Original Research Article

A comparative study between intravitreal bevacizumab and intravitreal triamcinolone in recalcitrant diabetic macular edema

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Abstract

Background: Macular edema is an important cause of visual loss in patients with diabetic retinopathy. Intravitreal Triamcinolone acetonide has proven effective in reducing macular thickness in DME, both as an initial treatment and as a second line therapy after unsuccessful laser therapy. Bevacizumab is a main anti-vascular endothelial growth factor agent used for DME. **Aim:** To compare the visual outcomes associated with intravitreal injection of Triamcinolone acetonide versus Bevacizumab for the treatment of recalcitrant diabetic macular edema. **Material and Methods:** Fifty-two eyes of 48 patients with refractory DME not responding to conventional laser treatment were included in the study. The patients were randomly chosen to be injected with 1.25 mg of intravitreal Bevacizumab and 4mg of Triamcinolone acetonide respectively and were reviewed at 1, 4, 8, and 24 weeks after the injection. The clinical course of best corrected visual acuity (BCVA) was monitored up to 24 weeks after the injection. **Results:** Before the injection, BCVA was logMAR 1.05+0.13 in the Bevacizumab injected eyes, and logMAR 0.99+0.17 in the Triamcinolone injected eye; there was no significant difference between the groups. Four weeks after injection, the eyes in both the groups showed significant regression of macular edema and improvement in BCVA. The resolution was most marked at 8 weeks post injection. The mean logMAR in the eyes treated with intravitreal Bevacizumab were 0.84+0.10, 0.64+0.18 and 0.64+0.19 and intravitreal Triamcinolone were 0.87+0.11, 0.64+0.16 and 0.71+0.26 at 4, 8 and 24weeks post-injection. **Conclusion:** Intravitreal Bevacizumab and Triamcinolone acetonide were equally effective in improving visual acuity in DME not responding to laser treatment. But, Bevacizumab was superior with stability of intraocular pressure and lesser chances of side effects, other than injection related complications in comparison to Triamcinolone acetonide.

Key Words: Recalcitrant diabetic macular edema, Intravitreal Bevacizumab, Intravitreal Triamcinolone acetonide, best corrected visual acuity

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INTRODUCTION

Diabetic retinopathy is a microvascular complication of both type 1 and type 2 diabetes mellitus of more than 10-years duration, which can eventually lead to blindness. Diabetic maculopathy is a separate entity and is the most common cause of visual impairment in diabetic retinopathy.[1]Recalcitrant diabetic macular edema is characterized by the accumulation of plaques of hard exudates in a grossly edematous retina, not responding to the standard modalities of treatment and showing a very poor visual potential. These patients usually have a poorly controlled glycemic status of long duration with associated co-morbid condition such as systemic hypertension, dyslipidemia and chronic renal failure.

In addition to glycemic control, the treatment options for DME include laser photocoagulation, intravitreal steroids, intravitreal anti-vascular endothelial growth factor (anti-VEGF) and vitrectomy. Intravitreal Triamcinolone

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acetonide (Kenacort) injection has proven effective in reducing macular thickness in DME, both as an initial treatment and as a second line therapy after unsuccessful laser therapy, and depending on the macular ischemia, an increase in visual acuity. However, its effect is temporary, and a number of side effects have been reported. Consequently, its therapeutic value remains unclear.[2-5] Bevacizumab (Avastin, Genentech Inc., San Francisco, CA) is a full- length humanized antibody that binds to all subtypes of VEGF; it has been used successfully as a systemic drug in tumor therapy.[6] Recent studies have demonstrated the usefulness of intravitreal injections of Bevacizumab in the reduction of macular edema. The present study was carried out to compare the visual outcomes associated with intravitreal injection of Triamcinolone acetonide versus Bevacizumab for the treatment of recalcitrant diabetic macular edema.

MATERIAL AND METHODS

The present prospective hospital based randomized clinical trial was conducted over a period of two years in tertiary care hospital after obtaining permission from Institutional Ethical Committee. Informed written consent was obtained from each patient.

