Original Article

Intravitreal Triamcinolone Acetonide and Bevacizumab versus Intravitreal Bevacizumab and Posterior Subtenon Triamcinolone Acetonide in Refractory Diabetic Macular Edema

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ABSTRACT

Purpose: To compare the effects of combined simultaneous injection of intravitreal triamcinolone acetonide and bevacizumab with intravitreal bevacizumab and posterior subtenon triamcinolone acetonide in treatment of refractory diabetic macular edema.

Study Design: Quasi experimental study.

Place and Duration of Study: Rawalpindi Medical University from January 2019 to December 2019.

Methods: Forty pseudophakic diabetic patients with refractory diabetic macular edema with central retinal thickness (CRT) of > 350 ʯm on OCT were included in the study. Group A was given simultaneous injection of intravitreal bevacizumab 1.25 mg/0.05 ml with posterior sub-tenon triamcinolone 40mg while group B had intravitreal bevacizumab with simultaneous intravitreal triamcinolone 2 mg/0.05 ml. Changes in the BCVA, IOP and CRT were evaluated in both groups.

Results: Group B showed a more significant decrease in the median CRT at 1 month ($p = 0.0002$). After 3 months, the reduction in CRT was not statistically different between the two groups ($p > 0.05$). Both groups had significant improvement in BCVA compared to pre-injection baseline visual acuity. Five eyes in group B and none in group A developed IOP beyond 22 mmHg. At 12 weeks, 7 patients of group A and 6 of group B developed recurrent macular edema and required repeated injections.

Conclusion: Posterior subtenon triamcinolone is as effective as intravitreal triamcinolone in conjunction with intravitreal bevacizumab in reducing CRT and improving and stabilizing BCVA. Posterior subtenon injection is safer as compared to intravitreal injection in terms of rise of IOP.

Key Words: Diabetic macular edema, Intravitreal injection, Posterior subtenon injection, Central Retinal thickness, Optical Coherence Tomography.

How to Cite this Article: Gul A, Niazi FAK, Raza A. Intravitreal Triamcinolone Acetonide and Bevacizumab versus Intravitreal Bevacizumab and Posterior Subtenon Triamcinolone Acetonide in Refractory Diabetic Macular Edema. Pak J Ophthalmol. 2022, **38 (3):** 186-192.

Doi: 10.36351/pjo.v38i3.1400

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Received: April 11, 2022
Accepted: June 9, 2022

INTRODUCTION

Diabetes mellitus is a metabolic disorder with multiple complications involving end organs like retina. Diabetic retinopathy (DR) is leading cause of visual disturbance among diabetics.[1] Neovascularization of retina and diabetic macular edema (DME) are major clinical manifestations of diabetic retinopathy potentially adding to visual loss.[1] Ocular factors

affecting this morbidity are severity of diabetic retinopathy and systemic factors like type, duration and poor control of diabetes leading to higher hemoglobin A1C levels.[2] Despite availability of several treatment options for DME, it is one of the principal causes of visual disability among diabetic patients. The prevalence of DME is 2.7-11% and 30% particularly in diabetics with duration of ailment for more than 20 years.[1-3]

Pathogenesis of DME is multifaceted and intricate. It is not entirely understood because of several etiologic agents. Leakage of exudates from retinal capillary hyper permeability, leukostasis, ischemia and pro inflammatory reactions play role. Inflammatory mediators like enzymes, growth factors such as VEGF, interleukins, and cytokines like TNF, TGF-beta and certain metabolic changes result in loss of tight junctions between endothelial cells. It leads to disruption of inner blood retinal barrier and interstitial edema.[4] Early DME occurs due to inflammation and vascular dysfunction and in long standing persistent DME, anatomical changes occur in harmony with neurotoxic effects. Most important test in diagnosing and monitoring progression of DME is OCT. Persistent refractory diabetic macular edema is one of the most frequent and untreatable causes of visual loss among diabetics. Macular edema not responding to anti VEGF agents is refractory or resistant macular edema.[4] The frequency of resistant or refractory DME is approximately 50%.[5] There is no clear cut off value in definition of refractory DME in published literature. Parameters used in labeling DME as recalcitrant include; no gain in visual acuity, reduced anatomical responses or frequent requirement of injections. DME refractory to medical or laser treatment is a challenge for ophthalmologists. Different types of interventions are proposed for resistant DME like intravitreal steroids, newer anti-VEGF agents, and combination drugs. Sequence of treatment regimens and shift from one regimen to another is also not clearly understood.[6]

