# EFFECT OF INTRAVITREAL BEVACIZUMAB IN COMBINATION WITH POSTERIOR SUB-TENON TRIAMCINOLONE ON DIFFERENT LEVELS OF DIABETIC MACULAR EDEMA

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## ABSTRACT

***Objective:*** To compare the efficacy of Intravitreal Bevacizumab in combination with Posterior Subtenon Triamcinolone for treatment of different levels of diabetic macular edema.
***Study Design:*** Comparative cross sectional study.
***Place and Duration of Study:*** This study was done in Retina Clinic, Al Shifa Trust Eye Hospital, Rawalpindi, from Jul 2017 to Dec 2017.
***Methodology:*** Total of fifty-two patients were included in the study which were divided into two groups on the basis of foveal thickness (group 1 = Foveal Thickness <500µm, group 2 = Foveal Thickness >500µm).
***Results:*** Both groups were treated with combination of Intra-vitreal Avastin and Posterior Subtenon Triamcinolone. The percentage decrease in foveal thickness after 6 weeks of injection in group 1 was 30.08 ± 13.035% as compared to 38.88 ± 8.883% in group 2 ($p$=0.006). While the improvement in BCVA in both groups after 6 weeks of injection was same (0.2 ± 0.2 in Log MAR) ($p$=0.521).
***Conclusion:*** It is concluded that the use of Intravitreal Bevacizumab in combination with posterior subtenon triamcinolone for treatment of macular edema is more effective in foveal thickness >500µm as compared to thickness <500µm.

**Keywords:** Bevacizumab, Macular edema, Optical coherence tomopraphy, Triamcinolone acetonide, Visual acuity.



## INTRODUCTION

Millions of people worldwide are affected from Diabetic macular edema (DME) secondary to diabetic retinopathy which is one of the biggest causes of blindness. It can occur at any stage of retinopathy[1]. In type 1 diabetes, visual loss secondary to proliferative changes is more common while in type 2 diabetes, visual loss is more commonly due to macular edema[2]. It's a big challenge to find out the best treatment strategy for DME[3]. Number of treatment options has been postulated with different levels of success.

Laser is one of the most commonly used treatment modality for DME[4]. Intravitreal triamcinolone acetonide (IVTA) is another treatment modality used for the reduction of macular edema[5]. Posterior sub-tenon kanakort or triamcinolone (PSTK) injections have been used either as monotherapy or as adjunctive therapy for the treatment of DME[6]. Intravitreal bevacizumab (Avastin/IVB) is a humanized monoclonal Anti-Vascular Endothelial Growth Factor (VEGF) antibody and is another treatment currently used in DME. It has an anti- exudative and anti- angiogenic effects[7]. In recent times, the IVTA injection for the management of DME showed very good results[8]. However, some complications like cataract, glaucoma, retinal detachment and endophthalmitis were reported[9].

Another effective method for ocular inflammation and disease is Posterior subtenon injection and is used for treatment of cystoid macular edema and posterior uveitis[10]. Recent studies have shown that PSTK is also effective for

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treatment of diffuse diabetic macular edema[11]. One study by Shimura *et al*[12] has shown the enhanced effect of combination of IVB & PSTK on DME greater than 400µm. Kim *et al*[13] in his study showed that the DME greater than 300µm not responding to IVB alone responded well to PSTK. This study is structured to see the efficacy of Intravitreal Bevacizumab (IVB) in combination with posterior subtenonat different levels of foveal thickness in macular edema in our setup.

