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Effect of combined Intravitreal Injections of Bevacizumab and Triamcinolone Acetonide vs intravitreal Bevacizumab in Diffuse Diabetic Macular Edema

[1]Ambade Rakhee, [2]Ambade Ajay, [3]Sagdeo M
[1]MD, Associate professor, Department of physiology, NKP Salve Institute of Medical Sciences and Research center, Digdoha hills, Higna, Nagpur-440019
[2] Mch(opthal),DOMS,Consultant, Ambade Eye Hospital, Indora Square Nagpur-440017,
[3]MD, Prof. and Head, Department of physiology, NKP Salve Institute of Medical Sciences and Research center, Digdoha hills, Higna, Nagpur-440019

Abstract
Purpose: *To evaluate and compare the efficacy of two treatment strategies intravitreal anti-VEGF(bevacizumab-IVB) and steroid (triamcinolone acetonide-IVTA) combination in comparison to intravitreal anti-VEGF (IVB) in treatment of diabetic macular edema.*
Material and Methods*: 98 eyes of 81 subjects with diabetic macular edema were included in this prospective, randomized, interventional study, divided into two groups of 49 each. Group A was treated with bevacizumab(0.05ml; 1.25mg) and Group B (IVB+IVTA)with bevacizumab and triamcinolone at 0 ,1 and 2 months respectively. Each eye was evaluated at baseline, at 3 months and at 6 months for central macular thickness (CMT), BCVA (logMAR) and intraocular pressure. Result: Parameters identified for comparative study included CMT, BCVA (logMAR) and intraocular pressure. The difference in mean CMT between the two groups at the end of 3 months was significant (Grp. A 360.59±92.44 vs. Grp. B 345.10±76.62) and much more so at the end of 6 months (Grp A 332.24±91.78 vs. Grp B 292.82±88.84), the other criteria like BCVA (logMAR) also showed marked improvement in Grp B at the end of 6months.The rise in IOP was found to be significant at the end of study period in Grp B.*
Conclusion: *In the treatment of diffuse diabetic macular edema, using a combination of IVB+IVTA is definitely more effective than using IVB alone, though caution has to be exercised in patient selection and close IOP monitoring is required in patients treated with IVTA.*
Key words: *Diffuse diabetic macular edema, bevacizumab, intra-vitreal triamcinolone acetonide, central macular thickness, intraocular pressure.*

I. Introduction

Diabetic retinopathy (DR) is an important cause of acquired visual loss and impairment in working age group worldwide.[1-4]The Salisbury Eye Evaluation Study showed that diabetic retinopathy was the third most important cause for visual impairment.[1]Diabetic macular edema (DME) is a manifestation of diabetic retinopathy that produces loss of central vision .[2]In the Early Treatment Diabetic Retinopathy Study (ETDRS), focal photocoagulation of eyes with clinically significant macular edema (CSME) reduced the risk of moderate visual loss by approximately 50%.[5]In spite of treatment, 12% of treated eyes developed moderate visual loss. Furthermore, central retinal thickening remained in approximately 40% and 25% of treated eyes after 12 months and 36 months, respectively.[5-7]Recently, a series of studies suggested post-laser release of inflammatory factors, accumulation of leucocytes in the non-photocoagulated posterior pole, and up-regulation of angiogenic growth factors, such as vascular endothelial growth factor (VEGF), play a role in the pathogenesis of the edema.[9–13] VEGF is up-regulated in diabetic retinopathy,[12,13] so administration of some kind of anti VEGF agent seems a logical option. Several studies are currently evaluating the role of anti- VEGF agents for the treatment of ocular disease associated with choroidal and/or retinal neovascularization and exudative processes, especially age-related macular degeneration [14,16] and diabetic retinopathy.[17-22] Corticosteroids also may work through multiple mechanisms of action. They are known to reduce vascular permeability, reduce blood–retinal barrier breakdown, down-regulate VEGF production, and inhibit some matrix metalloproteinase.[9, 10, 23, 24]Some studies have evaluated this drug effect in DME. [22, 23]There are many factors that are involved in pathogenesis of DME, so many alternatives may be suggested for these patients (pharmacologic or surgical). The increase in retinal capillary permeability and subsequent retinal edema may be the result of a breakdown of the blood–retinal barrier mediated in part by VEGF.