Pars plana vitrectomy with or without ILM peeling and laser photocoagulation is another option to treat DME. Laser photocoagulation was considered to be the gold standard in improving vision but has definite side effects like macular scarring and fibrosis along with visual field defects. Now-a-days anti VEGF agents have become gold standard for treatment of DME. Newer agents like monthly injections of intravitreal Ranibizumab and Aflibercept have shown promising results in treatment of DME; however, cost is an issue in this treatment.[6] Moreover, all diabetic patients with DME do not demonstrate favorable and optimal response to intravitreal anti-VEGF agents. Almost 50% of patients showed post treatment CRT of more than 275 ʯm when treated with intravitreal Ranibizumab in RESTORE study.[7] Anti VEGF agents block the production of VEGF responsible for chronic low grade inflammatory and metabolic changes leading to macular edema. They need to be given repeatedly due to which risk of ocular and systemic side effects are high along with compliance problems.[7]

Intravitreal steroids are second line treatment particularly in pseudo phakic eyes due to side effects of cataract and intraocular pressure elevation. Corticosteroid options include triamcinolone acetonide, dexamethasone implant and flucinolone acetonide insert. Neurodegenerative and inflammatory pathways leading to breakdown of inner blood retinal barrier and vascular hyper-permeability are inhibited by corticosteroids.[8] They also recover the integrity of blood retinal barrier by restoring proteins at cellular border, consequently a neuroprotective effect on retina.[9] Intravitreal triamcinolone acetonide is effective in treating DME but its limitations are glaucoma and cataract. With any intravitreal injection there is risk of iatrogenic vitreous hemorrhage, retinal tear or detachment and endophthalmitis (sterile or infectious). Posterior sub tenon injection of TA is mostly used in treatment of intermediate uveitis and post cataract surgery cystoids macular edema. It is less invasive technique than intravitreal injections and its comparable therapeutic concentrations are achieved in vitreous and delivered to macula. Posterior subtenon injection has shown promising results in treatment of persistent refractory DME.[10]

In refractory or resistant cases, there is generally need for repetitive injections to maintain their therapeutic effect due to prolonged clinical course of DME. The debate is going on whether single or combined simultaneous agents would be sufficient in limiting the disease with respect to safety, economy and effectiveness. Purpose of discovering treatments of combined therapies in resistant cases is to increase the duration of effective role of these agents; hence to eliminate the necessity for repeated injections intimidating complications along with benefit of cost effectiveness.

The aim and objectives of present study were to evaluate and compare the effects of intravitreal Triamcinolone acetonide versus posterior sub-tenon

Triamcinolone acetonide in conjunction with intravitreal Bevacizumab in treatment of persistent refractory DME after repeated monotherapy failure with IVB.

METHODS

This Quasi-experimental study of 12 months duration was conducted at ophthalmology department of Rawalpindi Medical University. After approval from institutional ethical board of university, we explained objectives of this study to patients enrolled in this study. Patients were registered from Diabetic Retinopathy Project in the DR clinic of department from January 2019 to December 2019. Informed written consent was obtained from all patients along with details of interventional treatment given to them and its possible side effects. We included 40 pseudo-phakic eyes of diabetic patients in current study. Inclusion criteria was patients exclusively diagnosed with refractory diabetic macular edema with mean CRT of ≥ 350 Ч‌m on OCT with a minimum (< 15%) or no reduction in CRT for the last 6 months. Most of these cases had been given ≥ 3 consecutive IVB injections in normal dosage of 1.25mg/0.05ml at intervals of 4 or 6 weeks. Furthermore, they showed an increase or no decrease in CRT after IVB monotherapy before switching to other regimen. Patients who were steroid responders showing an increase in IOP, previous intraocular surgery or laser treatment within three months, previous corticosteroids treatment for DME, known case of glaucoma, ischemic cardiovascular or cerebrovascular events in last 6 months, ischemic maculopathy or vitreomacular adhesion were excluded. We divided patients into two groups. Group A was given intravitreal injection of bevacizumab 1.25 mg/0.05 ml in conjunction with 40mg of posterior subtenon injection of triamcinolone acetonide in the same sitting. Group B was given intravitreal injection of bevacizumab 1.25 mg/0.05 ml in conjunction with 2 mg/0.05 ml intravitreal injection of triamcinolone acetonide in the same sitting.