## METHODOLOGY

The study was conducted after the approval by the hospital ethical committee in Retina Clinic of Al Shifa Trust Eye Hospital, Rawalpindi, in period of 6 months from July, 2017 to December, 2017. As per the protocol of the hospital, every patient referred to the retina clinic has his complete ophthalmological examination done in the general OPD. That included the visual acuity testing by the optometrist on duty and slit lamp examination by an ophthalmologist. Then the patients were selected for the study taking into consideration the inclusion and exclusion criteria. The sample size was calculated with the help of latest study[11] by using WHO sample size calculator. Patients of any age and gender having diabetic macular edema regardless of the stage of diabetic retionopathy were included in this study. Any patients having history of previous intraocular injection, other pathologies that may contribute to macular edema like Branch retinal vein occlusion, central serous chorioretinopathy, use of systemic steroids were excluded from this study. Any patient having a macular edema secondary to diabetic retinopathy regardless of its stage was also advised OCT testing to measure foveal thickness which is done by a retina consultant using "Carl Zeiss Meditec Stratus OCT" after taking consent. For treatment, the patient then landed in the retina clinic. Sampling was done by using non-probability (consecutive) sampling technique. Patients were allocated into two groups based on foveal thickness (group 1 = Foveal Thickness <500 microns, group 2 = Foveal Thickness >500 microns).

Both groups were given intravitreal avast in and posterior sub-tenon triamcinolone by a senior retina consultant on the same visit. Intravitreal injection of 1.25mg/0.05ml Avastin and PSTK 4mg/0.1ml (40mg/1ml) was given in retina clinic under sterile conditions. Patients started using ciprofloxacin eye drops four times per day one day before the injection and continued to do so for four days after the injection.

Follow up after completion of therapy was done in the retina clinic of the hospital. Visual acuity testing was done by the optometrist in the general OPD after 6 weeks of treatment while foveal thickness was measured with the help of OCT (Carl Zeiss Meditec Stratus OCT) by an ophthalmologist at the end of 4 and 6 weeks. All the observations along with demographic information of patients were noted on a pre-designed structured Proforma.

### Data Analysis

Data analysis was done using Statistical Package for Social Sciences (SPSS) version 17. Descriptive statistics like frequency was presented for gender, type of diabetes and eye involved. Mean and standard deviation was calculated for numerical variable i.e. Age, Visual acuity and foveal thickness at presentation and on follow ups. Independent sample t-test was used to compare the post injection visual acuity and decrease percentage in foveal thickness between two groups. A *p*-value of <0.05 was considered significant.

## RESULTS

A total of 52 patients were included in this study, which were divided into 2 groups depending upon their foveal thickness. Group 1 included patients having foveal thickness less than 500 microns and group 2 having greater than 500 microns. Mean age of the patients is 58.50 ± 7.036 years. There were 22 (42.31%) male patients and 30 (57.69%) female patients in the study. Out of 52 eyes, 29 (55.77%) were right eyes and 23 (44.23%) were left eyes (figure). Out of 52

patients, 51 (98.08%) were having type 2 diabetes while 1 (1.92%) was having type 1 diabetes.

In group 1, pre-injection foveal thickness was 395.19 ± 74.359 microns which reduced to 304.65 ± 54.371 microns after 4 weeks of injection and to 276.31 ± 48.543 microns after 6 weeks. Total difference of pre and post treatment was 118.88 ± 60.827 microns which was 30.08 ± 13.035% (table-I). In group 2, pre-injection foveal thickness was 617.54 ± 91.286 microns which reduced to 443.62 ± 93.876 microns after 4 weeks of injection and to 377.50 ± 78.283 microns after 6 weeks. Total difference of pre and post treatment was 240.04 ± 66.009 microns which was 38.88 ± 8.883% (table-I). The difference between the percentage decrease of foveal thickness after injection in two groups is statistically significant ($p$=0.006) (table-II).

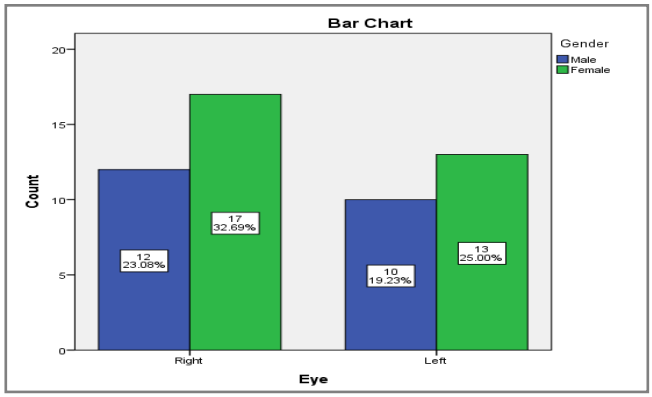


**Figure: Gender & Eye distribution in two groups ($p$-value=0.879).**

In group 1, pre-injection BCVA (LogMar) was 0.8 ± 0.2 which improved to 0.6 ± 0.2 after 6 weeks of injection. Total difference of pre and post treatment was 0.2 ± 0.2 (table-III). In group 2, pre-injection BCVA (LogMar) was 0.9 ± 0.2 which improved to 0.7 ± 0.2 after 6 weeks of injection. Total difference of pre and post treatment was 0.2 ± 0.2 (table-III). The difference between the BCVA after injection in two groups is not statistically significant ($p$=0.521) (table-IV).

