

## Comparison of intravitreal triamcinolone and posterior subtenon triamcinolone in diffuse diabetic macular edema

P.S.S. Soujanya<sup>1</sup>, Sikander A. K. Lodhi<sup>2\*</sup>

<sup>1</sup>Assistant Professor, <sup>2</sup>Associate Professor, Dept. of Ophthalmology, Malla Reddy Medical College for Women, Hyderabad, India

**\*Corresponding Author:**

Email: sikanderlodhi@gmail.com

### Abstract

**Aim:** To assess the efficacy and complications of the intravitreal injection of Triamcinolone Acetonide (IVTA) as compared to posterior subtenon injection of triamcinolone (PST) for the treatment of diabetic macular edema.

**Materials and Methods:** Twenty four patients with type II diabetes, having diabetic retinopathy with macular edema were recruited. One eye of each patient was assigned to 4mg IVTA and the other eye was given 40 mg PST. Before and one, three and six months after treatment we measured visual acuity as well as thickness of the macula, with optical coherence tomography (OCT), and intraocular pressure (IOP).

**Results:** In the IVTA group, a reduction in foveal thickness of 150 $\mu$  was observed ( $p = 0.012$ ) at 3 months compared to baseline. A reduction of around 70 microns was observed in the PST group which was not statistically significant ( $p = 0.290$ ). In the IVTA group, the mean visual acuity increased from 1.048 $\pm$ 0.512 at baseline to 0.707 $\pm$ 0.552 at 6 months, which was statistically significant ( $p = 0.001$ ). In the PST group, the mean visual acuity improved from 0.797  $\pm$ 0.425 at baseline to 0.727  $\pm$ 0.448 after 6 months with visual improvement maintained in 9 eyes (45%) throughout the study period. IOP rise in IVTA group was not statistically significant; whereas, in the PST group it became statistically significant. However, IOP rise lost its significance at 6 months ( $p = 0.09$ ) owing to treatment with anti-glaucoma medications.

**Conclusion:** Both IVTA and PST can be used as effective treatment options for diabetic macular edema.

**Keywords:** Diabetic macular edema, Foveal thickness, Intravitreal injection, Posterior subtenon injection, Triamcinolone acetonide, Visual acuity.

### Introduction

Macular edema is a leading cause of visual impairment in diabetic patients and affects more than 30% of them with diabetes of 20 years duration.<sup>1</sup> Early treatment diabetic retinopathy study (ETDRS) has demonstrated that macular photocoagulation is an effective treatment for clinically significant macular edema, but the visual loss present before the treatment is not restored.<sup>2</sup> Laser treatment has a modest effect (50%) in preventing further visual loss.<sup>3</sup> Other alternative treatments for diabetic macular edema include intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, intravitreal steroid injections and peribulbar long-acting steroids. Intravitreal triamcinolone acetonide (IVTA) and posterior subtenon's triamcinolone (PST) are both effective in the treatment of diabetic macular edema. We conducted this prospective study to see the effectiveness and biosafety of PST and IVTA.

### Aim

To compare the effectiveness and complications of intravitreal versus posterior sub-tenon's triamcinolone injection in the management of bilateral diabetic macular edema.

### Primary Objective

1. To compare the BCVA scores between IVTA and PST groups following injections.
2. To compare the change in the foveal thickness between IVTA and PST groups following injection.

### Secondary Objectives

1. To compare raised IOP and cataract progression between the groups.
2. To look for any other potential complications like endophthalmitis, vitreous hemorrhage etc.

### Materials and Methods

This was a prospective, comparative study conducted on 46 eyes of 24 patients with diabetic macular edema (DME) who attended the outpatient of Retina Services at Sarojini Devi Eye Hospital, Hyderabad from April 2010 to May 2011. They were randomly assigned to receive a single injection of 4mg of intravitreal triamcinolone (IVTA) in one eye and 40mg of posterior subtenons triamcinolone (PST) in the other eye. Different treatment options and their potential complications were explained to the patient and informed consent was taken. The institutional ethics committee of Sarojini Devi Eye Hospital approved this study.

