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VISUAL OUTCOME OF COMBINED INTRAVITREAL BEVACIZUMAB AND TRIAMCINOLONE ACETATE IN PERSISTENT DIABETIC MACULAR EDEMA

Ophthalomology

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ABSTRACT

Background: Macular edema is the main cause of visual acuity loss in diabetic patients. It may occur at any stage of the retinal disorder and is the most common cause of sight reductions in these patients. **Objective:** To evaluate the functional and anatomical outcome following combined intravitreal triamcinolone acetate and bevacizumab in persistent diabetic macular edema. **Method:** In a prospective and observational study,100 eyes of diabetic aptients were diagnosed with persistent DME after being treated with three or more intravitreal injections. Eyes with residual mean central macular thickness of ≥300um were administered combined intravitreal triamcinolone acetate and bevacizumab. Initial and final best corrected visual acuity; central macular thickness and IOP were measured. **Results:** Hundred eyes of100 patients were studied. The mean age of the patients was 58.9 years ± 9.36. The average HbA1c was 7.2%.The mean best corrected visual acuity (BCVA) in our study was 1.09±0.44 logMAR at baseline which was improved to 0.70±0.25logMAR, 0. 56±0.25 logMAR, 0.48±0.25 logMAR at 1, 3 and 6 months respectively (p value <0.001). The mean central macular thickness (CMT) was 573.73±189.19 µm at baseline, 309.97±90.67 µm at 1 month, 234.47±76.11 µm at 3 months, and 214.81±67.38 µm at 6 months (p value < 0.001). The mean intra ocular pressure was 14.96± 2.60 at baseline, 14.89±2.71 mmHg at 1 month, 16.13±2.71mmHg at 3 month and 17.27±2.63mmHg at 6 months. (p value<0.001) **Conclusion:** Our analysis reveals that combined intravitreal injection of bevacizumab and triamcinolone acetate is safe and effective in persistent macular edema. It improves anatomic and functional outcomes in patients with persistent diabetic macular edema.

KEYWORDS

Diabetic macular edema, bevacizumab, triamcinolone acetate

INTRODUCTION

Diabetic retinopathy is the leading cause of blindness among individuals between 25 and 74 years of age in the industrialized world.[1] It affects three out of four diabetic patients after 15 years of disease duration. The importance of long-term glycemic control has been conclusively established in the landmark clinical trials including the Diabetes Control and Complications Trial (DCCT),[2]and the UK Prospective Diabetes Study (UKPDS).[3]

Diabetic macular edema is the most important cause of vision loss in patients with diabetic retinopathy (DR). It is characterized by breakdown of the blood–retina barrier, leading to leakage of proteins and fluid from blood vessels, tissue edema, and eventually neurodegeneration and permanent visual loss.[4]Diabetic macular edema is associated with a high patient burden and high societal costs because of the growing number of patients with diabetes mellitus and has become a serious global health issue. [5,6,7] The pathophysiology of DME is multifactorial, complex, and not fully understood. Vascular endothelial growth factor A is a major mediator[8]

VEGF-A has been demonstrated to exert potent effects on retinal vascular permeability, and concentrations of certain VEGF-A isoforms in the retina and vitreous are elevated in diabetic retinopathy.The intravitreal injection of bevacizumab potentially reduces not only VEGF but also stromal cell derived factor 1α.

Corticosteroids block the release of arachidonic acid from cell membranes by inhibiting enzyme COX and thus reduce the synthesis of prostaglandins, but they also have a multitude of other anti-inflammatory effects by acting, among others, on IL-1 and by reducing vascular permeability.[9] Steroids specifically stabilize endothelial tight junctions and increase their number.[10,11] They also down regulate the production of the VEGF, which, in turn, renders the BRB tighter. Triamcinolone also inhibits IL-6 and VEGF induced angiogenesis downstream of the IL-6 and VEGF receptors.[12] The Müller cells represent a further site of action of steroids.[12]Macular edema is thought to be partly linked to the down regulation of the Müller cell protein Kir4.1. The resultant increase in intracellular K+ leads to the uptake of proteins and osmotic swelling of the Müller cells via aquaporin 4 channels. The administration of triamcinolone reduces the production of VEGF, arachidonic acid, and prostaglandins, allowing the reactivation of fluid clearance by Müller cells via endogenous adenosine and an increase in TWIK-related acid-sensitive potassium (TASK) channels. These processes lead to an efflux of potassium, thus correcting the down regulation of the Kir4.1 protein.[13]

MATERIALS AND METHODS

This study was a prospective and observational study conducted in the Postgraduate Department of Ophthalmology, Government Medical College Srinagar over a period of one and a half year. Clinically and OCT supported persistent Diabetic Macular edema (CMT ≥300um) patients who had received three or more intravitreal bevacizumab injections were included in the study. Patients with history of glaucoma, chronic uveitis and those on drugs that can be associated with the risk of developing macular edema such as glitazones, prostaglandin analogs, alkylating agents, antineoplastic agents were excluded from the study. None of the patients included in the study had prior laser therapy.