## DISCUSSION

Diabetic Macular Edema (DME) produces loss of central vision. Several modalities are used to treat DME. In past laser photo-coagulation, intensive glycemic control and blood pressure control were considered as the main course of treatment.

PSTK is still a treatment of choice in macular edema[14]. In recent times, studies comparing intravitreal avastin and subtenon triamcinolone have been done[11,12] but uptill now no study exists in which there is a comparison is of effect of Intravitreal Avastin in combination with PSTK at different levels of foveal thickness is made.

In our study, results suggest that intravitreal bevacizumab injection given in combination with PSTK appears to be effective in the treatment of DME with foveal thickness more than 500 microns as compared to foveal thickness less than 500 microns. This study was carried out on 52 eyes and demonstrated significant improvement in visual acuity taken as Log MAR following injections of intravitreal bevacizumab with PSTK in both groups. The results of our study confirm previous reportsin a study done by Shimura *et al*[12] showing the marked decrease in DME treated with combined intravitreal bevacizumab and

**Table-I: Effect of Avastin+PSTK on Foveal Thickness at 4 and 6 weeks.**

| Effect of Avastin + PSTK on Foveal Thickness (microns) | Pre-Injection Thickness (microns) | Thickenss after 4 weeks (microns) | Thickness after 6 weeks (microns) | Difference (microns) | Percentage Decrease in Thickness |
|---|---|---|---|---|---|
| Foveal Thickness <500 Microns (Group 1) | 395.19 ± 74.359 (257-499) | 304.65 ± 54.371 (210-451) | 276.31 ± 48.543 (193-426) | 118.88 ± 60.827 (19-242) | 30.08 ± 13.035 (7-58) |
| Foveal Thickness >500 Microns (Group 2) | 617.54 ± 91.286 (503-794) | 443.62 ± 93.867 (243-640) | 377.50 ± 78.283 (214-597) | 240.04 ± 66.009 (125-364) | 38.88 ± 8.883 (24-59) |

PSTK. According to his study, PSTK along with IVB for the treatment of DME not only reduced macular edema greater than 400 microns but also reduced the frequency of IVB injections as well.

In another study, Kim *et al*[13] showed the effects of PSTK injection on refractory DME after IVB injection failure. The results showed that the average baseline macular thickness was 476 µm which decreased to 368 µm at 2 months, 374 µm at 4 months ($p$<0.001). Visual acuity improved from 0.56 to 0.50 at 2 months ($p$=0.023), 0.50 at 4 months ($p$=0.083). He took only those patients in his study sample which were having DME >300 µm and those who were already treated with IVB. That is why, it is different from our study.

Recently, different combinations of steroids, anti-VEGFs and lasers have been studied for the treatment of diabetic macular edema. Yamada *et al*[15] in their study estimated the effect of posterior subtenon triamcinolone injection (PSTK) in combination with pan-retinal photocoagulation laser (PRP) on progression of diabetic macular edema (DME). The foveal thickness of the PSTK+PRP group (308.15 ± 69.16 µm at 7 weeks, 283.8 ± 60.75 µm at 11 weeks & 281.13 ± 35.29 µm at 15 weeks) was significantly lower as compared to that of the PRP-alone group (340.21 ± 77.91 µm at 7 weeks, 335.7 ± 67.70 µm at 11 weeks & 316.58 ± 54.89 µm at 15 weeks). Although these results almost match with our study but the follow-up period was shorter in our study and we compared the combination of Avastin and PSTK.