### Inclusion Criteria:

1. Best corrected visual acuity (BCVA) less than 6/12
2. Macular edema diagnosed by slit-lamp biomicroscopy.
3. Fluorescein angiography showing evidence of leakage
4. Optical coherence tomography (OCT) showing increased foveal thickness

**Exclusion Criteria:**

1. Macular edema due to other causes like retinal vein occlusions, uveitis, pseudophakia.
2. Any tangential or vitreomacular traction
3. Any previous intravitreal injections
4. Previous laser photocoagulation of the retina
5. History of glaucoma

Each patient underwent general examination and complete comprehensive eye examination. BCVA, measured in Snellen's lines, was converted into logarithm of minimum angle of resolution (logMAR) scale for analysis.

Patients were investigated for fasting and postprandial blood sugar, glycosylated hemoglobin, serum lipids and serum creatinine. Patients with any abnormal findings were referred to the physician for control of these parameters.

Both the injections were given under sterile conditions in the operating room maintaining a gap of around 1 week between them. All patients received gatifloxacin eye drops for two days before intravitreal injection and for three days following the injection. Injections were given in the operation theatre with strict aseptic precautions.

Surface anesthesia for intravitreal injections was achieved by instilling proparacaine hydrochloride 0.5% eye drops. Asepsis was achieved by surface preparation of the eye including the lashes using povidone-iodine. Two to three drops of 5% povidone-iodine solution are also instilled in the lower fornix. IVTA (4mg in 0.5ml) was given using 27-gauge needle through pars plana in the inferotemporal quadrant, 3.5 mm posterior to limbus in pseudophakic eyes and 4 mm posterior to limbus in phakic eyes.

For the posterior subtenon's injection, after sterile draping of the eye and instilling topical proparacaine eye drops, the injection was given in the superotemporal quadrant. The patient was asked to look inferonasally; the conjunctiva and tenon's capsule were penetrated 8 mm away from the superotemporal limbus with the bevel of the needle towards the globe. The needle was carefully negotiated towards the macular area, remaining in contact with the globe, until the hub reached the conjunctival fornix and then the triamcinolone (40mg in 1 ml) was slowly injected.

Patients with IVTA were advised to use gatifloxacin eye drops 3-4 times a day for one week. Patients were followed-up at 1 day, 1 week, 1 month, 3 months and 6 months after the injection.

Patients with PDR without high risk characteristics (HRC) underwent PRPC two weeks after receiving the injection while those with HRC were given injections after PRPC.

Patients were retreated in the presence of documented recurrent macular edema and in the absence of the contraindications.

The data thus collected was statistically evaluated using the Wilcoxon signed rank test, Mann-Whitney test and t tests wherever applicable. SPSS (Version 17) windows software was used. The level of statistical significance was  $P < 0.05$ .

**Observation and Analysis**

Out of the total 24 patients (46 eyes), who received injections, three patients were lost to follow-up. Therefore, 40 eyes of 21 patients with a minimum follow-up period of 6 months were included for analysis. In 19 out of 21 patients, one eye was subjected to IVTA and PST was given in the other eye. In patient number 20, only IVTA was given in one eye and in patient number 21 only PST was given.

Variables including age, gender, duration of diabetes, degree of hyperglycemia and co-morbid risk factors, the type of diabetic retinopathy and diabetic macular edema were noted at baseline. BCVA, lens status, IOP, FFA and OCT findings were recorded at baseline and at each follow-up visit.

The data after statistical evaluation was presented as Mean +/- SD.

Our study comprised predominantly of males. 16 out of 21 patients were males (67.16%) while 5 were females (23.80%). The mean +/- SD of age distribution for IVTA group was 54.4 +/- 11 years while that in the PST group was 53.85 +/- 11.24 years with a range of 21 to 70 years in either group. The number of eyes with more than 50 years of age were 15 (75%) in IVTA group and 14 eyes (70%) in the PST group.