Evaluation consisted of a complete medical, surgical, and ophthalmic history followed by a thorough ophthalmic examination. Data included Age,Gender,BCVA,Slit lamp examination,Intraocular pressure (IOP),Dilated fundus examination,OCT documented central macular thickness (Zeiss-Cirrus HD-OCT), and fundus fluorescein angiography at presentation.Best corrected visual acuity (BCVA) was recorded as a snellen visual acuity and converted to logarithm of minimal angle of resolution (LOGmar) units for statistical analysis.

The following steps were adopted and observed:

Before the injection all the risks and benefits were explained to the patients and written informed consents were obtained. Intravitreal injections of 2 mg triamcinolone acetonide and 1.25 mg of bevacizumab were given under aseptic conditions. The injections were administered with an insulin syringe with a detachable 27G needle. The injection site was marked with caliper at 4mm, 3.5mm and 3mm posterior to the limbus in phakic, pseudophakic and aphakic eyes respectively. Clear portion of triamcinolone acetonide (40mg/ml) was taken into the syringe. Conjunctiva was grasped with forceps and displaced few mm toward limbus and 0.1 ml was injected in inferotemporal quadrant. The second syringe with 0.05 ml of bevacizumab was injected in superotemporal quadrant in the vitreous cavity. The needle was removed and entry wound was pressed with a cotton bud for few seconds so that liquid vitreous did not escape. Postoperatively, moxifloxacin eye drops 0.5% (Vigamox ®) were given QID for next 05 days in all cases. Patients were instructed not to lie down for 6 hours.

FOLLOW UP

Follow up was done at day 1, day 3, and day 7 of injection followed by 1 month, 3 month and 6 month of injection. The IOP, BCVA, and clinical findings were documented on every follow up. OCT was done to evaluate CMT on 1 month, 3 month and 6 month of injection.

OBSERVATIONS AND RESULTS

GENDER

Table 1: Gender Wise distribution of patients (n= 100)		
Gender	Frequency	Percentage (%)
Male	72	72
Female	28	28

There were 72 (72%) males and 28 (28%) female patient in our study showing that there was preponderance of males over the females.

Table 2: Age wise distribution of patients (n =100)		
Age	Frequency	Percentage
35-44	2	2
45-54	28	28
55-64	41	41
65-74	21	21
≥75	8	8

Out of total 100 patients, maximum number 41(41%) of patients belonged to the age group 55-65 years. Mean ± SD age of the patients was 58.03 ± 9.1 years

Table 3: HbA1c status		
HbA1c	Frequency	Percentage
<7	52	52
≥7	48	48

Table 3 shows HbA1c status of the patients included in our study. Out of 100 patients, 52 patients (52%) had HbA1c <7 and 48 patients (48%) had HbA1c ≥7

Table 4: Grade of diabetic retinopathy		
Grade of diabetic retinopathy	Frequency	Percentage
Very mild	0	0
Mild	0	0
Moderate	44	44
Severe	33	33
Very severe	10	10
Low risk PDR	10	10
High risk PDR	3	3

Out of 100 participants, 44 (44%) had moderate NPDR, 33 (33%) had severe NPDR, 10 (10%) had very severe NPDR, 10 (10%) had low-risk PDR and 3 (3%) had high-risk PDR.

Table 5: Type of diabetic macular edema		
Type of diabetic macular edema	Frequency	Percentage
Cystoid	28	28
Spongy	72	72
Serous	0	0

In our study, Spongy type of DME (72%) was the most common type followed by serous DME (28%).

Table 7: Lens status of patients		
Lens status	Frequency	Percentage
Clear	41	41
NS1-2	10	10
PSC	2	2
NS3-4	0	0
Pseudophake	47	47

Majority of study eyes (47%) were pseudophakic, while 41% were phakic. 12 patients had cataractous lens, and they underwent cataract extraction surgery and intra-ocular implantation in 1-2 months of follow up.

