foveal thickness significantly improved from baseline inboth the sub-groups. There was no statistically significant difference in the mean foveal thickness measurement at baseline (p=.723) or at 3rd month (p=.878) between both the sub-groups.

	1mg (N=11)	P Value	4mg (N=15)	P Value	P between sub-groups
Baseline	376.45+-175.48		371.13+-158.48		.723
3 Months	233.00+-129.29	.016	211.47+-126.87	.001	.878

Table 3

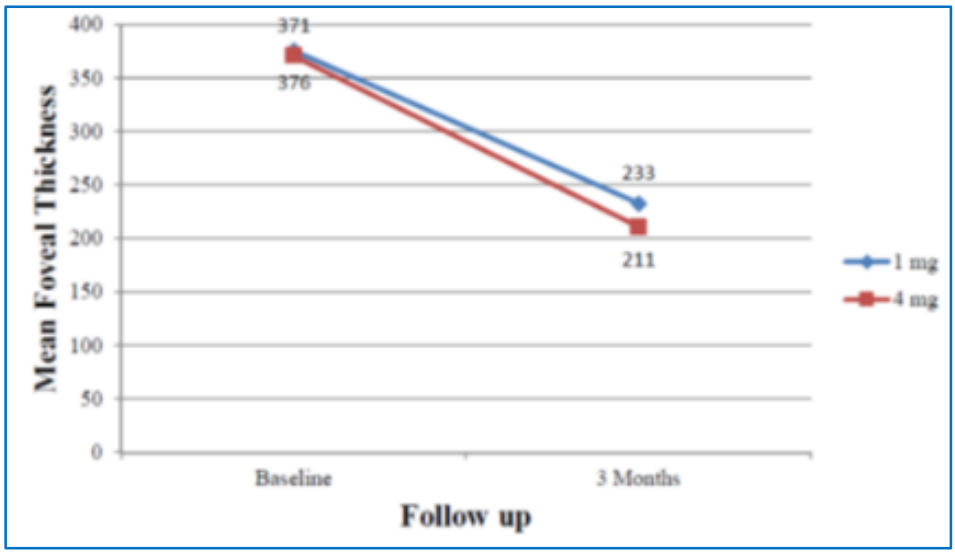

Figure 6

Figure 7a &7b: OCT, Pre IVTA 1mg showing cystic spaces and subfoveal neurosensory detachment.

Fig. 7a

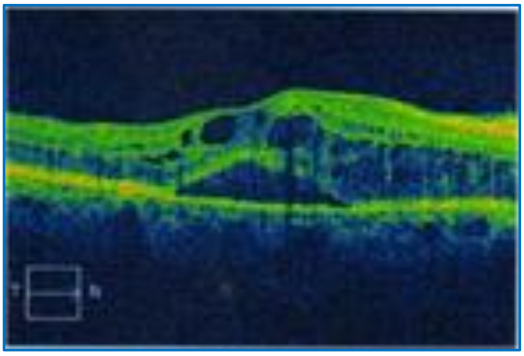

Fig. 7b

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Figure 8a & 8b: Post IVTA 1mg, OCT at 3months showing decreased foveal thickness.

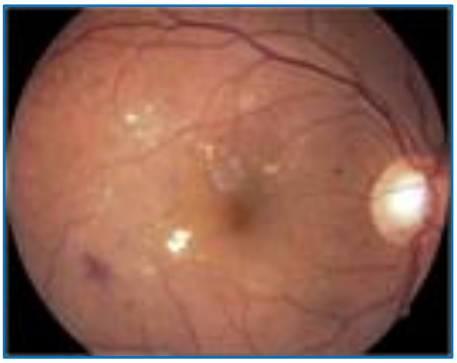

Fig. 8a

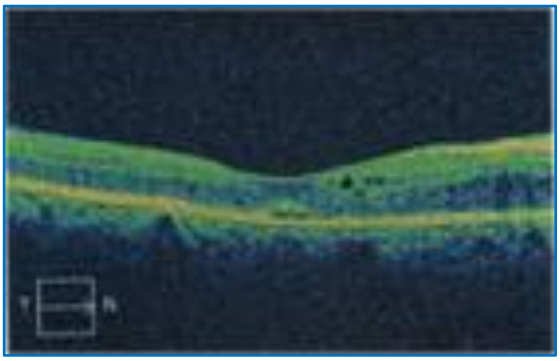

Fig. 8b

Figure 9a & 9b: Pre IVTA 4mg OCT shows increased foveal thickness with cystic spaces.

