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Original Research Article

Comparison of Therapeutic Efficacy of Intravitreal Bevacizumab plus Macular Laser versus Intravitreal Triamcinolone Acetonide plus Macular Laser in Primary Treatment of Diabetic Macular Edema

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Abstract: To compare the efficacy of intravitreal bevacizumab and macular laser vis-a-vis intravitreal triamcinolone acetonide and macular laser in primary treatment for diabetic macular edema. Randomised, prospective, comparative two-arm, non-interventional study with five time points. 60 eyes of 30 patients with bilateral DME and no previous ocular intervention participated in the study and were randomised into two groups. Both eyes of Group A patients received an intravitreal injection of 1.25mg of Bevacizumab and Group B patients received 4mg of Triamcinolone acetonide. One week after injection, all patients underwent macular photocoagulation. The clinical course of best corrected visual acuity (BCVA) in decimal fraction system and average central retinal thickness (CRT) using optical coherence tomography was monitored for up to 12 weeks after the injection. Before injection, mean of CRT and BCVA were 411.37±165.71µ and 0.252±0.154 in Bevacizumab group (A) and 356.50 ± 152.26µ and 0.378 ±0.248 in Triamcinolone group (B). Two weeks after injection and one week after macular photocoagulation (MPC), both groups showed significant regression of macular edema and improvement in vision. Bevacizumab group showed better results at 2weeks.The difference in CRT and BCVA at 2 weeks from baseline were 84.40 ± 22.68µ (p= .008) & 0.111 ± 0.015 (p< .001) in group A and 52.30± 15.63µ (p= .023) & 0.089± 0.033 (p= .113) in group B. The efficacy of Triamcinolone improved 4th week onwards, became comparable to Bevacizumab group at 8th week. At 12 weeks, the Triamcinolone group achieved slightly better results than Bevacizumab group, which started showing recurrence of macular edema. The differences in CRT at baseline and at 12 weeks in group A and group B respectively are 102.47 ± 23.50 µ(p= .001) and 108 ± 21.60 µ(p< .001).The differences in between baseline and BCVA at 12weeks in group A and group B respectively are 0.210± 0.026 and 0.214±0.04. Within the study period and with the generally used concentration, intravitreal bevacizumab, as treatment modality brings earlier reduction in DME, but at 4 and 8 weeks, the efficacy in terms of p-value in between two groups is similar. At 12 weeks bevacizumab group starts showing the beginning of waning effect of drug, although still comparable to Triamcinolone group. No increase in IOP was seen in bevacizumab group while one eye developed raised IOP in Triamcinolone group.
Keywords: Intravitreal injections, Bevacizumab (Avastin), Triamcinolone Acetonide, Macular Laser Photocoagulation, Diabetic Macular Edema

INTRODUCTION

Diabetic macular edema (DME) is the most common cause of vision loss in diabetic patients [1,2]. Intensive glycemic control [3,4], Blood pressure control [5], Focal/grid photocoagulation [6] are the most widely accepted methods to reduce the risk of vision loss from DME.

The ETDRS reported that Focal/ grid photocoagulation of eyes with edema involving or threatening the fovea reduced the 3-year risk of losing 3 or more lines of visual acuity by 50%, from 30% in the control group to 15% in the laser group. Lee and Olk [7] demonstrated that with modified grid macular laser, visual acuity was stabilized in 60.9%, decreased in 24.6%, and increased in only 14.5% of eyes with diffuse DME. In the diabetic model, retinal VEGF

levels are increased by 3.2- fold after 1week; this increase is accompanied by increased vascular permeability and breakdown of the blood–retinal barrier [8]. Therefore, alternative or adjunct treatments for DME, such as intravitreal triamcinolone acetonide (IVTA) [9,10] and anti-vascular endothelial growth factor (VEGF) antibody therapy [11] such as intravitreal bevacizumab have been the focus of the most recent attentions.

Over a decade or more, studies [12-16] have evaluated that intravitreal administration of triamcinolone acetonide is a promising therapeutic modality for reducing diabetic macular edema that fails to respond to conventional laser therapy.