Inclusion criteria

- Patients with Diabetic Macular Edema not responding to laser photocoagulation.
- Refractory DME (defined herein as the presence of "clinically significant macular edema" (as per ETDRS criteria) by biomicroscopic evaluation, which had persisted despite macular laser photocoagulation performed at least 12 weeks earlier.
- CMT (defined as the average thickness of a central macular region 1000 μm in diameter centred on the patient's foveola) greater than 300 μm on optical coherence tomography (OCT)

Exclusion criteria

- Untreated Diabetic macular edema
- Inflammatory ocular neovascularization (ION)
- Pseudophakic cystoid macular edema
- Eyes with age-related macular degeneration
- History of glaucoma or ocular hypertension (defined as an intraocular pressure higher than 22 mmHg)

Methodology

All patients received a comprehensive ocular examination before and after the treatment. The best-corrected VA with the Snellen's chart (6m) and retinal thickness by optical coherence tomography (OCT) (Zeiss-STRATUS OCT, Carl Zeiss Meditec, Inc., Dublin, California, USA) were measured during the follow-up examinations. A macular thickness map was made from six radial scans that intersected at the fovea using the OCT retinal thickness mapping program. This program calculates mean thickness in nine regions: the central 1000μm area, and the four quadrants of the inner and outer rings. The diameters of the inner and outer rings were 1000μm to 3000μm and 3000μm to 6000μm, respectively. In this study, foveal thickness was defined as the value of a 1000μm central area. IOP was measured during the clinical course.

Indirect ophthalmoscopy and slit-lamp biomicroscopy of the posterior segment with a +20D and +90D (Volk, Mentor, Ohio, USA) were performed to establish the presence of DME. Fundus photographs were taken. Fundus fluorescein angiography (FFA) was performed to detect and assess diffuse leakage around the fovea. The renal parameters were controlled before undergoing FFA. The patients were randomly chosen to be injected with 1.25 mg of Intravitreal Bevacizumab (Avastin, Genetech, California,USA; Dose:1.25mg/0.05ml) and 4mg of Triamcinolone acetonide (Kenacort, Piramal Healthcare, Mumbai, India; Dose:4mg/0.1ml) respectively and were reviewed at 1, 4, 8,and 24 weeks after the injection. The best- corrected Snellen visual acuity (VA), near vision, color vision, amsler grid test and OCT were conducted.

Technique of injection

- All intravitreal injections were carried out under sterile conditions in an operation room. Procedure was performed with dilated pupils.
- Lids were scrubbed with 10% betadine. 2 drops of 5% betadine instilled in conjunctival sac. After draping with a sterile drape lid speculum applied, topical anaesthesia achieved with Proparacaine.
- Triamcinolone acetate 4mg in 0.1ml suspension/Bevacizumab 1.25mg in 0.05ml was withdrawn into a Tuberculin syringe after cleaning the top of the vial with a spirit swab. A 30-gauge needle then attached to the syringe and air freed.
- With the bevel of the needle facing anteriorly and the needle aimed posteriorly into midvitreous and perpendicular to the surface of the globe, needle inserted through the pars plana in the inferotemporal quadrant, 3.0 mm from limbus in aphakic, 3.5 mm in pseudophakic and 4 mm in phakic eyes.
- After injecting the drug slowly, needle is removed with the application of a cotton tipped applicator over its entry site to prevent regurgitation of the injected material.
- Indirect ophthalmoscopy done after every procedure to check for central retinal artery (CRA) pulsation,

intravitreal Kenacort sediment and to rule out any complication.

- An anterior-chamber paracentesis is done to avoid regurgitation of drug or persistent IOP elevation.
- Topical antibiotic ointment administered and pad bandaged. Patient sent home with topical antibiotic drops to be used for one week.

Follow up

- Patients were reviewed at 1, 4, 8 and 24 weeks after the injection. Patients were reviewed more frequently in case any complications warranted this.
- Patients were instructed to report at the first sign of worsening vision, pain and redness.

Follow up examinations

- Visual Acuity was determined using Snellen's charts.
- Amsler grid test conducted.
- Slit-lamp biomicroscopy was performed, specifically evaluating intraocular cells and flare as well as lens opacities.
- Evaluation of macular edema using slit lamp biomicroscopy with a 90D and 78D lens (Volk, Mentor, Ohio, USA).
- Intraocular pressure (IOP) recorded using Schiotz tonometry.
- At each visit patients were asked to describe any changes they have noticed in visual status compared to their baseline before injection and whether they would rate their current visual status better or worse than at baseline.
- Colored fundus photograph was taken.
- Fundus fluorescein angiography(FFA) was done to check for any leakage in the macular area and Central macular thickness was measured with STRATUS – OCT.

Statistical analysis

The data collected was compiled and analyzed with following statistical procedures using the Statistical Package for Social Science (SPSS) software. For each of the treatment descriptive statistics were computed to have firsthand observations of the results in terms of mean, range, standard deviation, etc. Cross Tabulation of Age and Sex Vis-à-vis allocation of subject to different treatments (eg. Fisher's Exact Test) along with Chi-square test was undertaken to find out the independence of attributes like age and sex with allocation of subjects to different treatment. As the sample size is small, i.e., twenty-six in each treatment group, non-parametric tests like Wilcoxon Signed Ranks Test and Mann-Whitney Test to study and compare the efficacy of both the drug treatments.

