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TO EVALUATE THE SHORT TERM EFFICACY AND SAFETY OF INTRAVITREAL BEVACIZUMAB IN TREATMENT OF DIABETIC MACULAR EDEMA AND TO COMPARE IT WITH CONVENTIONAL LASER THERAPY AS A PRIMARY THERAPY.

Ophthalmology

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ABSTRACT

Aims: To evaluate efficacy, safety & tolerability of bevacizumab (1.25mg/0.05ml) in diabetic macular edema & compare the results of intravitreal bevacizumab in diabetic macular edema with that of laser therapy.

Materials & Methods: This prospective, interventional, randomized, comaparative study was conducted on 40 patients with diabetic macular edema, divided into Group A and Group B consisting of 20 patients each. The patients were treated with modified macular grid photocoagulation or intravitreal bevacizumab in group A and group B respectively.

Results & analysis:

Conclusion: The anatomic and functional improvement in both groups was statistically significant from baseline to end of study but there was no significant difference between groups. Our results also show that bevacizumab was well tolerated and no ocular & systemic adverse events were noticed during the study.

KEYWORDS

bevacizumab, diabetic macular edema,photocoagulation, intravitreal.

INTRODUCTION:

Diabetes mellitus (DM) is a major cause of avoidable blindness in both the developing and the developed countries. Patients with diabetic retinopathy (DR) are 25 times more likely to become blind than non-diabetics. Diabetic macular edema is leading cause of visual loss in diabetic patients. Good glycemic control arrests the development and progression of DR and decreases the visual loss. Diabetic retinopathy results in leakage at level of the retinal pigment epithelium (outer blood retinal barrier) as well as the more clinically apparent leakage at the level of retinal capillaries (inner blood retinal barrier). The gold standard in treatment of DME is laser photocoagulation. If focal thickening /leakage - focal photocoagulation & diffuse thickening /leakage –grid or modified grid photocoagulation. Intravitreal bevacizumab is a new treatment modality which is currently being tried out for use in macular edema following central retinal vein occlusion (CRVO), wet age-related macular degeneration (ARMD), rubeosis irides, proliferative diabetic retinopathy (PDR) and retinopathy of prematurity. Although intravitreal use of bevacizumab is an off-label option its use has risen exponentially in the last few months mainly due to its efficacy and economic considerations. Based on these observations we evaluated intravitreal bevacizumab in DME in which VEGF is known to play a key role in increasing vascular permeability and breaking down the blood retinal barrier.

AIMS:

This study evaluate efficacy, safety & tolerability of intravitreal bevacizumab (1.25mg/0.05ml) in treatment of diabetic macular edema & compare the results of intravitreal bevacizumab in diabetic macular edema with that of laser therapy.

MATERIALS & METHODS:

This prospective interventional, randomized, comparitive study was conducted in SMS medical college eye department. 40 patients with diabetic macular edema were included in this study. They were divided into Group A and Group B consisting of 20 patients each. The patients were treated with modified macular grid photocoagulation or intravitreal bevacizumab in group A and group B respectively. Patients between 18 to 70 years of age with confirmed diagnosis of diabetes with diffuse diabetic macular edema in Fundus Fluorescein angiography (FFA) with best corrected visual acuity between 20/200 & 20/40, glycosylated hemoglobin < 11 mg/dl, were included in study. All patients gave informed consent to participate in the trial and to receive intravitreal injection of bevacizumab, were able to complete follow up of at least 6 months. All Patients had sufficiently clear media to allow clinical examination and investigation. Patients with NVE, NVD on FFA, Only focal macular edema attributable to focal leaks from micro aneurysm, presence of any other macular pathology like ARMD or any vascular occlusive diseases affecting macula, optic disc pathology were excluded from study. Patients who were previously treated with pan retinal photocoagulation (PRP) and grid laser within last six months, with vitreomacular traction, ischemic maculopathy , with uncontrolled diabetes, hypertension, chronic renal failure and history of stroke were excluded from the study. Duration of follow up was 6 months from recruitment. After explanation of therapeutic option available to the patients and expression of willingness to enroll into the study, registration, total work up and documentation of clinical state was done. ECG, urine complete, blood sugar fasting & post prandial, glycosylated Hb level, renal function test , liver function test, complete blood count, coagulation profile (BT, CT, INR) was done in all patients. Complete ophthalmological examination, best corrected visual acuity by ETDRS, log MAR acuity & near visual acuity, contrast sensitivity measured by Pelli –Robson chart, slit lamp biomicroscopy of anterior segment, biomicroscopy of the fundus, Indirect ophthalmoscopy, Fundus photography, fundus fluorescein angiography, IOP by Applanation tonometry noted in all patients. Vision specific health related quality-of-life (HQROL) assessment by adapted translated NEI-VFQ 25 questionnaire was done. All these parameters also noted during follow up visits at 1.5, 3 & 6 months. The patients were explained the procedure and an informed, written consent were taken.