Combination therapy of intravitreal triamcinolone acetonide with macular photocoagulation was found to be more effective than each single therapy [17]. In combination with Pan Retinal Photocoagulation (PRP) [18,19], IVTA prevents aggravation of macular edema without transient visual disturbance post laser in patients requiring immediate PRP.

In various studies [20-26] intravitreal bevacizumab in DME yielded a better visual outcome at 12 weeks compared with MPC and its effect was blunted yet statistically significant at 24 weeks.

It is proposed that reduction in macular edema prior to laser therapy, due to intravitreal triamcinolone or bevacizumab, may lead to better uptake of laser by retinal pigment epithelium and reduce the dose of laser therapy required.

"Keeping macular photocoagulation, as a gold standard treatment for diabetic macular edema, this study aims to compare efficacy of intravitreal triamcinolone acetonide and macular photocoagulation vis-à-vis intravitreal bevacizumab and macular photocoagulation for reducing foveal thickness, and to evaluate the visual prognosis of diabetic macular edema."

MATERIALS AND METHODS

Patient eligibility

60 eyes of 30 patients of Indian origin suffering from bilateral clinically significant diabetic macular edema confirmed on fundus fluorescein angiography and OCT, were included in this study.

Patients who had previous therapies for macular edema, including laser treatment, intravitreal injection of any drugs, vitrectomy, those having severe hypertension, diabetes mellitus, history of coronary artery disease/stroke, ongoing anticoagulant therapy, renal disease and those diagnosed with glaucoma and/or ocular hypertension, concurrent retinal or optic nerve disorder other than diabetic retinopathy were excluded from the study. All patients had HbA1c controlled at less than 8% for at least six months prior to the beginning of the study and during the study period.

Study Design

Randomised, comparative, prospective two-arm study with 5 time points.

All patients received a comprehensive ocular examination before and after treatment including best corrected visual acuity, 90D slit-lamp biomicroscopy and Goldmann three-mirror fundoscopy, applanation tonometry and anterior segment examination particularly for lens opacity (graded according to LOCS3 classification) were performed at baseline. Fundus Fluorescein angiography was done at baseline before starting treatment and at 12 weeks of follow up after treatment was given. Optical coherence tomography (Zeiss –Humphrey Stratus) for assessment of macular thickness and intraretinal changes was done before starting treatment and at each follow up visit. The O.C.T scans were performed in each eye at each visit using the six radial line patterns each 6mm long passing through the centre of fixation. For this study nine measurements of retinal thickness were considered. These 9 values were automatically obtained in 9 retinal locations: a central disc area of 1mm in diameter centered on the patients' fixation which was assumed to correspond to the central fovea and in a peripheral ring area 5mm in diameter in, 4 retinal quadrants – papillomacular, superior, temporal and inferior. The peripheral ring area of 5mm was further divided into 2 areas, inner macula extending upto 2mm from the central circle and outer macula extending upto 2mm from the central circle and outer macula extending a further 3mm from the middle circle.

Patients included in the study were randomized to bevacizumab group (group A) or triamcinolone acetonide group (group B). Both eyes of a patient received either triamcinolone acetonide or bevacizumab (avastin). The benefits and potential risks of the off label use of avastin were discussed with patients. Each patient signed a comprehensive consent form before

intravitreal administration of either drug. One week after intravitreal drug administration macular laser was performed, based on assessment of preoperative fundus fluorescein angiography leakage points and neovascularisation areas.

The procedure was carried out under aseptic conditions. After anaesthetizing the conjunctiva using topical anaesthesia and applying betadiene over lids and conjunctiva, patient's eyes were draped. Intravitreal injection of 1.25 mg (0.05cc) of preservative free Bevacizumab or 0.1 ml of triamcinolone acetonide (4mg, 40 mg /ml of vial) was given using a 30 gauge needle on 1 ml tuberculin syringe through inferotemporal pars plana (4 mm from limbus) after visualizing needle in vitreous cavity by indirect ophthalmoscopy. If the intraocular pressure was greater than 25 mm Hg as measured by hand –held applanation tonometer or the optic nerve head was not adequately perfused 20min after the injection, a paracentesis was performed. After injection, central retinal artery was examined to look for any obstruction due to high intraocular pressure. At the end of procedure, topical antibiotic was instilled and a light patch was applied. Patients were instructed to unpatch the eye after 2 hours and to administer topical antibiotic for 7 days. Patients were followed up on next day for any lens opacity, intra ocular tension and any vitreous complications.