Table 8: comparison of pre-injection visual acuity with vision at final follow up visit.					
	Baseline	1 month	3 month	6 month	P-value$
VA	1.09±0.44	0.70±0.25	0.56±0.25	0.48±0.25	<0.001*

*Statistically Significant Difference (P-value<0.05); $ Baseline vs 6 Months; Paired t-test

Table 9: comparison of pre-injection mean central macular thickness with mean CMT at final followup					
	Baseline	1 month	3 month	6 month	P-value$
CMT	573.73± 189.19	309.97± 90.67	234.47± 76.11	214.81± 67.38	<0.001*

*Statistically Significant Difference (P-value<0.05); $ Baseline vs 6 Months; Paired t-test

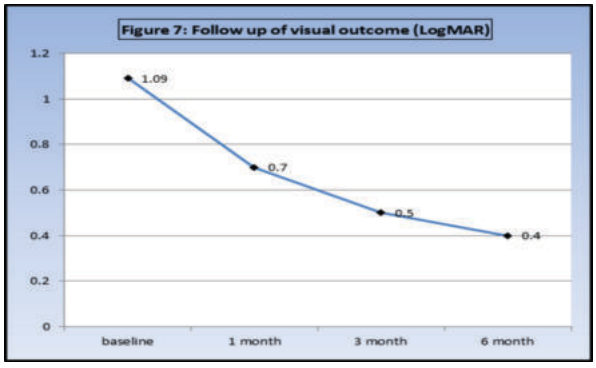


Figure 7 is a graphical representation of the follow up of visual outcomes recorded as mean logMAR visual acuities

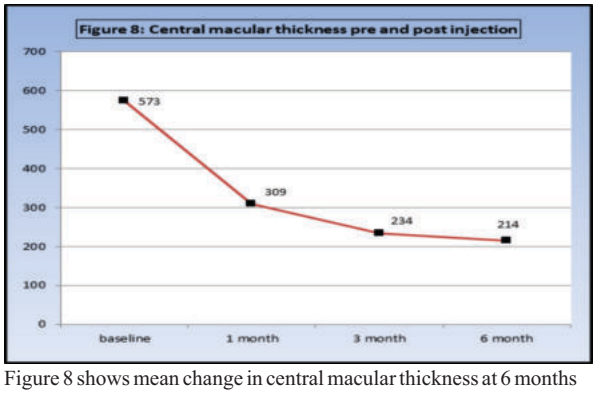
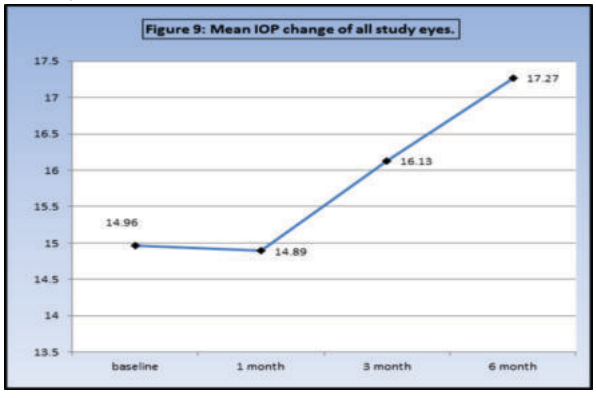
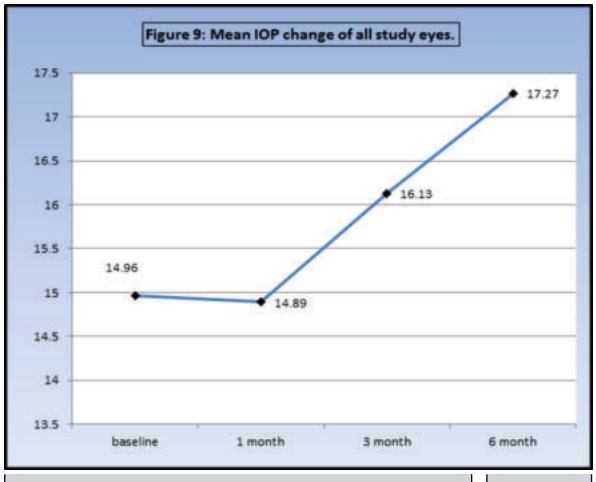


Figure 8 shows mean change in central macular thickness at 6 months

Table 10:Pre-injection and post-injection mean IOP values					
	Baseline	1 month	3 month	6 month	P-value$
IOP	14.96±2.60	14.89±2.88	16.13±2.71	17.27±2.63	<0.001*

*Statistically Significant Difference (P-value<0.05); $ Baseline vs 6 Months; Paired t-test