Procedure of laser Group A: Topical anesthesia proparacaine eye drops were used in each case. Modified grid laser treatment given by double frequency Nd YAG laser machine with help of contact lens. After laser topical anti-inflammatory eye drops (ketorolac) were given to all patients for 7 days. Evaluation of post intervention events were include, pain, corneal abrasion, foveal burn, optic disc damage, lens opacity, blurring of vision.

Procedure for intravitreal Avastin: The patients were explained the procedure and an informed, written informed consent were taken. Topical antibiotic prophylaxis was given to all patients. The patients was explained the procedure. For topical anesthesia proparacaine eye drops were used in each case. 5% povidone - iodine solution was used to rinse the ocular surface and cul-de-sac generously while lids was scrubbed with cotton tipped applicator soaked in 5% providone – iodine. After placing a sterile eyelid speculum, application of 5% povidone – iodine directly over the injection site was done. The conjunctiva in the quadrant opposite to that chosen for the injection is grasped with a forceps and the globe is held steady. The pars plana injection of 1.25mg /0.05ml of bevacizumab was delivered 3 to 4 mm posterior to the limbus depending upon the phakic status using 30 gauge needle. After the needle is injected through the sclera, it is visualized in the mid vitreous space. The drug is then injected steadily and at a moderate pace into the anterior vitreous space. A rotatory motion of the plunger may be employed to ensure this. In order to avoid

the vitreous wick syndrome, surgeons might shift the conjunctiva a with a cotton-tipped applicator prior to injection & then roll a cotton tipped applicator over the entry site to minimize reflux as the needle is withdrawn. An oblique beveled entry may also be employed to prevent reflux. The fundus was checked with indirect ophthalmoscopy following the injection to rule out any retinal tears, detachment, confirm central retinal artery perfusion and assess any lens trauma. All patients were instructed to instill topical antibiotics for 7 days. Evaluation of post intervention events were include increased inflammation, infective and non infective endophthalmitis, increased intraocular pressure, intraocular hemorrhage, injury to intraocular structures, cataract formation, retinal perforation and retinal tear leading to retinal detachment. Follow up was done 1.5, 3 & 6 months after injection. Parameters were assessed and recorded during follow-up visits All the readings was performed by a single observer to avoid bias, both pre and postoperatively.

Observations:

Table 1: Age & diabetic status of study groups

	Group	N	Mean	Std. Deviation	Sig. (2-Tailed)
Age	A	20	60.8500	4.89118	.912
	B	20	61.0000	3.56887	
DM duration	A	20	9.4500	3.34782	.132
	B	20	11.4000	4.56992	
Fbs	A	20	110.5000	13.65939	.104
	B	20	117.4500	12.74228	
Hba1c	A	20	7.6316	.60190	.257
	B	20	7.4000	.65131	

Base line fasting blood sugar & HbA1C level are comparable in both groups. The mean age in group A=60.85 years & in group B =61.00 years. The mean duration of diabetes in group A =9.45 years& in group B =11.40 years.

Table 2: Grade of Retinopathy in study eye

Grade Of Retinopathy	GROUP A		GROUP B		Total	
	No.	%	No.	%	No.	%
Mild NPDR	0	0	0	0	0	0
Mod NPDR	12	60.00	12	60.00	24	60.00
Severe NPDR	8	40.00	8	40.00	16	40.00
Total	20	100.00	20	100.00	40	100.00

Chi-Square = 0.104 with 1 Degree of Freedom; P = 0.747
The groups were similar in terms of their grade of retinopathy.