After one week the patients were taken for macular grid photocoagulation. It was done under topical anesthesia with 532 nm Nd- YAG laser using Carl Zeiss Visual 532S frequency doubled Nd: Yag laser with Zeiss slit lamp attachment with the following parameters:

- Modified C grid within the arcade
- Spot size of 50-200 microns
- Power and time adequate enough for a 'gray' reaction (laser burn)
- The mainster standard lens was used with a coupling device for the macular grid laser photocoagulation.

The laser photocoagulation was done in all the patients by a single person only.

Follow up

Best corrected visual acuity, applanation tonometry, detailed fundal examination including three-mirror biomicroscopic examination of both eyes and quantitative and qualitative retinal evaluation on OCT at 2 weeks, 4 weeks, 8 weeks and 12 weeks was performed. At 12 weeks follow-up repeat fundus fluorescein angiography was performed to assess and document the efficacy of treatment.

Statistical Method

Snellen visual acuities were converted to the decimal equivalent for facilitation in statistical analysis. All the quantitative data was presented using various summary statistics (Mean, Standard deviation, Median and Range).The qualitative data like sex was presented in the form of proportion. In view of the data distribution, the data were explored using parametric as well as non parametric method. Accordingly, to see the changes in visual acuity as well as foveal thickness over the time period, repeated measure analysis of variance (ANOVA) with Greenhouse-Geiser correction was used. A p value of less than .05 was considered statistically significant. All the analysis was carried out using statistical package SPSS version 13.

RESULTS

Sixty eyes of thirty patients (21 males, 09 females) aged 41-70 years (mean age 56.37±5.97 years) with bilateral diabetic macular edema were studied. All patients had type-2 diabetes, and the mean duration of diabetes was 11 ± 6 years.

Before the administration of intravitreal drugs and macular laser intervention, mean central thickness was 411.37±165.7µ in Group A and 356±152.26µ in Group B. Also, the mean of baseline visual acuities in Group A was 0.252 ± 0.154, Group B 0.378 ± 0.248.

Alteration of Central Retinal Thickness (CRT)

Two weeks after bevacizumab injection (and one week after macular photocoagulation), mean CRT decreased significantly to 326.97± 112.64µ (p=0.008) and progressively decreased till 8 weeks. At 12 weeks, mean CRT in Group A was 308.90±102.489µ which is still a significant decrease in comparison with the baseline value (p=0.001), (Table 1). Similarly in Group-B, there was consistent and statistically significant decrease in CRT at 2, 4 and 8 weeks follow-up with mean CRT at 12 weeks being 247±47.549µ (p< .001), Table-2. The mean CRT values in both groups show a similar decreasing pattern till 8 weeks follow-up; however, between 8-12 weeks, the graphical difference appears significant (figure-1),

Table-1: Mean Of C.R.T on OCT and Mean Difference Values within Group- A

Duration	Mean of C.R.T	Std. Deviation	Mean Difference as compared to baseline value	ANOVA p value
BASELINE	411.37	165.716	---	---
AT 2 WEEKS	326.97	112.645	84.400*	.008
AT 4 WEEKS	294.90	86.962	116.467*	<.001
AT 8 WEEKS	288.90	79.538	122.467*	<.001
AT 12 WEEKS	308.90	102.489	102.467*	.001

Table-2: Mean of C.R.T on OCT and Mean Difference Values in Group- B

DURATION	Mean of C.R.T on O.C.T	Std. Deviation	Mean Difference as compared to baseline value	ANOVA p value
BASELINE	356.50	152.265	---	---
AT 2 WEEKS	304.20	115.181	52.300*	.023
AT 4 WEEKS	276.50	75.134	80.000*	.001
AT 8 WEEKS	262.00	61.232	94.500*	<.001
AT 12 WEEKS	247.73	47.549	108.767*	<.001