Intravitreal bevacizumab has been effective in cases with center involved DME in the improvement of visual acuity, reduction of macular edema, fibro vascular proliferation in retinal NV and resolution of vitreous

hemorrhage, but in cases with center involved DME refractory to focal grid laser studies have shown that IVTA has superior efficacy than IVB.[21-23]Available literature on the subject indicates that adding intravitreal steroid to intravitreal anti-VEGF agent may intensify and/or consolidate effect of both agents.

Thus, the purpose of this study is to evaluate the efficacy and safety of the combined effect of triamcinolone acetonide and bevacizumab in comparison to Avastin in the management of DME. The aims of our study were to compare, using an interventional case series design, the efficacy of intravitreal injection of bevacizumab and triamcinolone combination for reducing foveal thickness, and to evaluate the visual prognosis and anatomic alterations of macular edema using spectral domain OCT

Materials and method

It is a prospective, randomized, comparative interventional case series of 98 eyes of 81 subjects with diabetic macular edema. This study was conducted in accordance with ethical standards and the Helsinki declaration. The patients were fully informed on the risks and the benefits of treatments, and accordingly written informed consents were obtained.

The study duration was of six month and included patients of type-II diabetes above forty years of age hailing from central India.

A detailed systemic evaluation including medical history, blood pressure, serum HbA1c (glycosylated hemoglobin) levels, renal profiles and complete ocular examination was performed for each enrolled patient. Ocular examination included best corrected visual acuity (BCVA), intraocular pressure (IOP), presence of lens opacities using the Lens Opacities Classification System III (LOCS III), fundus examination, and macular thickness measurement by the optical coherence tomography (optovue–spectral domain OCT).

Inclusion criteria –Patients with very severe NPDR to high-risk PDR with clinically significant macular edema (CSME –ETDRS definition) were considered for enrollment into the study. The central macular thickness (CMT)> 300µ on cross hair protocol (SD – OCT) reported in the central 1 mm macular thickness map was taken as the mean retinal thickness of the macula. OCT criteria included more than 50% of area with cystoid changes on Emm5 protocol. Pre-operative assessment of all the patients included the best-corrected visual acuity, applanation tonometry and fundus examination.

The exclusion criteria were macular edema related to recent intraocular surgery or other procedures, vitreous traction (based on OCT), history of any treatment for diabetic retinopathy at any time or anticipating the need for pan retinal laser photocoagulation (PRP)in the 6 months following randomization, uncontrolled glaucoma, steroid responders, recent history of arterial thromboembolic event, and poorly controlled hypertension, use of systemic steroids and/or systemic anti-VEGF.

All intravitreal injections were performed using a standard protocol under topical anesthesia and sterile operating conditions. Bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA, USA)(0.05 ml; 1.25 mg) was injected superotemporally using 30 G needle through pars-plana. Simultaneously Triamcinolone acetonide (Trilon, Ajanta Pharma India) (0.05 ml; 2 mg) was injected in a separate syringe using 30 G needle inferotemporally through pars-plana for the IVTA+IVB group. Central retinal artery was assessed after injection. Post operative anti-glaucoma medication was started for all patients. Patients were followed at 24 hours post-operatively and weekly thereafter for the assessment of anterior chamber reaction and/or intraocular pressure (IOP). Two more such injections were repeated after an interval of one month. Therefore a total of three intravitreal injections of Avastin were given in group A and IVB+IVTA in group B. Best-corrected visual acuity, funduscopy, fluorescein angiography, and posterior segment OCT were conducted at baseline, 3rd month and 6th month post-operatively. Complications like cataract formation, vitreous hemorrhage, and endophthalmitis were recorded.