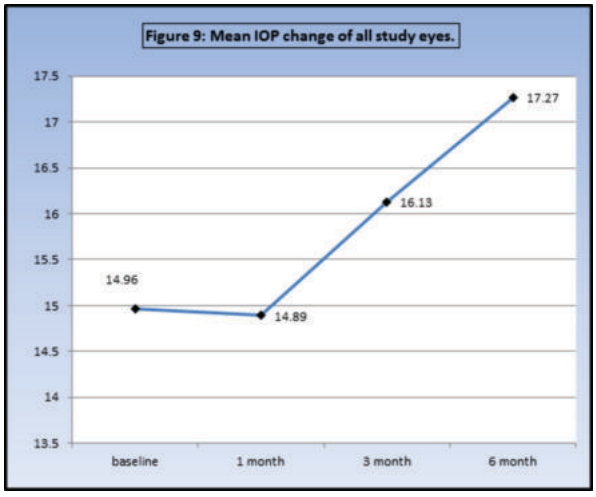
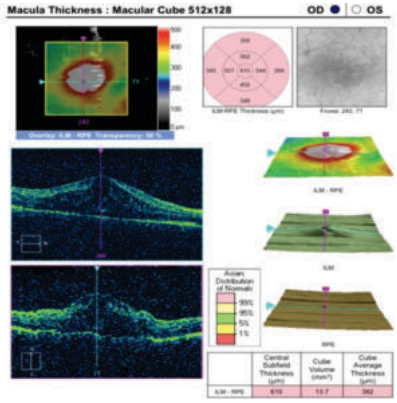


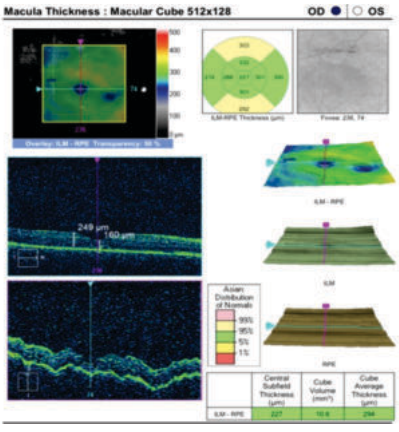
Figure 9 shows the mean IOP change during the follow up period. There was a significant increase in intraocular pressure

Table 12: Complications of combined injection	
Complications	Frequency
Uneventful	36
Mild pain / Irritation	27
SCH	20
Raised IOP	5
Cataract	12

SCH=subconjuctival hemorrhage, IOP = intraocular pressure



A 65 year old diabetic with reduced visual acuity in right eye to the level of 1.3. Intravitreal bevacizumab was injected 3 times in the same eye. OCT cross sectional scans through the macula shows diabetic macular edema (serous). The macular thickness in the fovea measured by OCT was 615 µm. The colour coded map corresponds to the area of maximal thickening.



Cross sectional and macular thickness map of the same eye (figure 6) 6 months after combined IVA+ IVTA revealed total resolution of the diabetic macular edema. The central macular thickness was 227µm. The colour coded topographic map confirmed the presence of diffuse flattening of the macula.

DISCUSSION

The combination of intravitreal triamcinolone and bevacizumab counters both acute and chronic mechanism of diabetic macular edema. Both bevacizumab and triamcinolone are the most cost-effective drugs, and therefore are widely used in DME.

The mean best corrected visual acuity (BCVA) in our study was 1.09±0.44 logMAR at baseline which was improved to 0.70±0.25logMAR, 0. 56±0.25 logMAR, 0.48±0.25 logMAR at 1, 3 and 6 months respectively (p value <0.001).Arain MA et al (2017)[14] reported a significant improvement in VA from 0.708±0.12 before injection to 0.586±0.13 after injection. Minimum follow up was 3 months. Similar to our study, significant improvement in logMAR visual acuity was seen in patients with refractory diabetic macular edema. In the study by Yolcu U et al (2013)[15] mean BCVA improved significantly from logMAR 0.8 to logMAR 0.6 at final follow up. The results of our study are comparable with the above studies.Tsilimbaris MK et al (2009)[16] observed an overall mean BCVA improvement from 1.08±0.56 logMAR at baseline to 0.77±0.56 logMAR at final follow up.