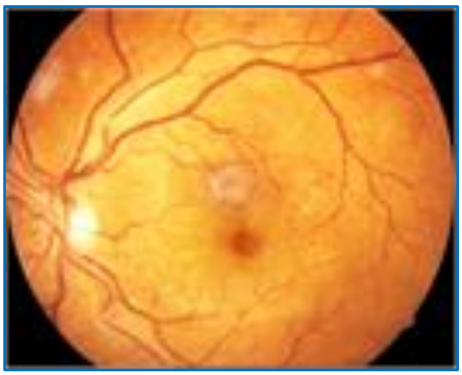

Fig. 9a

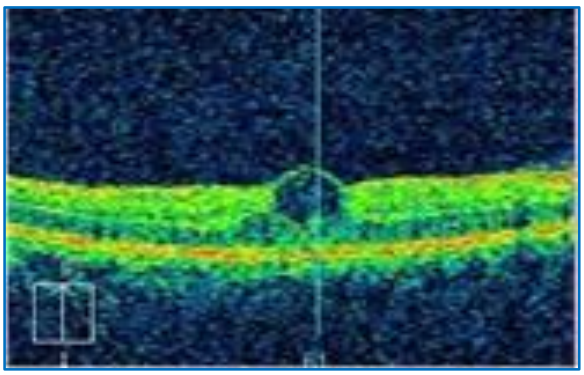

Fig. 9b

Figure 10a &10b: Post IVTA 4mg OCT shows decreased fovial thickness with normal foveal contour.

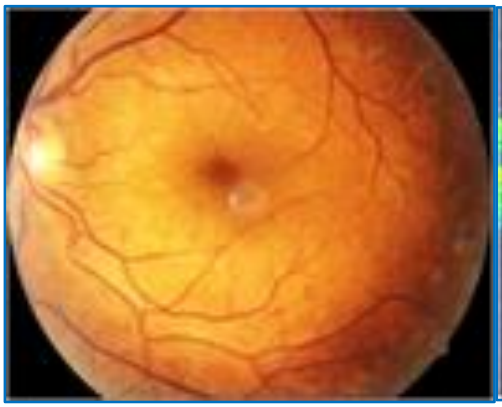

Fig. 10a

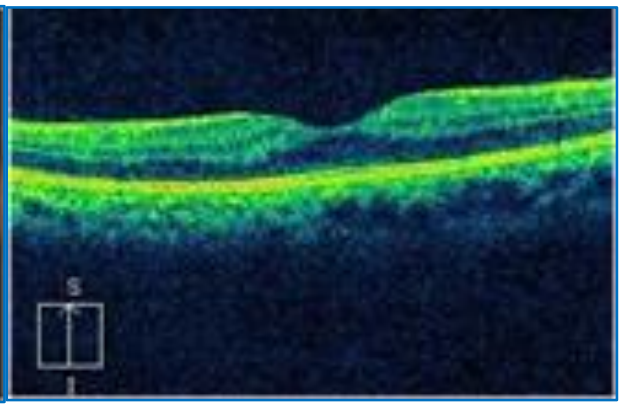

Fig. 10b

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Mean change in BCVA:

Visit	1-mg (n=20)	p value	4-mg (n=20)	p value	p between sub-groups
Baseline	1.01±0.37		1.05 ± 0.52		.754
1st Day	0.96 ± 0.36	0.114	0.74 ± 0.48	<.0001	.192
1 Week	0.84 ± 0.32	<.0001	0.70 ± 0.46	<.0001	.301
1 Month	0.62 ± 0.39	<.0001	0.68 ± 0.46	<.0001	.758
3 Months	0.47 ± 0.42	<.0001	0.69 ± 0.51	<.0001	.183
6 Months	0.57 ± 0.44	<.0001	0.68 ± 0.51	.001	.461