Statistical analysis

The primary efficacy outcomes in the study were CMT, BCVA (logMAR) and IOP at 3 and 6 months as compared to baseline. Repeated measure analysis of variance (ANOVA) was performed to evaluate the statistical significance of change of each parameter with time in each treatment group. Assumption of sphericity was evaluated using Mauchly's test for each parameter. When the assumption was violated, Greenhouse-Geisser ($\varepsilon < 0.75$) or Huynh-Feldt ($\varepsilon > 0.75$) corrections were used to decide statistical significance of difference across time. Upon significant, post hoc analysis was carried out following Bonferroni correction. Visual acuity was correlated with CMT at 3 and 6 months using Pearson's correlation coefficient.

Results

A total of 98 eyes of 81 patients with diabetic macular edema were included in this study.Equal number i.e., 49 eyes were randomly assigned to Avastin (Group A)and IVTA+IVB(Group B) groups. Summary statistics for baseline characteristics in terms of age, macular thickness, visual acuity and IOP between two groups were compared as shown in Table 1.The mean age of the patients in Avastin group was 54.73 ± 11.91 years, whereas

in IVTA+IVB group it was 58.18 ± 11.22 years; and the mean difference was statistically insignificant with *P*-value of 0.151. Another baseline characteristic, duration of diabetes, in Avastin group had a mean of 11.34 ± 6.69 years, while in IVTA+IVB group it was 10.97 ± 4.65 years and the difference was statistically insignificant (*P*-value: 0.765). Further, mean CMT in Avastin group (478.10 ± 142.78 µm) differed insignificantly from that of IVTA+IVB (474.71 ± 96.29 µm) with a *P*-value of 0.889. Mean IOP before treatment in Avastin group (15.10 ± 1.74 mm Hg) and in IVTA+IVB (15.26 ± 1.38 mmHg) also differed insignificantly (*P*-value: 0.654). BCVA expressed in terms of logMAR (minimum angle resolution) showed statistically insignificant difference between Avastin (0.82 ± 0.14) and IVTA+IVB (0.86 ± 0.09) with *P*-value of 0.096.

Table 1: Baseline characteristics of patients in two treatment groups

	Treatment type		
Characteristics	Avastin	IVTA + IVB	*P*-value
No. of Eyes	49	49	
Age in years [Mean ±SD]	54.73 ± 11.91	58.18 ± 11.22	0.151
Duration of Diabetes [Mean ± SD]	11.34 ± 6.69	10.97 ± 4.65	0.765
CMT (µm) [Mean ± SD]	478.10 ± 142.78	474.71 ± 96.29	0.889
BCVA [Mean(log MAR) ± SD]	0.82 ± 0.14	0.86 ± 0.09	0.096
IOP (mm Hg) [Mean ± SD]	15.10 ± 1.74	15.26 ± 1.38	0.642

After ascertaining the baseline features of two groups, the treatment effect within each group was evaluated considering CMT,BCVA(logMAR) and IOP as dependents and using repeated measure one-way analysis of variance. The post-treatment effects for each of these parameters were compared with the baseline in respective groups.

Central macular thickness

In Avastin group, CMT differed significantly across time points (F=40.527; P< 0.0001) with a Greenhouse-Geisser correction in repeated measure ANOVA (Table 2). Post hoc tests using Bonferroni correction revealed that mean CMT decreased significantly at month 3 and 6 when compared with the baseline with P< 0.0001 (Table 3). However, the difference between month 3 and 6 differed insignificantly (P = 0.062). On similar lines, CMT changes were evaluated in IVTA+IVB group. Repeated measure ANOVA with Greenhouse-Geisser correction revealed statistically significant reduction in mean CMT (F=109.03; P< 0.0001) across time points. Post hoc analysis also showed significant difference between all pair wise comparisons (Table 3). Figure 1 shows the line plots for mean CMT across time points for two groups. The difference in the mean CMT between two groups at the end of 6 months was statistically significant according to *t-test for independent samples* (P= 0.034).