All patients received detailed ophthalmic examinations at baseline in DR clinic. Best corrected visual acuity by Snellen decimal chart was measured. After assessing the IOP by Goldman applanation tonometry and pupil reaction to rule out any RAPD; dilated fundus evaluation was done on slit lamp biomicroscope with 90 D lens and staging of diabetic retinopathy was recorded. All patients had baseline spectral domain OCT for CRT. FFA was done to rule out ischemic maculopathy. Changes in the BCVA (Snellen decimal fraction), IOP, and CRT were reevaluated in both groups at subsequent follow-up visits planned at 1, 2 and 3-months post treatment. Retreatment was performed at 6 weeks interval whenever indicated by OCT. Repeated treatment with combined simultaneous injections was only suggested for cases who responded to first injection with decrease in CRT by at least 10-15%. If an eye showed an increase in CRT after first combined injection, additional treatment was suspended.

Combined simultaneous injection of IVB and IVTA to group A patients were given under strict aseptic measure in operation room by a single consultant ophthalmologist. After povidone iodine scrubbing and sterile draping of eye, 1.25mg/0.05ml of intravitreal bevacizumab was injected then intravitreal triamcinolone acetonide 2mg in 0.05 ml was injected in the same fashion. After injection, if any sign of central retinal artery compression was seen; anterior chamber paracentesis was done immediately. Post injection IOP was checked after 4 hours and at day 1. Patients were given topical Moxifloxacin eye drops one day before injection and 4 hourly for seven days after injection to protect against endophthalmitis. If any raised IOP was documented, topical antiglaucoma medications were started. Group B was given intravitreal bevacizumab and posterior subtenon triamcinolone acetonide (PSTA).PSTA was given in dosage of 40 mg of TA in 1ml with 27-gauge needle. Patient was asked to look down and needle was penetrated into conjunctiva in superotemporal fornix with bevel downwards. Then needle was advanced under tenon along the contour of globe with side to side movements to test for engagement of globe or sclera in tip of needle and drug was injected. All patients were followed on day 1, 7 and 14 for complications due to raised intraocular pressure or endophthalmitis.

Primary outcome measure was CRT reduction on OCT (anatomical success) and secondary outcome measures were BCVA (functional visual acuity improvement), number of patients requiring repeated injections and side effects of treatment like elevated IOP.

Statistical Analysis was done by SPSS software version 21. Comparative analysis of CRT, BCVA and IOP was done at baseline (pre-injection), 1 and 3 months (post-injection) by paired sample t test and p

value less than 0.05 was taken as statistically significant. Qualitative variables like gender, type of diabetes, control of diabetes and staging of diabetic retinopathy were expressed as percentages and frequencies. Quantitative variables such as age, duration of diabetes, CRT, BCVA and IOP were expressed as mean ± SD.

RESULTS

Mean age in group A was 59.9 ± 9.12 with a range of 42 – 75 years. Duration of diabetes was 7 – 22 years with a mean duration of 13.1 ± 4.30. Right and left eye was involved in 10 patients each. There were 50% males and 50%females. Four (20%) patients had type 1 diabetes and 16 patients (80%) had type 2 diabetes. Nine patients (45%) had uncontrolled diabetes and 11 (55%) patients had controlled diabetes. In Group A, 14 (70%) patients had NPDR and 6 (30%) had PDR.

Mean age in group B was 63.6 years ± 9.39 with a range of 47 – 78 years. Mean duration of diabetes was 13.85 ± 5.98 with a range of 6 – 26 years. Right eye was involved in 11 and left eye in 9 patients. There were 45% males and 55% females. Three patients (15%) had type 1 diabetes and 17 (85%) patients had type 2 diabetes. Five patients (25%) in group B had uncontrolled diabetes and 15 (75%) patients had controlled diabetes. In group B, 5 patients (25%) had PDR and 15 (75%) had NPDR. Considering the demographic variables both groups were well matched in terms of age, gender, type, duration, control of diabetes and staging of diabetic retinopathy. The difference in demographic variables was not statistically significant between two groups (p > 0.05).