The mean (±SD) baseline BCVA was 1.01±0.37 in 1-mg sub-group and 1.05±0.52 in4-mg sub-group. In 1-mg sub-group, the mean BCVA was significantly improved from baseline to0.84±0.32 (p<.0001), 0.62±0.39 (p<.0001), 0.47±0.42 (p=<.0001), 0.57±0.44 (p=<.0001) at 1week, 1 month, 3 months and 6 months respectively. In 4-mg sub-group, the mean BCVA wassignificantly improved from baseline to 0.74±0.48 (p<.0001), 0.70±0.46 (p<.0001), 0.68±0.46(p<.0001), 0.69±0.51 (p<.0001), 0.68±0.51 (p=.001) at 1 day, 1 week, 1 month, 3 months, 6months respectively. There was no statistically significant difference observed in the meanbaseline BCVA between the two sub-groups (p=.754). There was no statistically significantdifference observed in mean BCVA between the two sub-groups at any follow up visit.

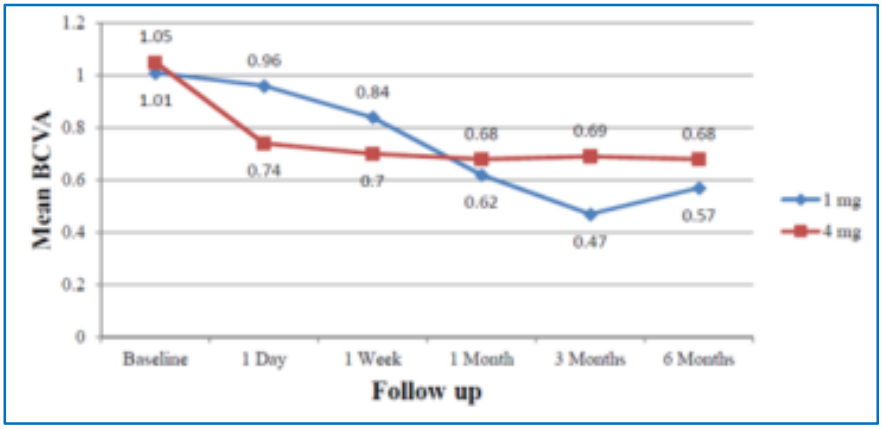

Figure 11

Visual Acuity Change in Snellen's Lines:

Change In Snellen's lines	1-mg	4-mg
1-3 lines	6(30%)	9(45%)
4-5 lines	10(50%)	7(35%)
>5lines	3(15%)	3(15%)
Not responded	1(5%)	1(5%)
Worsening after initial improvement	2	2

Table 4

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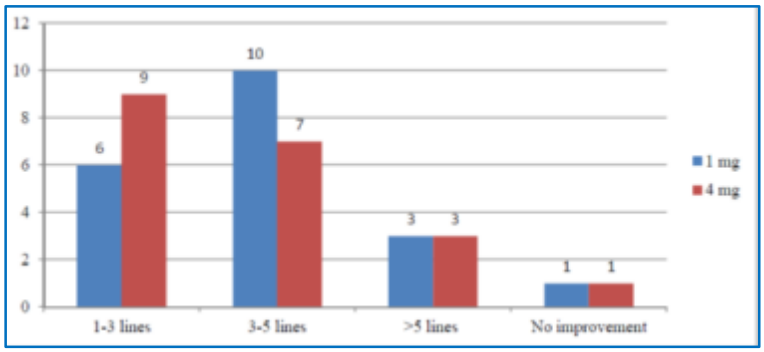

Figure 12

Mean change in IOP during follow up period:

Visit	1-mg (n=20)	p value	4-mg (n=20)	p value	p between sub-groups
Baseline	16.1 ± 2.63		16.2 ± 2.23		.898
1st Day	15.7 ± 2.61	.530	16.3 ± 2.36	.834	.452
1 Week	17.1 ± 2.63	.056	17.6 ± 2.94	.012	.575
1 Month	19.1 ± 4.51	.001	19.8 ± 6.25	.004	.687
3 Months	17.5 ± 3.17	.031	18.2 ± 3.48	.005	.511
6 Months	16.7 ± 2.27	.230	17.2 ± 1.88	.038	.453

The mean(±SD) baseline IOP was 16.1±2.63 in 1-mg sub-group and 16.2±2.23 in 4-mg sub-group. In 1-mg sub-group, the mean IOP was significantly increased from baseline to19.1±4.51 (P=.001), 17.5±3.17 (P=.031) at 1 month and 3 months respectively. In 4-mgsubgroup, the mean IOP was significantly increased from baseline to 17.6±2.94 (P=.012),19.8±6.25 (P=.004), 18.2±3.48 (P=.005), 17.2±1.88 (P=.038) at 1 week, 1 month, 3 months, 6months respectively. There was no statistically significant difference observed in the meanbaseline IOP between the two sub-groups (P=.898). There was no statistically significantdifference observed in IOP between the two sub-groups at any follow up visit.