Visual acuity

In Avastin group, repeated measure ANOVA showed significant improvement in visual acuity using Huynh-Feldt correction (F=40.988; P< 0.0001) across time points (Table 2). Subsequent post hoc analysis suggested significant difference in all pair wise comparisons (Table 3). Similar was the observation in IVTA+IVB group. The Greenhouse-Geisser correction in repeated measure analysis revealed significant increase in visual acuity (F=112.55; P< 0.0001) and further post hoc analysis showed highly significant difference between all pair wise comparisons (Table 3). Line plots showing the change in the mean logMAR score for two groups are shown in Figure 1. At the end of six months, the difference of mean logMAR score between two groups was statistically insignificant as per t-test for independent samples (P=0.341).

Intraocular Pressure

The post-treatment change in IOP was analyzed in both the groups using repeated measure ANOVA. Analysis revealed that in Avastin group, the increase in IOP with time was insignificant as indicated by *P*-value of 0.061 (F=3.057) after using Huynh-Feldt correction. A marginal increase in post-treatment mean IOP with reference to baseline is evident through Figure 1. However, in the IVTA+IVB group, IOP followed assumption of sphericity (P=0.151) and showed significant increase after treatment as compared to baseline (F=40.142; P<0.0001). Post hoc analysis revealed that the difference between month 3 and baseline as well as month 6 and baseline were statistically significant (P<0.0001); while the change from month 3 to month 6 was insignificant (P=0.999), which is evident in Figure 1. The difference of mean IOP at the end of 6 months suggested significant increase in IVTA+IVB group as compared to Avastin group (P=0.00003).

Table 2: Statistical significance of difference in different parameters using repeated measure one-way ANOVA

Parameter	Treatment group	Time scale			Mauchly's Sphericity test (p-value)	F value	DF	P value
		Baseline	Month 3	Month6				
Central macular thickness (CMT)	*Avastin*[1]	478.10 ± 142.78	360.59 ± 92.44	332.24 ± 91.78	< 0.0001			
	IVTA+IVB[2]	474.71 ± 96.29	345.10 ± 76.62	292.82 ± 88.84	< 0.0001	40.527	1.35 4†	< 0.0001
Visual acuity (VA)[log(MAR)]	*Avastin*[1]	0.82 ± 0.14	0.64 ± 0.19	0.52 ± 0.27	< 0.0001	109.03	1.44 1†	< 0.0001
	IVTA+IVB[2]	0.86 ± 0.09	0.72 ± 0.18	0.57 ± 0.26	< 0.0001	40.988	1.58 8‡	< 0.0001
Intra-ocular pressure (IOP)	*Avastin*[1]	15.10 ± 1.74	15.45 ± 1.90	15.22 ± 1.80	0.003	112.55	1.41 7†	< 0.0001
	IVTA+IVB[2]	15.26 ± 1.38	16.83 ± 1.84	16.79 ± 1.79	0.151	3.057	1.68 9‡	0.061

†Greenhouse-Geisser correction (ε< 0.75); ‡Huynh-Feldt correction (ε> 0.75); *No correction since sphericity assumption holds; [1]*n*=49; [2]*n*=49

Table 3: Post-hoc test for pair wise statistical significance between time points

Parameter	Treatment group	Paired comparison*		
		Baseline vs Month 3	Baseline vs Month 6	Month 3 vs Month 6
Central macular thickness (CMT)	*Avastin*	< 0.0001	< 0.0001	0.062
	IVTA+IVB	< 0.0001	< 0.0001	0.002
Visual acuity (VA)	*Avastin*	< 0.0001	< 0.0001	0.001
	IVTA+IVB	< 0.0001	< 0.0001	< 0.0001
Intra-ocular pressure (IOP)	*Avastin*	NA	NA	NA
	IVTA+IVB	< 0.0001	< 0.0001	0.999