Mean baseline BCVA in group A was 0.100±0.04 with a range of 0.03 – 0.16 by Snellens decimal visual acuity chart. Mean baseline CRT was 449.5 Ч m ± 101.18 with a range of 375 – 716 Ч m. Mean baseline IOP was 15.2 mmHg ± 2.66 with a range of 11 – 20 mmHg. There was significant reduction in mean CRT of 286.45 Ч m ± 5.735 with a range of 269 – 298.00 Ч m in group A at 1 month after combined injection of IVB and PSTA (p value 0.001). Mean BCVA was 0.21 ± 0.12 with a range of 0.05 – 0.50, this illustrated an obvious improvement in BCVA from baseline (p value 0.002). Mean IOP was 17.3 ± 2.31 mmHg with a range of 13 – 21 mmHg, which demonstrated a slight rise in IOP from baseline but none of the patients showed a glaucomatous rise in IOP beyond borderline of 21 mmHg. Mean CRT at 3 months after treatment was 288.20 Ч m ± 36.96 with a range of 212 – 388 Ч m which was considerably less than baseline but there was no statistically significant difference from CRT reduction at 1 month (p value > 0.05). Mean BCVA at 3 months was 0.46 ± 0.32 with a range of 0.05 – 0.8 snellens decimal chart. There was evident improvement in BCVA from baseline. Mean IOP was 14.8 mm Hg ± 2.36 with a range of 10–18 mm Hg at 3 months post injection. IOP showed no statistically significant difference from baseline IOP (p value > 0.05) and was closer to baseline IOP. Extrafoveal hard exudates were present in 16 (70%) patients and subfoveal hard exudates in 4 (30%) patients in group A.

Mean baseline BCVA in group B was 0.091 ± 0.043 with a range of 0.01 – 0.16 by Snellens decimal visual acuity chart. Mean baseline CRT was 500.95±103.67Ч m with a range of 389–709Ч m. Mean baseline IOP was 14.95 mmHg ± 2.60 with a range of 10 – 19 mmHg. There was significant reduction in mean CRT of 263.45 Ч m ± 20.89 SD with a range of 220 – 283 Ч m in group B at 1 month after combined simultaneous injection of IVB and IVTA (p value of 0.0002). Mean BCVA at end of 1ST month in group B was 0.24 ± 0.13 with a range of 0.03 – 0.50. This showed an improvement in BCVA from baseline. Mean IOP after 1 month of injection was 20.4 ± 3.01 mmHg with a range of 17 – 26 mmHg, which revealed a significant rise in intraocular pressure from baseline (p value 0.042). Five out of 20 patients showed a glaucomatous rise in IOP beyond borderline of 21 mmHg which was treated with antiglaucoma medications. Mean CRT at 3 months after treatment was 289.4 Ч m ± 25.89 with a range of 261 – 328 Ч m which was considerably less than baseline but showed a slight increase compared to CST at 1 month. Mean BCVA at 3 months was 0.43 ± 0.30 with a range of 0.03 – 0.8 Snellens decimal chart. There was marked improvement in BCVA (p value = 0.000). Mean IOP was 16.15 mmHg ± 1.56 with a range of 14 – 20 mmHg at 3 months post injection. This IOP was comparable to baseline IOP (p value 0.49) which means there was transient increase in IOP at 1 month, which returned to baseline at an interval of 12 weeks. Extrafoveal hard exudates were present in 15 (75%) patients and subfoveal hard exudates in 5 (25%) patients in this group B.

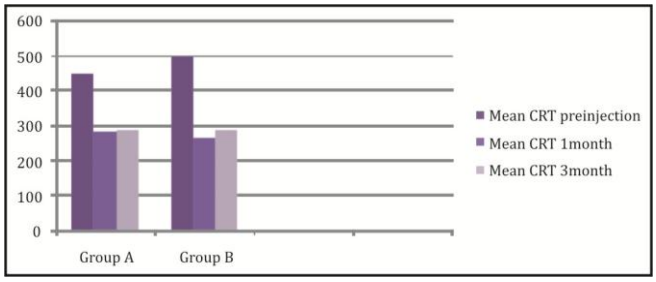

Figure 1: Mean CRT comparison between two groups' pre-injection, 1 and 3 months.