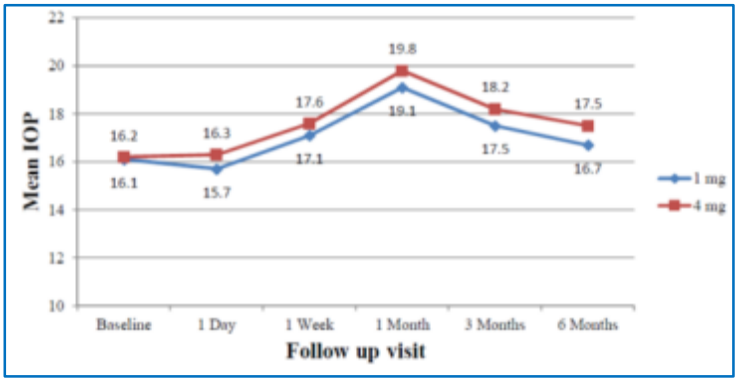

Figure 13

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Incidence of Elevated IOP/Glaucoma:

Within and including 6 months	1-mg	4-mg
Increase ≥ 5 mmHg from baseline	6(30%)	8(40%)
Increase ≥ 10 mmHg from baseline	1(5%)	3(15%)
30% increase from baseline	6(30%)	9(45%)
IOP lowering medication	4(20%)	6(30%)
Glaucoma Surgery Trabeculectomy	0	1(5%)

Table 5

6 eyes (In 1-mg sub-group) and 8 eyes (In 4-mg sub-group) had an elevation of ≥5mmHg of IOP from baseline. One eye (in 1-mg sub-group) and 3 eyes (In 4-mg sub-group) hadan elevation of ≥10 mmHg of IOP from baseline. Six eyes (in 1-mg sub-group) and 9 eyes (In 4-mg sub-group) had ≥30% elevation from baseline. IOP lowering medication required in 4 eyes(In 1-mg sub-group) and 6 eyes (in 4-mg sub-group). One eye underwent trabeculectomy in4-mg sub-group for refractory elevation of IOP.

Cataract:

Within and including 6 Months	1-mg (N=15)	4-mg (N=19)
Lenticular initiation/progression		
Nuclear Sclerosis	1	2
Posterior Subcapsular Cataract	0	2
Cataract Surgery	0	1

Table 6

15 eyes were phakic and 5 eyes were pseudophakic at presentation in 1 mg subgroup. In 4-mg sub-group, 19 eyes were phakic and 1 eye was pseudophakic at presentation. Out of 15 eyes, 1 patient showed increase in nuclear sclerosis in 1-mg sub-group. Out of 19 eyes, 2patients showed increase in nuclear sclerosis and 2 patients developed posterior subcapsular cataract in 4-mg sub-group. In 4-mg sub-group, 1 patient underwent cataract surgery 6 months post injection.

Other Complications: No other potential injection related complications like vitreous haemorrhage, retinal detachment, endophthalmitis, ptosis, globe perforation or orbital fat atrophy were encountered in our study groups.

DISCUSSION: We observed that in 1-mg sub-group, 16 eyes (80%) showed at least 1 line improvement, 8 (40%) eyes showed more than 3 lines improvement and 2 (10%) eyes showed more than 5 lines of improvement at the end of 6 months follow up. In 4-mg sub-group, 17 eyes(85%) showed at least 1 line improvement, 8 (40%) eyes showed more than 3 lines improvement and 2 (10%) eyes showed more than 5 lines of improvement at the end of 6 months follow up.

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One eye in each sub-group showed worsening of visual acuity after initial improvement. DRCR net study[7] concluded that at 4 months, mean visual acuity was better in the 4-mg IVTA group than in the 1-mg IVTA group. By 1 year, there were no significant differences in visualacuity among groups.