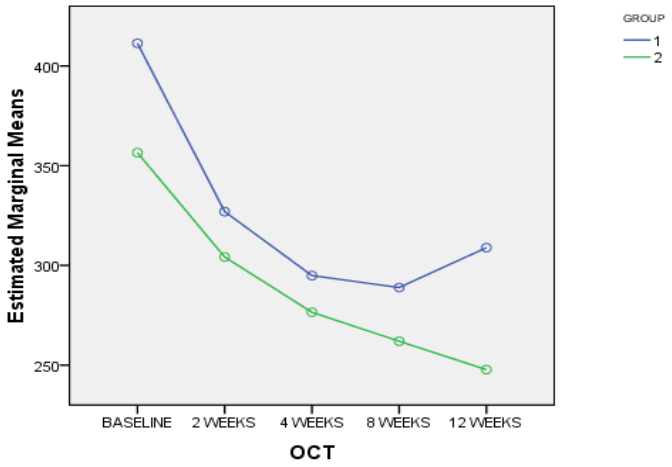

Fig-1: Comparison oF CRT (OCT) Values in Between Group A & B

Alteration of Visual Acuity (VA)

Mean VA in Group-A (Table 3) improved from 0.252±0.1541 to 0.363±0.198 at 2 weeks follow up and increased steadily as compared to baseline at 4, 8 and 12 weeks, the difference being statistically significant (p=0.000). The mean VA in Group-B (Table 4) also improved at 2 weeks but was statistically significant at 4,8 and 12 weeks follow up, when mean VA increased by 0.214±0.039 from baseline mean value.

Table-3: Mean Visual Acuity Values and Mean Differences in VA of Group-A

Duration	Mean of visual acuity	Std. Deviation	Mean Difference in visual acuity	ANOVA p value
BASELINE	.252	.1541	---	---
AT 2WEEKS	.363	.1981	-.111*	<.001
AT 4WEEKS	.405	.1799	-.153*	<.001
AT 8WEEKS	.452	.2410	-.200*	<.001
AT 12WEEKS	.462	.2298	-.210*	<.001

Table-4: Mean Visual Acuity and Mean Differences in VA Values of Group B

Duration	Mean of visual acuity	Std. Deviation	Mean Difference in visual acuity	ANOVA p value
BASELINE	.378	.2480	---	---
2 WEEKS	.467	.2550	-.089	.113
4 WEEKS	.506	.2362	-.129*	.006
8 WEEKS	.557	.2462	-.179*	<.001
12 WEEKS	.592	.2460	-.214*	<.001

Table-5: Reduction Ratios in Group A & B

No. of weeks after intravitreal injection	Bevacizumab group	p- value bevacizumab group	Triamcinolone Acetonide group	p- value triamcino-lone group
2	20.51%		14.6%	
4	28.31%	<.001	22.4%	<.001
8	29.7%	<.001	26.5%	<.001
12	24.9%	.001	30.5%	<.001

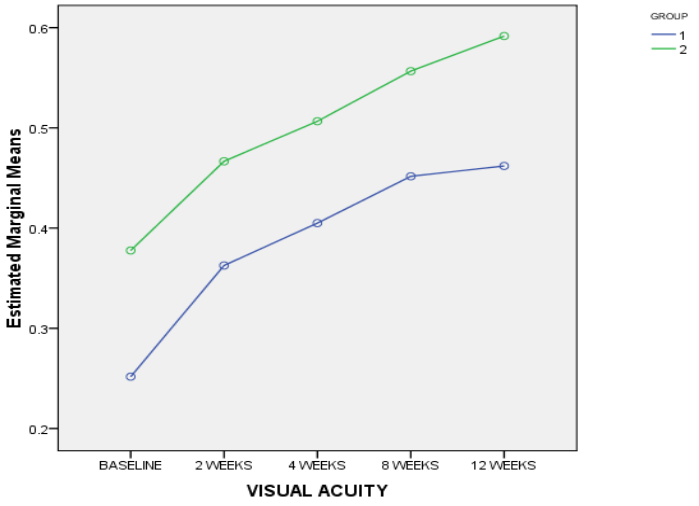

Fig-2: Comparison of Visual Acuity in Between Group A (1) & B (2)

Between the two groups, there was no statistically significant difference of VA at 12 weeks (p=0.222) implying no difference in the efficacy of two drugs used in the study as also evident from figure-2.