*Bonferroni correction

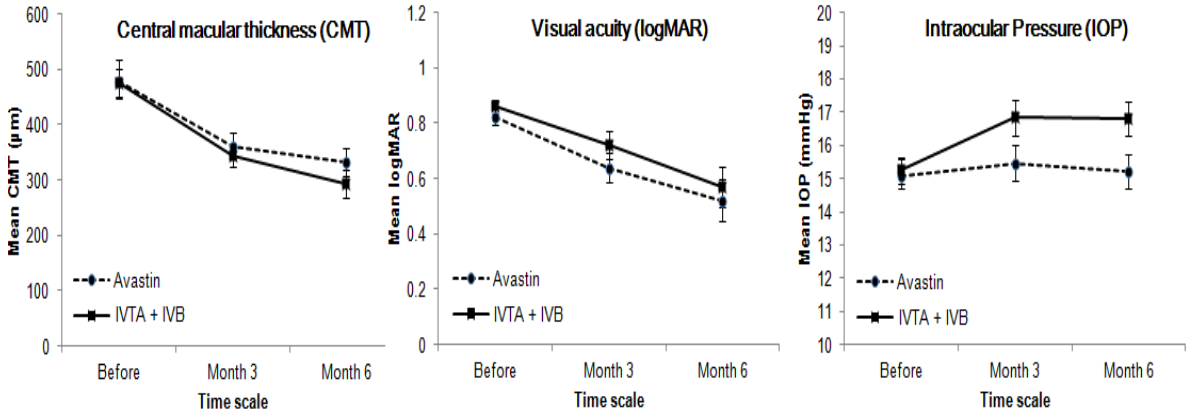
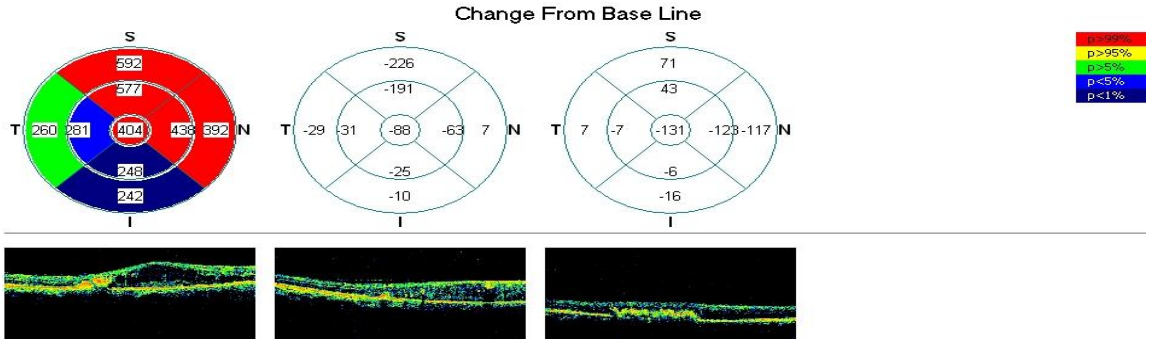
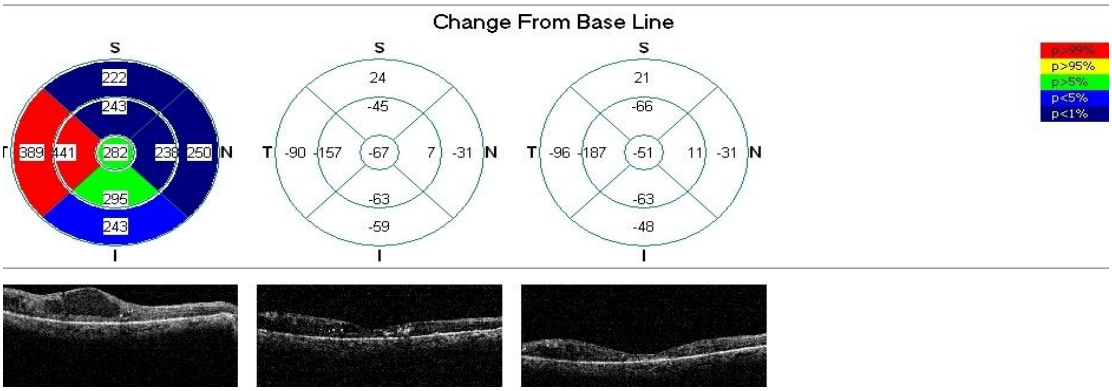


Figure 1: Line plots showing mean parameter values for two groups across time points.