RESULTS

This study includes 52 eyes of 48 patients diagnosed to have Diabetic Macular Edema not responding to laser photocoagulation, treated with 1.25 mg of intravitreal Bevacizumab and 4mg in 0.1 ml intravitreal Triamcinolone acetonide randomly as a secondary treatment modality. Patients were reviewed at 1 week, 4weeks, 8weeks and 24weeks.

In this study, the youngest patient was 45 years old. The eldest patient was 79 years old. The average age of the patients included in the study was 60 yrs. The incidence of macular edema was higher in people older than 50 yrs (94.3%), compared to those younger than 50 yrs (5.7%). Out of 48 patients, 3 (6.25%) patients were less than 50 years of age while 45 (93.75%) were older than 50 yrs. Among our study subjects 80.8% were males and 19.2% females. In addition to uncontrolled diabetes mellitus (21%), altered renal status (23%), lipid profile (29%) and hypertension (31%) were found to be associated with recalcitrant macular edema. The mean duration of DM was 12.5yrs. Statistical analysis of the pre-existing systemic status of both the groups was found to be comparable on the Fisher's Exact Test (Exact Sig.(2-sided) =1.00) and the Pearson Chi-Square test (Asymp. Sig. (2-sided) =1.00). Majority of the eyes with recalcitrant diabetic macular edema (80.5%) had visual acuity less than 6/60 before intravitreal Bevacizumab and intravitreal Triamcinolone acetonide demonstrating the degree of visual morbidity caused by DME. Eight of our study eyes had clear crystalline lenses pre intravitreal Bevacizumab and intravitreal Triamcinolone acetonide, 10 were pseudophakic and 34 had senile immature cataract. None of the study eyes were aphakic. All of the eyes (100%) had IOP within normal range of 10-21mm Hg before intravitreal Bevacizumab and intravitreal Triamcinolone. None of the cases included in the study had pre intravitreal injection ocular hypertension (IOP > 21mm Hg.) All of the 52 eyes (100%) had confluent leaking microaneuryms, which suggested the source of the diffuse macular edema. In addition to the leaking microaneurysms, 37 eyes (71.15%) had macular ischemia and capillary non-perfusion areas and 33 eyes (63.46%) had block fluorescence due to hemorrhages and hard exudates in the cases with recalcitrant diabetic macular edema. Macular ischemia and block fluorescence due to hemorrhages and hard exudates are likely to affect visual prognosis. All of the eyes (100%) with diffuse macular edema were included in the study. Twenty eyes (38.46%) of the diffuse macular edema had cystoid pattern and 31 eyes (59.62%) had spongy pattern. Twenty-six eyes (50%) had foveal detachment along with cystoid or spongy macular edema and 6 eyes (11.54%) had hard exudate encroaching the centre of the macula. An

improvement in the visual acuity by at least one line on Snellen's chart at 2 months of administering intravitreal Bevacizumab and intravitreal Triamcinolone Acetonide was considered as clinically significant visual improvement. Similarly, deterioration in the visual acuity of at least one line on the Snellen's chart was considered as significant visual deterioration. For the purpose of statistical analysis and for comparison with other studies, the Snellen's acuity was converted into LogMAR.

Table 1: Comparison of Visual outcome at 4weeks

	No of eyes with Visual Imorovement	%	Pret/t BVCA (logMAR)	Post t/t BVCA(logMAR)	Average increase in vision	`p'value Wilcoxon Signed rank Test
IVB	19/26	73.0	1.05	0.85	1 line	0.00
IVTA	17/26	65.4	0.99	0.87	1 line	0.00
Total no. of eyes	36/52	69.2	1.01	0.86	1line	0.00

73% eyes treated with intravitreal Bevacizumab and 65.4% eyes with intravitreal Triamcinolone acetonide showed significant visual improvement. Seven of the eyes showed no change in visual acuity post-intravitreal Bevacizumab and 9 eyes post-intravitreal Triamcinolone acetonide injection. All the eyes with improvement of visual acuity showed an improvement of almost 1 line. Using 2 tailed Wilcoxon Signed Rank Test the statistical analysis showed a significant difference in visual acuity at 4weeks in both the study groups ('p'value= 0.000). But there was no significant difference found in the affect of intravitreal Triamcinolone acetonide and Bevacizumab (Mann Whitney 'p' value= 0.39).