In our study, the mean central macular thickness (CMT) was 573.73±189.19 µm at baseline, 309.97±90.67 µm at 1 month, 234.47±76.11 µm at 3 months, and 214.81±67.38 µm at 6 months (p value < 0.001). Overall, there was statistically significant improvement in central macular thickness at final follow up.Arain MA et al (2017)[14] reported mean pre op CSFT of 439.10 ±54.64 um while mean post op CSFT was 382.80±56.12 um. There are statistically significant difference of CSFT in pre op and post op data comparison by paired t-test (p <0.001). The study results are akin to our study.In a similar study by Yolcu U et al (2013)[15] median CMT of the cases were 575 (502-1049) before the combined injection, 370 (179-983) µm at 6 months and 410 (198-929) µm at 12 months. The overall results are corresponding to our study.Synek S et al.[17] evaluated the effect of IVB alone or combined with IVTA in the first injection for treatment of refractory diabetic macular oedema and found out that central macular thickness was reduced significantly in both the IVB and IVB/IVTA groups. This study also supports our results.

Our results are comparable with other studies using simultaneous therapy of intravitreal dexamethasone implant and bevacizumab for diabetic macular edema.[18,19] Overall, this study found improvement in functional and anatomic outcomes which are in line with the previously published studies.[14,15,16,17,19,20]

The complication rate was low in our study. There was no intra operative complication noted in our series. In our study, the mean intra ocular pressure was 14.96± 2.60 at baseline, 14.89±2.71 mmHg at 1 month, 16.13±2.71mmHg at 3 month and 17.27±2.63mmHg at 6 months. (p value<0.001. IOP transiently increased after injection in 5 patients (5%), but returned to baseline level by 6 months with one topical beta blocker.Yolcu U et al (2013)[15] reported mean IOP (18.32±1.54mmHg) was higher at 12 months compared to baseline IOP (16.12±3mmHg), but was still within normal range. The overall results are in line with our study. In a study by Arain MA et al (2017),[14]three eyes out of 50 eyes had increased intraocular pressure, which were controlled by topical medication. Our study results are comparable to this study.

In our series, cataract developed/progressed in 12 patients (12%) and we performed cataract surgery in these patients. The procedure was uneventful, and visual acuity improved postoperatively.

No endophthalmitis, retinal detachment, vitreous hemorrhage or drug related systemic adverse effects occurred.

We have reported significant improvement in visual acuity and decrease in central macular thickness for most patients enrolled in our study. To the best of our knowledge, no other studies on Kashmiri populations in North India have been generated on this topic till date. We found combined intravitreal triamcinolone and bevacizumab to be a safe and effective treatment in persistent diabetic macular edema in this population.

SUMMARY

- This prospective, observational study was carried out in the Postgraduate Department of Ophthalmology, Government Medical College, Srinagar over a period of one and a half years. 100 eyes of 100 patients with persistent diabetic macular edema

received combined intravitreal triamcinolone acetate and bevacizumab.

- Out of 100 patients, majority of patients (n=69, 69%) were in age group 45-65. Mean±SD was 58.3±9.106 years. Range of data set was 35-85 years.
- There was a preponderance of males over females in our study. The male to female ratio was 2.57:1.
- 51 patients had an urban residence and 49 patients had rural residence.
- Out of 100 eyes included in our series, 55 were right eyes and 45 were left eyes.
- History of hypertension was the most common systemic history. It was controlled in 51% of patients and uncontrolled in 49% of patients.
- History of phaco/SICS was common ocular history (n=49, 49%).
- Out of 100 patients, 47% were pseudophake while 41% had clear lens.
- 12 patients had a cataractous lens that underwent cataract extraction and intraocular lens implantation in the follow up period.
- We observed significant improvement in LogMAR visual acuity, the mean best corrected visual acuity (BCVA) was 1.09±0.44 log MAR at baseline which was improved to 0.70±0.25logMAR, 0.56±0.25ogMAR, 0.48±0.25logMAR at 1, 3 and 6 months respectively (p value <0.001).
- In our study, the mean central macular thickness (CMT) was 573.73±189.19 µm at baseline, 309.97±90.67 µm at 1 month, 234.47±76.11 µm at 3 months, and 214.81±67.38 µm at 6 months (p value < 0.001). Overall, there was a statistically significant improvement in the central macular thickness at final follow up.
- During the follow up period, there was a transient increase in IOP in 5% of patients, but returned to baseline level by 6 months with one topical beta blocker.

CONCLUSION

- We found combined intravitreal triamcinolone acetate and bevacizumab to be safe and effective for persistent diabetic macular edema.
- Minimal complications were encountered with combined injection.
- We observed favourable visual and anatomic outcomes in our study.
- It is likely that combined therapy will become an increasingly important element in our armamentarium for therapy in persistent diabetic macular edema.
- We expect more studies to be generated on this topic and also a wider adoption of this therapy.

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