Picture 1. Macular thickness change seen in a patient treated with Intravitreal Bevacizumab



Picture 2 Macular thickness change seen after combine Intravitreal Bevacizumab and Triamcinolone acetonide

Discussion

DME is one of the major causes of visual impairment in patients with diabetic retinopathy. It has been characterized by inflammation, including intravitreous induction of pro-inflammatory cytokine, intraretinal expression of pro-inflammatory caspases and mediators, and therefore, many clinical investigators have found that Intravitreal injection of a corticosteroid like triamcionoloneacetonide may reduce macular edema. Although the reduction effect of triamcinolone on macular edema improves visual function, recurrence of macular edema was often observed within 24 weeks after treatment and IOP was occasionally increased in this therapy. Therefore, safer and longer-acting therapy for DME was sought for. Paccola et al.[3o]showed that a single intravitreal injection of triamcinolone acetonide has advantage over Avastin in the short-term management of refractory DME ,specially with regards to changes in CMT. In the present study the beneficial effect of triamcinolone was maintained by repeating IVTA+IVB injection at one month interval for further two months. Since it was reported that the vitreous level of VEGF increased and correlated with the severity of macular edema in DME patients, anti-VEGF therapy is expected to show a dramatic reduction of DME.Haritiglou et al.[23] reported a significant reduction in macular thickness at 2(15%),6(17%) and 12weeks(25%) following monthly IVTA in patients with DME. This feature of IVTA is emulated in this study as well. In a study by Kriechbaum et al.(Diabetic Retinopathy Research Group)[29] 3 injections of 2.5mg bevacizumab and one 8mg triamcinolone were compared. After 6 month,visual rehabilitation was comparable but reduced in 12th month in triamcinolone group due to factors such as cataract formation.Our study shows a synergistic effect in group IVTA+IVB & which sustains till the end of the study. Though this effect was not statistically significant between groups but the percentage reduction of CMT at 3rdmonth in Avastin group was, 25.73% and in IVTA+IVB group, was 34.81%. This indicates that the combination has synergic effect on reduction of CMT. The aim of treatment is to gain visual acuity and the IVTA+IVB group show statistically significant improvement over IVB group.

One of the most important side effects of triamcinolone is raised IOP for this reason steroid responders were excluded and a lower dose of steroid was used in the study .Therefore, as expected, the dynamic change of IOP in the bevacizumab-injected eye was “safer” than that in the triamcinolone-injected eye. Still, careful observation is needed to perform Intravitreal injection because of the reported cases of endopthalmitis and systemic side effect. But since the doses of triamcinolone was half of the regular previous studies the expected IOP bounce was not seen in IVTA+IVB group.

The CMT reduction & visual acuity gain in IVTA+IVB group is better & statistically significant but close observation is required for control of IOP including selection of patient specially to exclude patient with uncontrolled glaucoma .

Thus it is suggested that DME can be well controlled & effectively managed by IVTA+IVB injection.
In this study cataract formation in triamcinolone group has not been considered. This is because of a lesser duration of study and a lower dose of steroid used.

Conclusion - This study demonstrates the synergistic effect of reduction in central macular thickness resulting in better visual acuity in patients of diffuse DME treated with combine IVTA+IVB. The beneficial effect can be sustained for a longer period of time when steroid and anti-VEGF are combined. The result of this study cannot be generalized, adequate patient selection and careful monitoring of patient for any uncontrolled rise in intraocular pressure is required during the post-operative period.

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