Table 3 : Grade of macular edema in study eye

Macular Edema	GROUP A		GROUP B		Total	
	No.	%	No.	%	No.	%
Mild	2	10.00		0.00	2	5.00
Mod	8	40.00	11	55.00	19	47.50
Severe	10	50.00	9	45.00	19	47.50
Total	20	100.00	20	100.00	40	100.00

Chi-Square = 0.000 with 1 Degree of Freedom; P = 1.000

They had severe macular edema in 10 patients in group A & 9 patients in group B. Patients with moderate macular edema were 8 in group A & 11 in group B (p= 1.00).

Table 4: Base line visual function data of sample

	Visual function	Mean	Standard deviation	Median	Range
Group A	BCVA fraction	0.1905	0.07030	0.16	0.1-0.32
	BCVA Log MAR	0.7500	0.15728	0.8	0.5-1.0
	Log MAR Near visual acuity	1.2895	0.12425	1.3	1.0-1.4
	Contrast sensitivity	0.8250	0.19160	0.9	0.6-1.05
Group B	BCVA fraction	0.1865	0.06360	0.16	0.1-0.32
	BCVA Log MAR	0.7600	0.15009	0.8	0.5-1.0
	Log MAR Near visual acuity	1.2550	0.17006	1.3	0.9-1.4
	Contrast sensitivity	0.8250	0.18532	0.75	0.6-1.2

Both the groups were comparable in terms of their best corrected visual acuity for distance BCVA Fr, Log MAR visual acuity, near visual acuity, contrast sensitivity.

Table 5: Baseline VFQ 25 in study sample

Group	N	Mean	Std. Deviation	Sig. (2-Tailed)
A	20	72.7000	3.70064	.946
B	20	72.8000	5.39590	

Testing for quality of life by the VFQ25 revealed comparable mean scores in both groups (72.700 group A & 72.800 group B; p =0.946).

Table 6: Baseline IOP in study sample

Group	Mean	Std. Deviation	Mode	Median	Range
A	17.6000	1.56945	18	18	14-20
B	16.2000	2.37531	15	16	12-21

The baseline intraocular pressure in the test eye is described in table. The baseline mean IOP in group A was 17.6mmHg & 16.2 mmHg in group B

Graph 1 : Glycated Hb (HbA1C)

Diabetic control of the patients during the study period was monitored by three monthly glycated Hb (HbA1C). None of the patients had gross worsening of glycemic control during study.

Table 7: Changes in distance visual acuity fraction (BCDVA Fr)

Group	Time Interval	N	Mean	Std. Deviation	Repeated Measures Anova*	Paired T-Test* (Pre treatment-6month)
A	Pretreatment	20	0.1905	0.07030	<0.001	<0.001
	At 1.5 Month	20	0.2335	0.07929		
	At 3 Month	20	0.2655	0.08690		
	At 6 Month	20	0.2685	0.10148		
B	Pretreatment	20	0.1865	0.06360	<0.001	<0.001
	At 1.5 Month	20	0.2255	0.07729		
	At 3 Month	20	0.2780	0.10191		
	At 6 Month	20	0.2845	0.10450		

*'P' Value

The mean BCDVA Fr was 0.1905, 0.2335, 0.2655, and 0.2685 in group A & was 0.1865, 0.2255, 0.27800, and 0. 2845 at pretreatment, 1.5, 3 & 6 months respectively. Repeated measure ANOVAs showed statistically significant change ($p<0.05$) in BCDVA with respect to time showing improvement in both groups. Overall change in BCDVA Fr during 6 months was also found statistically significant ($p<0.05$) in both the groups.

Table 8: Changes distance visual acuity (BCDVA ETDRS Log MAR)

Group	Time Interval	N	Mean	Std. Deviation	Repeated Measures Anova*	Paired T-Test* (Pre treatment -6month)
A	Pretreatment	20	0.7500	0.15728	<0.001	<0.001
	At 1.5 Month	20	0.6650	0.14965		
	At 3 Month	20	0.6150	0.14965		
	At 6 Month	20	0.6100	0.16827		
B	Pretreatment	20	0.7600	0.15009	<0.001	<0.001
	At 1.5 Month	20	0.6800	0.15079		
	At 3 Month	20	0.5950	0.17313		
	At 6 Month	20	0.5800	0.17045		

*'P' Value

The mean BCDVA ETDRS Log MAR 0.7500, 0.665, 0.615, and 0.6100 in group A & was 0.7600, 0.6800, 0.5950, and 0.5800 at pretreatment, 1.5, 3 & 6 months respectively. Repeated measure ANOVAs showed statistically significant change ($p<0.05$) in BCDVA with respect to time showing improvement in both groups.Overall change in BCDVA ETDRS Log MAR during 6 months was also found statistically significant ($p<0.05$) in both the groups.