Alteration in Intraocular Pressure

A single case of post intravitreal injection rise in IOP to 60 mm Hg, in group B was noted.

DISCUSSION

Diabetic macular edema (DME) occurs due to the breakdown of inner blood retinal barrier leading to leakage of fluid, lipoproteins and other plasma constituents that causes thickening of retina.

In treating DME the goal is to stabilise the vision by attempting to stop the damaged blood vessels from leaking. Macular laser causes transient increase in macular thickness and slow improvement in visual acuity and sometimes only stabilises the vision.

In our study both Bevacizumab and Triamcinolone Acetonide injected eyes showed significant reduction in macular edema. Out of 30 eyes, in IVTA group one eye developed raised intra-ocular pressure to an alarming 60mm Hg, which had to be controlled on anti- glaucoma medication throughout 12 weeks. No IOP rise or cataract progression / induction was seen in Bevacizumab group confirming with study [27] which stated that intravitreal bevacizumab injections are safe and effective in treatment of DME.

In a study similar to ours by Shimura *et al*. [21] in 2007 compared the intravitreal efficacy of the two drugs over a period of 24 weeks after injection in absence of any MPC. The drug dosages in both studies were also same. They stated that recurrence of macular edema in bevacizumab group was observed at an earlier time than IVTA group and that anti-VEGF therapy is less established than the anti- inflammatory therapy except for being safer in IOP control.

A recent study in 2010, Forte R *et al*. [28] compared intravitreal bevacizumab (IVB) with intravitreal triamcinolone combined with macular laser grid (IVTA-MLG) for diffuse Diabetic macular edema concluded that at 6 and 12 months after first treatment for chronic DME, IVB provided significant improvement of BCVA and foveal thickness, whereas improvement after IVTA-MLG was not significant. Increased IOP occurred in 10.4% of patients who received IVTA, with patients requiring trabeculectomy.

For comparing the efficacy of the two drugs, decrease in CRT in central 1mm of macula, reduction ratio was calculated at 2, 4, 8, 12 weeks as compared to baseline value.

Reduction Ratio = $(F n – F_1) \div F 1$

Fn = Central Foveal thickness ‘n’ weeks after injection

F_1= Central Foveal thickness before injection.

The reduction ratio in bevacizumab injected eyes at 2 weeks was 20.51% while in intravitreal triamcinolone group was only 14.6%. As evident from Table –5, the reduction ratio increased steadily in both groups at 4 weeks and 8 weeks. However, at 12 weeks after the injection, the reduction ratio in bevacizumab group was 24.9% indicating a relative dip in its efficacy. In contrast, the reduction effect in intravitreal triamcinolone acetonide group was still 30.5% on an increasing trend, indicating that triamcinolone maintained its efficacy for 12 weeks after the injection.

Our results state that “Intravitreal bevacizumab injection as a treatment modality brings earlier reduction in macular edema as compared to IVTA group but at 4 weeks and 8 weeks, the efficacy in terms of p- value and reduction ratio in between two groups is similar. At 12 weeks bevacizumab group starts showing the beginning of waning effect of drug, although still comparable to IVTA group. Recurrence of macular edema was observed in bevacizumab injected eyes at an earlier time than in IVTA injected eyes, a fact also supported by a retinal penetration study[29]that revealed absence of bevacizumab four weeks after the injection, which may suggest a limited effect of bevacizumab on suppression of VEGF activation.

No increase in IOP was seen in bevacizumab group during the study period, while IVTA group had one eye which developed raised IOP during the clinical course. During the study duration of 12 weeks, both drugs showed statistically significant efficacy in reducing diabetic macular edema and improving visual acuity, while bevacizumab has advantage of greater IOP stability, triamcinolone acetonide is cost effective and has longer duration of action.

As the number of patients included in the study was less and study duration was 3 months, to apply the results on whole population, a larger population based study, over a longer period of follow-up, would probably give much more accurate results.

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