The mean +/-SD value of duration of diabetes was 13.65 +/- 5.02 years in the IVTA group and 14.15 +/- 5.13 years in the PST group with a range of 1 to 25 years in each group.

The mean +/-SD of baseline glycated hemoglobin % value in the IVTA group was 9.65 +/- 2.04 while in the PST group it was 9.62 +/- 2.06 with a range of 5.3% to 12.1% in either group. Only 4 patients (20%) in either group had a HbA1C value of less than 8% at presentation.

Out of total 20 eyes in each group, 7 eyes (35%) were diagnosed as PDR with CSME, 9 eyes (45%) as severe NPDR with CSME and 4 eyes (20%) as moderate NPDR with CSME.

In the IVTA group, hyperglycemia was noted in 18 patients (90%), hypertension in 10 patients (50%), hyperlipidemia in 11 patients (55%), diabetic nephropathy and anemia in 3 patients (15%) in each group. (Table 1) Whereas, in the PST group, hyperglycemia was noted in 18 patients (90%), hypertension in 11 patients (55%), hyperlipidemia in 11 patients (55%), diabetic nephropathy and anemia in 3 patients (15%) in each group. Baseline FFA showed diffuse macular edema in 15 eyes (75%) and cystoid macular edema in 5 eyes (25%) in either group.

Baseline OCT showed diffuse retinal thickness (DRT) in 9 eyes (45%), cystoid edema (CME) in 7 eyes

(35%), serous retinal detachment in 3 eyes (15%) and epiretinal membrane in one eye (5%) in either group.

**Table 1: Baseline Characteristics**

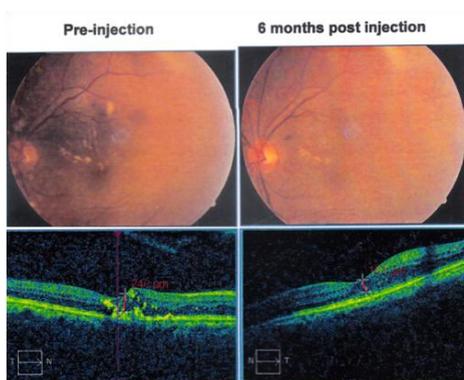
Variable	Group	
	IVTA	PST
<b>Age (y)</b>		
Mean ± 1 SD	54.4	53.85
	11	11.24
<b>Gender</b>		
Male	16 (76.19%)	16 (76.19%)
Female	5 (23.80%)	5 (23.80%)
Hypertension	10 (47.6%)	11 (52.4%)
Duration of diabetes (y)		
Mean ± 1 SD	13.65	14.15
	± 5.02	± 5.13
HbA 1c		
Mean ± 1 SD	9.65	9.62
	± 2.04	± 2.06
Hyperlipidemia	11 (55%)	11 (55%)

SD Standard Deviation, HbA1c Glycosylated Hemoglobin

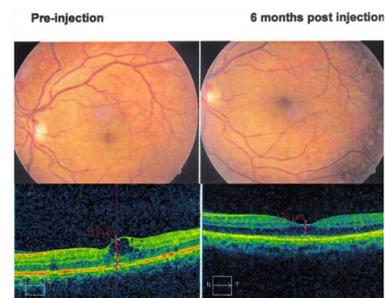
**Table 2: Macular thickness comparison between the groups**

	IVT		PST		P between groups
	Mean +/-SD	P value	Mean +/-SD	P value	
Baseline	355.66+/-173.62		308.80+/-186.98		0.410
3 Months	207.77+/-126.91	0.012	238.93+/-198.19	0.290	0.271