In another study done by Choi *et al*[16], he showed that the mean visual acuity after 1 month in a posterior subtenon injection group was (0.650 ± 0.281; $p$=0.011) from baseline and (0.623 ± 0.264; $p$=0.007) after 3 months. This study showed no significant difference between the 2 groups i.e. PSTK and IVTA (both as monotherapies) while indivisually both groups showed significant improvement in visual acuity. This differs from our study as we didn't use PSTK as a mono-therapy and we didn't have the 3 month follow up.

Avastin was compared with intravitreal steroid implant (DEX-Implants) in a study conducted by Kodjikian *et al*[17]. It showed greater improvement in Visual Acuity in DEX-Implant groupas compared to the Avastin group, particularly for higher baseline VA (BVA). Mean improvement for subgroups of patients with BVA<50 letters, 50<BVA<60 letters, and BVA>60

**Table-II: Percentage decrease in foveal thickness after 6 weeks of injection.**

| Percentage Decrease in Foveal Thickness after injection | N | Mean | Std. Deviation | $p$-value |
|---|---|---|---|---|
| Foveal Thickness <500 Microns (Group 1) | 26 | 30.08 | 13.035 | 0.006 |
| Foveal Thickness >500 Microns (Group 2) | 26 | 38.88 | 8.883 | |

**Table-III: Effect of Avastin + PSTK on BCVA (LogMar).**

| Effect of Avastin + PSTK on BCVA (LogMar) | Pre-Injection BCVA | BCVA after 6 weeks | Difference in BCVA |
|---|---|---|---|
| Foveal Thickness <500 Microns (Group 1) | 0.8 ± 0.2 (0.3 - 1) | 0.6 ± 0.2 (0.2 - 1) | 0.2 ± 0.2 (-0.2 - 0.5) |
| Foveal Thickness >500 Microns (Group 2) | 0.9 ± 0.2 (0.3 - 1) | 0.7 ± 0.2 (0.2 - 1) | 0.2 ± 0.2 (-0.3 - 0.5) |

**Table-IV: Pre & post injection difference in BCVA.**

| Pre & Post Injection Difference in BCVA | N | Mean | Std. Deviation | $p$-value |
|---|---|---|---|---|
| Foveal Thickness <500 Microns (Group 1) | 26 | 0.212 | 0.1532 | 0.521 |
| Foveal Thickness >500 Microns (Group 2) | 26 | 0.242 | 0.1880 | |

letters are +4.3, +5.8, and +3.1 letters, respectively, in the Avastin group and +10.5, +9.3, and +8.8 letters, respectively, in the DEX-implant group. This study showed the superiority of steroid over avastin but in our study we used both these drugs as a combination and steroid in which later was injected thru posterior sub-tenon route.

In another study conducted by Bonini-Filho MA[18], he compared IVTA with PSTK in the treatment of diabetic macular edema. The results showed that the IVTA was more effective as compared to the PSTK for the anatomic/functional aspects of improvement. In our study we compared the effect of Avastin (IVB) in combination with PSTK in different levels of foveal thickness and didn't include intravitreal triamcinolone injections.

This study has various strengths and limitations side by side. To the best of our knowledge this is the first local study that has evaluated the efficacy of IVB and PSTK at different levels of DME. In this research, the aim was to explore new horizons in the treatment of DME. As IVTA is more prone to increase IOP than PSTK, later was used in combination with avastin instead of IVTA. The therapeutic effects were present in both groups after[6] weeks and there were no side effects noted in our study. However to evaluate the long-term efficacy of avastin, the side effect profile when PSTK is concomitantly given and exploration of further horizons in treatment of diabetic macular edema further studies will be required with prolonged followups.

## CONCLUSION

The effect of Intravitreal Bevacizumab in combination with Posterior Sub-Tenon Triamcinolone was directly proportional to the severity of Diabetic Macular Edema i.e. more the thickness of macula, more the effect of the treatment. This combination can be a treatment of choice in severe and resistant Diabetic Macular Edema.

## CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

## REFERENCES


1. Safi SZ, Qvist R, Kumar S, Batumalaie K, Ismail IS. Molecular mechanisms of diabetic retinopathy, general preventive strategies, and novel therapeutic targets. Biomed Res Int 2014; 2014: 801269.
2. Patelli F, Radice P, Giacomotti E. Diabetic macular edema. Dev Ophthalmol 2014; 54: 164-73.
3. Stitt AW, Curtis TM, Chen M, Medina RJ, McKay GJ, Jenkins A, et al. The progress in understanding and treatment of diabetic retinopathy. Prog Retin Eye Res 2016; 51(3): 156-86.
4. Silva PS, Cavallerano JD, Tolson AM, Rodriguez J, Rodriguez S, Ajlan R, et al. Real-Time ultrawide field image evaluation of retinopathy in a diabetes telemedicine program. Diabetes Care 2015; 38(9): 1643-49.
5. de Andrade FL, Lopes FS, de Andrade GC, Prata TS, Maia A. Simultaneous therapy with intravitreal dexamethasone implant and bevacizumab for the treatment of macular edema. Med Hypothesis Discov Innov Ophthalmol 2016; 5(1): 4-9.
6. Tost F, Kempin R, Grossjohann R, Herfurth S. Diabetic retinopathy - current aspects of therapy. Med Monatsschr Pharm 2016; 39(4): 148-56.
7. Do DV, Nguyen QD, Vitti R, Berliner AJ, Gibson A, Saroj N, et al. Intravitreal aflibercept injection in diabetic macular edema patients with and without prior anti-vascular endothelial growth factor treatment: outcomes from the phase 3 program. Ophthalmol 2016; 123(4): 850-57.
8. Mohamed QA, Fletcher EC, Buckle M. Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema. Boi Med J Clin Evid 2016; 2016.
9. Uparkar MP, Kaul S, Manning DR, Mudvari SS. Diagnostic and therapeutic challenges. Retina 2016; 36(3): 641-44.
10. Arikan-Yorgun M, Toklu Y, Mutlu M, Uysal BS, Cakmak HB. Efficacy of single-dose dexamethasone implantation in patients with persistent diabetic macular edema. Int Ophthalmol 2016; 36(4): 531-39.
11. Ercalik NY, Yenerel NM, Imamoglu S, Kumral ET, Vural ET. Combined intravitreal ranibizumab and sub-tenon injection of triamcinolone for the treatment of diabetic macular edema with retinal detachment. J Ocul Pharmacol Ther 2016; 32(4): 225-29.
12. Shimura M, Yasuda K, Minezaki T, Noma H. Reduction in the frequency of intravitreal bevacizumab administrations achieved by posterior subtenon injection of triamcinolone acetonide in patients with diffuse diabetic macular edema. Jpn J Ophthalmol 2016; 60(5): 401-07.
13. Kim MW, Moon H, Yang SJ, Joe SG. Effect of posterior subtenon triamcinolone acetonide injection on diabetic macular edema refractory to intravitreal bevacizumab injection. Korean J Ophthalmol 2016; 30(1): 25-31.
14. Carbonniere C, Couret C, Bleriot A, Lebreton O, Masse H, Le Meur G, et al. Treatment of macular edema: Comparison of efficacy and tolerability of subconjunctival triamcinolone injections, sub-tenon's triamcinolone injections and intravitreal dexamethasone implant. J Fr Ophtalmol 2017; 40(3): 177-86.
15. Yamada Y, Takamura Y, Matsumura T, Morioka M, Gozawa M, Inatani M. Posterior subtenon infusion of triamcinolone acetonide as adjunctive treatment to panretinal photocoagulation using pattern scan laser for diabetic retinopathy. Jpn J Ophthalmol 2018; 62(6): 686-92.

16. Choi YJ, Oh IK, Oh JR, Huh K. Intravitreal versus posterior subtenon injection of triamcinolone acetonide for diabetic macular edema. Korean J Ophthalmol 2006; 20(4): 205-09.
17. Kodjikian L, Bellocq D, Mathis T. Pharmacological management of diabetic macular edema in real-life observational studies. Biomed Res Int 2018; 2018: 8289253.
18. Bonini-Filho MA, Jorge R, Barbosa JC, Calucci D,. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: a randomized clinical trial. Invest Ophthalmol Vis Sci 2005; 46(10): 3845-49.

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