Subsequent result at follow up of 1.5 ,3 & 6 months using paired test shows significant visual improvement ($p < 0.05$) BCDVA Fr & ETDRS Log MAR in both the groups. In our study, no patient suffered a loss in visual acuity when compared to baseline.

Table 9: Change in near visual acuity (Log MAR)

Group	Time Interval	N	Mean	Std. Deviation	Repeated Measures Anova*	Paired T-Test* Pre treatment -6month
A	Pretreatment	19	1.2895	.12425	<0.001	<0.001
	At 1.5 Month	20	1.1500	.11921		
	At 3 Month	20	1.1000	.11239		
	At 6 Month	20	1.0500	.12773		
B	Pretreatment	20	1.2550	.17006	<0.001	<0.001
	At 1.5 Month	20	1.1600	.09403		
	At 3 Month	20	1.0650	.08751		
	At 6 Month	20	1.0450	.09445		

*'P' Value

Near visual acuity (in Log MAR) also showed a significant improvement ($p<0.05$) in both the group paralleling the distance visual acuity.Overall change in near vision during 6 months was also found statistically significant ($p<0.05$) in both the groups.

Table 10: Changes in contrast sensitivity (Pelli Robson chart)

Group	Time Interval	N	Mean	Std. Deviation	Repeated Measures Anova*	Paired T-Test* Pre-treatment -6month
A	Pretreatment	20	.8250	.19160	<0.001	<0.001
	At 1.5 Month	20	.9675	.14168		
	At 3 Month	20	1.0800	.14272		
	At 6 Month	20	1.1475	.17732		
B	Pretreatment	20	.8250	.18532	<0.001	<0.001
	At 1.5 Month	20	.9750	.18532		
	At 3 Month	20	1.1250	.17206		
	At 6 Month	20	1.1775	.18387		

*'P' Value

Contrast sensitivity function showed a significant improvement after intervention. Repeated measure ANOVAs showed statistically significant change ($p<0.05$) in contrast sensitivity visual acuity with respect to time showing improvement in both groups. Overall change in contrast sensitivity during 6 months was also found statistically significant ($p<0.05$) in both the groups.

Table 11: Changes in IOP

Group	Time Interval	N	Mean	Std. Deviation	Repeated Measures Anova*	Paired T-Test* (Pre-treatment -6month)
A	Pre-treatment	20	17.6000	1.56945	0.018	0.009
	At 1.5 Month	20	17.5500	1.70062		
	At 3 Month	20	17.1000	2.02355		
	At 6 Month	20	16.5000	1.87785		
B	Pre-treatment	20	16.2000	2.37531	0.009	0.287
	At 1.5 Month	20	15.0000	1.94666		
	At 3 Month	20	14.7500	1.48235		
	At 6 Month	20	15.7000	1.92217		

*'P' Value

In both the groups final IOP was found lesser than corresponding initial IOP. Moreover in group A this decrease was statistically significant ($p<0.05$) too. None of the patient in either group was observed to have rise in IOP to the extent requiring treatment.

Table 12: Changes in Quality of life NEI - VFQ 25 scores

Group	Time Interval	N	Mean	Std. Deviation	Paired T-Test*	Wilcoxon Signed Rank Test*
A	Pretreatment	20	72.7000	3.70064	0.892	>0.048
	At 6 Month	20	72.6000	4.50029		
B	Pretreatment	20	72.8000	5.39590	0.263	>0.048
	At 6 Month	20	71.9000	4.19147		

***'P' Value**

Quality of life as measured by NEI - VFQ 25 showed no significant improvement in both the groups. Overall change in NEI - VFQ 25 during 6 months was also found statistically insignificant in both the groups ($p>0.05$).

Complications of interventions

A continuous monitoring of the eyes given treatment revealed no serious complications. None of the eyes developed either infectious or noninfectious endophthalmitis, inflammation, increased intraocular pressure, vitreous hemorrhage, retinal detachment, thromboembolic events etc.