A statistically significant reduction in the mean foveal thickness of around 150 microns was observed in the IVTA group ( $p = 0.012$ ) at 3 months compared to baseline.(Fig. 3) Whereas in the PST group, a reduction in the mean foveal thickness of around 70 microns was observed which was not statistically significant ( $p = 0.290$ ). (Fig. 2) There was no statistically significant difference in the foveal thickness measurement at baseline ( $p = 0.410$ ) or at 3<sup>rd</sup> month ( $p = 0.271$ ) between both the groups. (Table 2, Fig. 1)



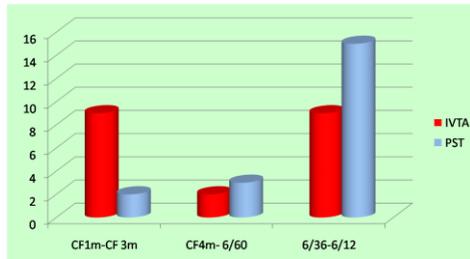
**Fig. 1: Showing pre-IVTA fundus and OCT with macular edema and 6 months post injection resolved macular edema**



**Fig. 2: Showing pre-PST fundus and OCT with macular edema and 6 months post-PST resolved macular edema with decreased foveal thickness**



**Fig. 3: There was no statistically significant difference in the mean baseline visual acuity between the groups ( $p = 0.09$ ).**



**Fig. 4:** Shows baseline visual acuity of both the groups

In the IVTA group, all the eyes responded to the treatment. (Table 3) The mean visual acuity increased from 1.048+/-0.512 at baseline to 0.707+/-0.552 at 6 months, which was statistically significant (p = 0.001). Visual improvement was maintained throughout the study period in 16 eyes (80%) while in the remaining four (20%), it worsened after initial improvement.

**Table 3: Visual Acuity – IVTA**

Visit	Mean+/-SD	P Value
Baseline	1.048+/-0.512	
1 day	0.747+/-0.489	0.0001
1 week	0.700+/-0.468	0.0001
1 month	0.687+/-0.459	0.0001
3 months	0.696+/-0.515	0.0001
6 months	0.707+/-0.552	0.0001

In the PST group, only 16 eyes (80%) showed response to the treatment with visual improvement maintained in 9 eyes (45%) throughout the study period, for 1 month in 5 eyes (20%) and for 3 months in 2 eyes (10%). The p-value between the groups at 6 months was also not statistically significant (p =0.900). (Table 4)

**Table 4: Visual Acuity – PST and comparison between the groups**

Visit	Mean+/-SD	P Value	P-Value between the groups
Baseline	0.797 +/-0.425		0.09
1 day	0.671 +/-0.470	0.0001	0.61
1 week	0.597 +/-0.487	0.0001	0.499
1 month	0.562 +/-0.483	0.0001	0.406
3 months	0.602 +/-0.440	0.0005	0.538
6 months	0.727 +/-0.448	0.39	0.900

**Complications:**

**Increase in Intraocular Pressure: (Table 5, Fig. 5)**

There was no statistically significant difference observed in the mean baseline IOP between the groups (p = 0.382). The mean IOP in the IVTA group increased from 16.40+/-2.64 at baseline to 17.50+/-6.35 at 1 month. There was a pressure rise in 4 out of 20 eyes (20%) at one month post-injection. All were well controlled with anti-glaucoma medications. The mean+/-SD of IOP at 6 months improved to 16.30+/-1.62. Statistically significant difference in the IOP rise was not observed at any visit.

The mean baseline IOP in the PST group increased from 15.70+/-2.36 at baseline to 17.30+/-3.15 at one week (p = 0.03) and to 19.60+/-7.61 at one month post-injection (p = 0.03). At one month post-injection, 5 out of 20 eyes (25%) showed IOP rise. Four patients were controlled with medical line of management while one patient developed intractable rise in IOP and had to undergo trabeculectomy.