In our study both the sub-groups showed decrease in foveal thickness from baseline. At 3 months the decrease in foveal thickness was similar in both the sub-groups. In DRCR net study,[7] the OCT results generally paralleled the visual acuity results, with a greater beneficial effect seen at the 4-month visit in the 4-mg IVTA group compared to 1-mg group, no difference between the 2 groups during the second year.

In our study, the incidence of adverse events were higher in the 4-mg IVTA sub-group compared with the 1-mg sub-group. Six (30%) eyes and 8 (40%) eyes showed ≥5mm Hgelevation of IOP from baseline in 1-mg and 4-mg sub-groups respectively. Four (20%) eyes in 1-mg sub-group and 6 (30%) eyes in 4-mg sub-group required IOP lowering medication. One eyein 4-mg sub-group underwent trabeculectomy for refractory elevation of IOP. In DRCRnetstudy,[7] 40% participants and 20% participants developed ocular hypertension in 1-mg and 4-mg groups respectively. There were 87 more eyes in the 4-mg triamcinolone group than in the 1-mg triamcinolone group that had elevation in intraocular pressure of 10 mmHg or more from baseline, intraocular pressure of 30 mmHg or more, initiation of IOP lowering medications or a diagnosis of glaucoma. Glaucoma surgery was performed in 4 eyes in the 4-mg IVTA group.

In our study, the incidence of lenticular changes was more in 4-mg sub-group than 1-mgsubgroup. One (out of 15) eyes and 4 (out of 19) eyes developed lenticular changes in 1-mg and4-mg subgroups respectively. One eye underwent cataract surgery in 4-mg sub-group. DRCRnetStudy[7] concluded that more eyes required cataract surgery in the 4-mg IVTA (51%) than in the1-mg IVTA group (23%).

CONCLUSION: The results of our study demonstrate that 1-mg dose of IVTA is as effective as 4-mg dose of IVTA in improving the functional and anatomical outcome in macular edema due to diabetic retinopathy.

It also demonstrates that in terms of complications, 1-mg dose of IVTA has less incidence of steroid induced elevation of IOP and less incidence of lenticular opacity development or progression. Therefore 1-mg dose of IVTA is a better and safe option compared to 4-mg dose of IVTA.

REFERENCES:

1. Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IV.Diabetic macular edema. Ophthalmology 1984; 91: 1464–74.
2. Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report no. 19. Early Treatment Diabetic Retinopathy Study Research Group. Arch Ophthalmol. 1995 Sep; 113(9): 1144-55.
3. G A Peyman, Eleonora M Lad, Darius M Moshfeghi. Department of Ophthalmology and Vision Science, College of Medicine, University of Arizona, Tucson, Arizona 85351, USA Intravitreal injection of therapeutic agents. Retina 2009; 29(7): 875-912.
4. Mason JO 3rd, Somaiya MD, Singh RJ. Intravitreal concentration and clearance of triamcinoloneacetonide in nonvitrectomizedhuman eyes. Retina. 2004 Dec; 24(6): 900-4.

DOI: 10.14260/jemds/2015/1336

5. Chu YK, Chung EJ, Kwon OW, Lee JH, Koh HJ Objective evaluation of cataract progression associated with a high dose intravitrealtriamcinolone injection. Eye (Lond).2008 Jul; 22(7): 895-9.
6. Smithen LM, Ober MD, Maranan L, Spaide RF Intravitreal triamcinolone acetonideand intraocular pressure Am J Ophthalmol. 2004 Nov; 138(5): 740-3.
7. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/gridphotocoagulation for diabetic macular edema. Ophthalmology. 2008 Sep; 115(9): 1447-9.

AUTHORS:

1. Sikander A. K. Lodhi
2. Sudhakar Reddy
3. Santosh Devulapally

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Ophthalmology, Osmania Medical College, Hyderabad.
2. HOD, Department of Ophthalmology, Osmania Medical College, Hyderabad.
3. Post Graduate, Department of Ophthalmology, Osmania Medical College, Hyderabad.

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NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sikander A. K. Lodhi,
'HILL VIEW', 10-3-300/3,
Humayun Nagar, Masab Tank,
Hyderabad-500028.
E-mail: sikanderlodhi@gmail.com

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