Table 2: Comparison of Visual outcome at 8 weeks

	No. of eyes with Visual Improvement	%	Pret/t BVCA (logMAR)	Post t/t BVCA (logMAR)	Average increase in vision	`p'value Wilcoxon Signed rank Test
IVB	26/26	100	1.05	0.64	2 lines	0.000
IVTA	24/26	92.3	0.99	0.64	2 lines	0.000
Total no. of eyes	50/52	96.1	1.01	0.64	2lines	0.000

100% eyes treated with intravitreal Bevacizumab showed significant visual improvement in comparison to 92.3% eyes with intravitreal Triamcinolone acetonide. Four (15.3%) of the eyes treated with intravitreal Bevacizumab and 2 (7.6%) of post-intravitreal Triamcinolone acetonide injection showed improvement in visual acuity of less than 1 Snellen line while 2 (7.6%) of the post- intravitreal Triamcinolone eyes showed no improvement in visual acuity due to accumulation of hard exudates in foveal region. All the eyes showed an improvement of almost 2 lines. The statistical analysis with 2 tailed Wilcoxon Signed Rank Test demonstrated a significant difference in visual acuity at 8 weeks (p value= 0.000) in both the study groups. But there was no significant difference found between the affect of intravitreal Triamcinolone acetonide and Bevacizumab (Mann-Whitney p value=0.59). Functional improvement with intravitreal injection of Bevacizumab and Triamcinolone appeared to be more marked at 8 weeks in comparison to 4 weeks follow up.

Table 3: Relationship between pre- and post IVB visual acuity at 8wks

		Post IVB Visual Acuity								Total
		6/6	6/9	6/12	6/18	6/24	6/36	6/60	<6/60	
Pre IVB	6/6(0)	-	-	-	-	-	-	-	-	0
Visual	6/9(0.18)	-	-	-	-	-	-	-	-	0
Acuity (logMAR)	6/12(0.3)	-	-	-	-	-	-	-	-	0
	6/18(0.5)	-	-	-	-	-	-	-	-	0
	6/24(0.6)	-	-	-	-	-	-	-	-	0
	6/36(0.78)	-	-	1	-	1		-	-	2
	6/60(1)	-	-	1	2	11	2	-	-	16
	<6/60(<1)	-	-	-	-	4	1	2	-	7
Total		-	-	2	2	16	3	2	-	26

The mean pre intravitreal Bevacizumab logMAR was 1.05 (S.D. 0.13) Visual acuity at 4 wk and 8 wks post intravitreal Bevacizumab being 0.84 (S.D. 0.1) and 0.64 (S.D. 0.16) respectively (a mean change of 1 line and 2 lines respectively). At the final observational period at 24 wks the visual acuity was maintained at logMAR 0.64 (S.D. 0.19). Statistical analysis of the pre and post intravitreal Bevacizumal logMAR Wilcoxon Signed Rank test showed the improvement in VA both at 4week, 8weeks and 24wks to be highly significant (p =0.00, 0.00 and 0.02 respectively).

Table 4: Relationship between pre- and post IVTA visual acuity at 8wks

		Post IVTA Visual Acuity								Total
		6/6	6/9	6/12	6/18	6/24	6/36	6/60	<6/60	
Pre IVB	6/6(0)	-	-	-	-	-	-	-	-	0
Visual	6/9(0.18)	-	-	-	-	-	-	-	-	0
Acuity (logMAR)	6/12(0.3)	-	-	-	-	-	-	-	-	0
	6/18(0.5)	-	-	-	-	-	-	-	-	0
	6/24(0.6)	-	-	-	-	-	-	-	-	0
	6/36(0.78)	-	-	-	2	6	-	-	-	8
	6/60(1)	-	-	-	-	10	-	2	-	12
	<6/60(<1)	-	-	-	4	-	-	2	-	6
Total		**-**	**-**	**-**	**6**	**16**	**-**	**4**	**-**	**26**