DISCUSSION

This study was prospective interventional, randomized, hospital based study where the safety & efficacy of Bevacizumab was assessed at various follow up interval & compared with conventional laser therapy**.** The study was undertaken on two groups which were comparable in terms of their diabetic status, visual function variable, quality of life, retinopathy status. In group A LASER treatment given & in group B two intravitreal injection of Bevacizumab (1.25mg/0.05 ml) given 6 weeks apart. During the course of the study, there was an improvement in the glycated Hb level in both the groups. This reflects better glycemic control over the study period. This improvement may be due to better motivation of the patients due to counseling at the start of the study & repeated contact with healthcare system during the study. Repeated measure ANOVAs showed statistically significant changes ($p<0.05$) in BCDVA Fr, Log MAR visual acuity & near visual acuity with respect to time showing improvement in both groups. At the end of 6th month visual acuity parameter showed no statistically significant difference between groups, with improvement in both groups from baseline to end of study.

The anatomical success of interventions was significant. All patients receiving the treatment had striking reduction in retinal thickness. The resolution of edema was significant in both groups during study. At 6th month there were minimal to no macular edema in most of the patients. The improvement in both groups was statistically significant from baseline to end of study but there was no significant difference between groups. The assessment of retinal thickening was subjective, even though the changes were remarkable. This was a limitation of the study.

No acute sight threatening complication No acute sight threatening complication of treatment was encountered in the study. We did not observe any case of infectious endophthalmitis. This was due to meticulous injection procedure followed. This included preinjection topical antibiotics & preparation as for any intraocular major surgery involving draping, instillation of povidone iodine in the conjunctival sac and all sterile precaution in the operating theaters. We did not encounter any non- infectious endophthalmitis either.

None of the eyes showed any increase in IOP for which treatment was required & no other ocular side effects like increased inflammation, vitreous hemorrhage and retinal detachment were noted in eyes injected with intravitreal Bevacizumab.

None of the patients injected with intravitreal Bevacizumab showed any systemic side effect like accelerated hypertension, stroke, MI or any other thromboembolic events.

None of the patients in laser group showed any adverse events including, pain, corneal abrasion, foveal burn, optic disc damage, lens opacity, blurring of vision during the follow up visits.

Our preliminary study provides evidence that inhibition of VEGF associated with both pathological ocular neovascularization and increased retinal vascular permeability in diabetic retinopathy may produce a clinically meaningful and statistically significant benefit in the treatment of DME.

SUMMARY & CONCLUSION

We report the results of 40 consecutive eyes with diffuse DME treated with either laser or intravitreal Bevacizumab which resulted in both anatomic and functional improvement. Our results also showed that Bevacizumab was well tolerated and no systemic adverse events were noticed during the study. Ocular tolerance was also high and no ocular inflammation was noted.

Though the positive results of this prospective, randomized study preclude any estimation of the long-term efficacy or safety of intravitreal Bevacizumab, they are quite promising and suggest the need for further longer prospective randomized studies**.**

To sum up the result of the study,

- There was significant benefit of interventions on all observed aspects of vision in each case in both groups.
- None of the patients develop decrease in visual parameters during study.
- There was marked anatomical success in both the groups, with resolution of macular edema.
- The quality of life was stable during the study period.
- The effect of injection lasted for six months.
- The magnitude of improvement was almost similar in both groups.
- The incidence of complication was acceptably low , with most being either preventable or treatable
- No systemic untoward effect like hypertensive crisis or stroke was observed.
- In conclusion, intravitreal Bevacizumab 1.25mg/0.05ml was found to safe & effective in treatment of diabetic macular edema when compared with laser therapy as primary treatment.

Although drugs used in the study is an off label treatment, still it has shown remarkable efficacy without any untoward effects on a short term basis. The drug, due to its low cost, has been widely accepted as a treatment of choice.

The long term efficacy & safety in terms of visual & anatomic ocular side effects as well as any morbidity due to its anti VEGF action needs further evaluation through large studies.

Our study also suffered from subjective nature of anatomic assessment which could not be quantitated due to unavailability of OCT at our institution, which is valuable tool for evaluation & documentation of foveal thickness & other contiguous features at presentation & during follow up & decision making for requirement of reinjection.