**Table 5: Increase in IOP**

IOP	IVTA		PST		P between groups
	Mean +/-SD	P value	Mean +/-SD	P value	
Pre-injection	16/40+/-2.64		15.70+/-2.36		0.38
1 day	16.0+/-2.75	0.506	15.60+/-3.15	0.874	0.67
1 week	15.50+/-3.54	0.290	17.30+/-4.21	0.031	0.14
1 months	17.50+/-6.35	0.486	19.60+/-7.61	0.011	0.34
3 months	16.0+/-2.24	0.550	17.60+/-3.26	0.001	0.07
6 months	16.30+/-1.62	0.883	18.70+/-7.68	0.09	0.17

The mean of +/-SD of IOP in the PST group at 3 months was 17.60+/-3.26 (p = 0.001) and at 6 months was 18.70+/-7.68 (p = 0.09). Statistically significant difference in the IOP rise was observed at 1 week, 1 month and 3 months post-injection.

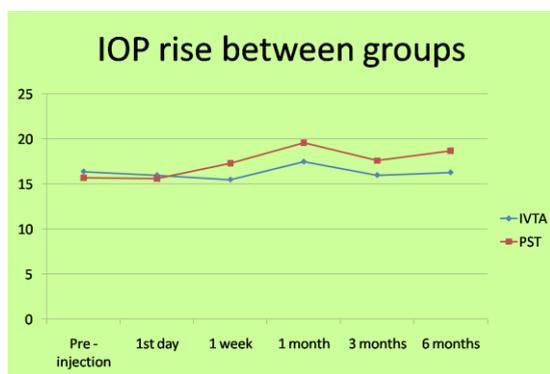


Fig. 5:

**Cataract:** All the 20 eyes in IVTA group were phakic at presentation while in the PST group, 18 eyes were phakic and 2 eyes were pseudophakic at presentation. Four out of twenty eyes (20%) in either group developed cataract. Two eyes in each group showed increase in nuclear sclerosis while two developed posterior subcapsular cataract. Two eyes in each group underwent cataract surgery 6 months post-injection.

One patient with PDR developed vitreous hemorrhage at 6 months. Additional/fill-in panretinal photocoagulation was done. Other potential injection related complications like, endophthalmitis, globe perforation, vitreous hemorrhage and retinal detachment were not encountered.

## Discussion

Macular edema is the most important cause of disturbance of visual acuity in diabetic patients.<sup>4,5</sup> Persistent hyperglycemia causes derangement of blood-retinal barrier with leakage of fluids and electrolytes causing retinal edema.<sup>6-8</sup> ETDRS and other studies have shown that macular photocoagulation prevents further visual loss in 50% of cases but cannot restore the lost vision. Macular photocoagulation is effective in focal leakage but is not very effective in diffuse macular edema.<sup>9,10</sup> Many studies have claimed that diffuse edema is refractory to macular photocoagulation and also that diffuse edema is an indicator of poor prognosis; but most of these are from case series and prospective clinical trials.<sup>11-13</sup> Other studies have suggested that diffuse macular edema responds best to intravitreal triamcinolone and focal edema to focal laser photocoagulation.<sup>14,15</sup> The clinical pattern of diabetic retinopathy with tissue edema, vasodilatation and increased permeability suggest chronic inflammation. This hypothesis of chronic inflammation is based on the finding of increased production of prostacyclin, vascular endothelial growth factor (VEGF) and macrophage cellular components.<sup>16,17</sup> The effect of corticosteroids in the management of diabetic edema is due to the inhibition of arachidonic acid cascade which down regulates cytokines, decreasing the damage to blood-retinal barrier.