The mean pre intravitreal Triamcinolone acetonide logMAR was 0.99 (S.D. 0.17). The visual acuity at 4 wk and 8 wks post intravitreal Triamcinolone acetonide being 0.87 (S.D. 0.11) and 0.64 (S.D. 16) respectively (a mean change of 1 line and 2 lines respectively). At the final observational period at 24 wks the visual acuity reduced to logMAR 0.71 (S.D. 0.26). Statistical analysis of the pre and post Triamcinolone acetonide logMAR using 2 tailed Wilcoxon Signed Rank test showed the improvement in VA both at 4 weeks, 8 weeks and 24 weeks to be highly significant (p = 0.00, 0.00 and 0.00 respectively).,All the eyes with Intravitreal Bevacizumab treatment which showed improvement in visual acuity at second follow up, 15.3% eyes (4 eyes) lost 1 or more lines at the 24weeks follow up in comparison to 24% of 24 eyes (6 eyes) with Intravitreal Triancinolone acetonide treatment. And all the other eyes in both the study group (84.7% and 75% respectively) maintained the improved visual acuity till the final follow up. Statistically the difference in deterioration at 24 weeks was not significant. Analysis of whether the duration of diffuse macular edema influenced outcome in the eyes with poor vision was not possible. Five (19%) of our study eyes treated with intravitreal Triamcinolone showed ocular hypertension (IOP > 21 mm Hg), which was controlled with medical therapy. None of the eyes of Bevacizumab group developed rise in IOP. In five of twenty-six eyes (19%) treated with intravitreal Triamcinolone acetonide developed ocular hypertension which resolved with antiglaucoma treatment. Subconjunctival hemorrhage was the commonest injection related complication seen (26.92% of all eyes).

DISCUSSION

Recalcitrant Diabetic Macular Edema (DME) involving the centre of the macula is the predominant cause of severe visual loss in patients with diabetic maculopathy despite conventional attempts at preventing and treating the edema. Twenty-two out of 26 eyes (84.7%) treated with intravitreal Bevacizumab maintained the improved visual acuity till the final follow up in comparison to 75% of Triamcinolone treated eyes. Statistically, the difference in maintenance of visual acuity at 24 weeks was not significant.

Table 5: Visual outcome with IVTA compared with other studies

	Total no of eyes	Improved		Mean BCVA: LogMAR		
		No.	(%)	Pre IVTA	Post IVTA	Change in BCVA
Martidis *et al*[7]	16	16	100%	1.0	0.6	2.4 lines
Jonas *et al*[8]	21	17	81%	1.0	0.70	1.5 lines
Ciardella *et al*[9]	30	30	100%	0.78	0.5	2.5 lines
Paccola *et al*[10]	13/26	-	-	0.92	0.65	2.2 lines
Shimura *et al*[11]	14/28	14	100%	0.63	0.32	2 lines
Present study	26/52	24	92.3	0.99	0.64	2 lines

This table shows that various studies have reported a mean improvement in BCVA with IVTA ranging from 1.5 - 2.5lines which was comparable with the visual outcome with mean improvement of 2 lines in our study eyes treated with intravitreal Triamcinolone.

Table 6: Visual outcome with IVB compared with other studies

	Total no of eyes	Improved		Mean BCVA: logMAR		
		No.	(%)	Pre IVB	Post IVB	Change in BCV
Hartiglou *et al*[12]	51	6	26%	0.86	0.75	3 lines
Ornek *et al*[13]	17	12	70%	-	-	1.6 lines
Paccola *et al*[10]	13/26	-	-	0.92	0.78	1 line
Shimura *et al*[11]	14/28	14	100%	0.61	0.36	2 lines
Arevelo *et al*[14]	48/101	16	33%	0.97	0.65	2.5 lines
Mehta *et al*[15]	36	-	-	0.71	0.6	1 line
Present study	26/52	26	91.6%	1.05	0.64	2 lines

This table shows that the visual outcome in our study eyes treated with intravitreal Bevacizumab was comparable with other studies. The various other studies have reported an improvement in BCVA with IVB ranging from 1-3 lines compared to a mean improvement in visual acuity by 2 lines in our study. The present study shows that either of the groups showed a maximum improvement at 8 weeks with the mean visual improvement being 2 Snellen's lines. The improvement in visual acuity was 1 to 4 or more lines on Snellen's chart. All the eyes treated with intravitreal Bevacizumab showed significant visual improvement in comparison to 92.3% eyes with intravitreal Triamcinolone acetonide at 8 weeks follow up. The functional improvement with intravitreal injection of Bevacizumab and Triamcinolone appeared to be more marked at 8 weeks in comparison to 4 weeks follow up. But statistically, there was no significant difference found between the effect of Intravitreal Triamcinolone acetonide and Bevacizumab.

CONCLUSION

Intravitreal Bevacizumab and Triamcinolone acetonide were equally effective in improving visual acuity in DME not responding to laser treatment. But, Bevacizumab was superior with stability of intraocular pressure and lesser chances of side effects, other than injection related complications in comparison to Triamcinolone acetonide.

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