We found that macular edema is the most vision threatening complication of diabetic retinopathy. We observed that DME is more common in type II DM, in patients older than 50 years of age and the severity of retinopathy increases with the duration of diabetes and the degree of uncontrolled hyperglycemia (higher HbA1c). We found all the associated risk factors mentioned in the literature although hypertension and hyperlipidemia were much commoner. The mean duration of diabetes in this study was 13.95 years which is similar to earlier studies.<sup>18, 19</sup>

The macular thickness in the IVTA group in our study reduced by 147 $\mu$  (41.58%) at three months post injection and was statistically significant ( $p = 0.01$ ). But in the PST group, the mean reduction at 3 months was 70 $\mu$  (21.32%) which was not statistically significant ( $p = 0.29$ ). On comparing the two groups, the difference in mean foveal thickness at baseline and at three months was not statistically significant. In a similar study by Cellini et al, the decrease in foveal thickness at 3 months in the IVTA group was 158 $\mu$  and 153 $\mu$  in the PST group.<sup>20</sup> Choi et al reported a decrease in macular thickness of around 43.5% at 3 months in the PST group compared to 46.2% in the IVTA group; but between the groups there was no statistically significant difference.<sup>18</sup> Our findings are similar to a study by Bonini-Filho et al, who reported a significant improvement in retinal thickness in the IVTA group compared with PST group at 2, 4, 6, 12 and 24 weeks after injection.<sup>21</sup> The reason for a better response in the IVTA group could be due to a better retinal bioavailability of drug allowing rapid delivery to the target site. In contrast, in the PST group, inadequate penetration of the drug through sclera and choroid might contribute to a less favourable response. Inoue et al have shown that IVTA leads to much higher vitreous concentration of steroid ( $1.29 \pm 0.41 \mu\text{g/mL}$ ) compared to PST ( $<0.001 \mu\text{g/mL}$ ).<sup>22</sup>

In our study, we observed that mean change in visual acuity (log MAR) after IVTA was 0.46 log MAR (43.85%;  $p=0.0001$ ), 0.35 log MAR (43.89%;  $p = 0.0001$ ) and 0.34 log MAR (32.44%;  $P = 0.0001$ ) at 1, 3 and 6 months respectively. While in the PST group it was 0.23 log MAR (29.48%;  $P = 0.0001$ ), 0.19 log MAR (24.46%;  $P = 0.0005$ ) and 0.07 log MAR (8.78%;  $P = 0.39$ ) at 1, 3 and 6 months respectively. No statistically significant difference was found between the groups at any stage. This was similar to Bonini et al who reported that mean visual acuities in log MAR at 4, 8 and 12 weeks follow up significantly higher in the IVTA group (0.74, 0.75, 0.82) compared to PST group (0.88, 0.88, 0.90).<sup>21</sup> However, we differed from Cellini et al who concluded that both IVTA and PST groups displayed significant improvement in visual acuity at 1 and 3 months.<sup>20</sup> However, IVTA group displayed significant worsening of visual acuity at 6 months unlike PST and the difference was statistically significant.

IOP rise in our IVTA group was never statistically significant with p values of 0.48, 0.55 and 0.88 at 1, 3 and 6 months respectively. Whereas, in the PST group it became statistically significant at 1 week, 1 and 3 months with p value of 0.03, 0.01 and 0.001 respectively. However, IOP rise lost its significance at 6 months ( $p = 0.09$ ) owing to treatment with anti-glaucoma medications. Bonini et al, in their study, found no difference in IOP between the groups at different points, but within the groups found statistically significant change in mean IOP from baseline at 4 and 8 weeks in the PST group and at 8 weeks in IVTA group.<sup>(21)</sup> This elevation in the IOP is a known adverse event of corticosteroid administration, topically and systemically, in about one third of the population. We found no difference in the cataract formation between the groups. Four out of 20 eyes in each group (20%) developed cataract, which was in accordance with the literature which describes a 20 to 50% incidence of cataract post triamcinolone injections.

### Conclusion

This study, though involving a limited number of eyes, suggests that both IVTA and PST can be used as an effective short term treatment for diabetic macular edema. In comparison; IVTA scores over PST in terms of functional and anatomical improvement, which is maintained beyond 3 months.

In terms of complications, both IOP rise as well as the development of cataract was similar in both the IVTA and the PST groups.

Therefore, a single intravitreal injection of triamcinolone (4mg) is an effective option in the management of diabetic macular edema compared to PST. However, the limitation our study is small sample size and limited follow-up.

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