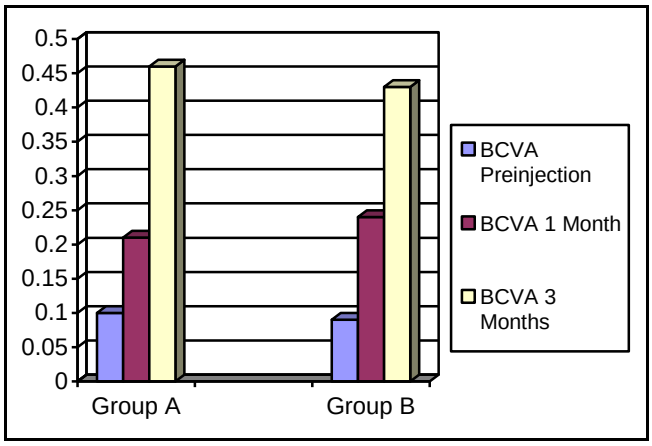

Figure 2: Mean BCVA comparison between two groups' pre-injection, 1 and 3 months.

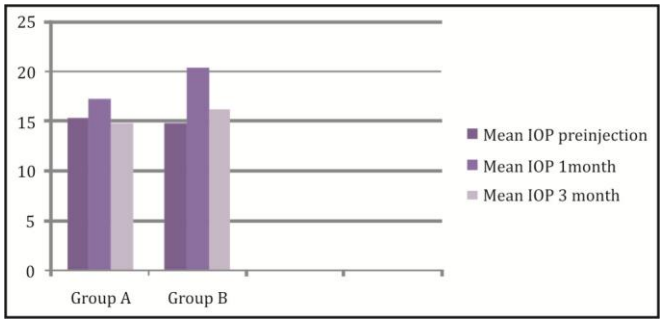

Figure 3: Mean IOP comparison between two groups' pre-injection, 1 and 3 months.

Both groups showed a reduction in CRT in all 40 (100%) patients. Group A showed improvement in BCVA in 16 (70%) patients and stabilization in BCVA in 4 (30%) patients. Group B showed an improvement in BCVA in 17 (85%) patients and stabilization in BCVA in 3 (15%) patients. BCVA changes in both groups were significantly better than baseline BCVA (p value < 0.05) but between two groups changes were not statistically significant. At 12 weeks, 7 patients in group A and 6 patients in group B developed recurrent macular edema and required repeated injections. Illustration of mean CRT, BCVA and IOP of both groups' pre-injection, 1 and 3 months are shown in figure 1, 2 and 3 respectively.

DISCUSSION

Combined injections of anti VEGF and corticosteroids have been intended to treat refractory persistent DME both by inhibiting VEGF production and proinflammatory mediators that cause vascular hyperpermeability. Current study showed significant improvement in refractory macular edema with reduction in CRT in all 40 patients (100%) from baseline at 1 and 3 months (p value < 0.05). Group A showed an improvement in BCVA in 70% while group B showed an overall improvement in BCVA in 85%. Freeman et al showed that superotemporal injection of steroids results in more precise delivery closer to macula by B-scan ultrasonography.[11] Geroski et al concluded that trans-scleral route was beneficial in placement of drug in retina.[12] Weijtens et al reported peribulbar injection of corticosteroids provided higher intravitreal concentrations.[13] Summarizing all these reports effective concentrations of TA in retina can be attained through sub-tenon route.

Ohguro et al reported the positive effect of PSTA in diffuse DME in eyes that had not shown significant response to vitrectomy.[14] Bakri and Kaiser conducted a study on refractory DME patients with PSTA injection and they found substantial improvement in VA after 1 month of injection and this effect was sustained for one year. So they proposed that PSTA was an alternative in treating DME.[15] Chan et al illustrated the effect of triple therapy that is PSTA in high dosage of 75 mg, IVB and argon laser photocoagulation in patients of refractory DME.[16] Choi YJ et al conducted a study of intravitreal versus posterior subtenon injection of triamcinolone acetonide in cases of DME and concluded that PSTA had an equivalent effect to IVTA and showed less risk of IOP elevation.[17] These studies indicate that the subtenon route provided therapeutic concentration of drugs to retina in a safer way. Current study also proved safety of PSTA route compared to IVTA.

Kim et al compared monotherapy of IVB,PSTA with combination of IVB-PSTA (4.0 mg) and they found superior anatomical (clinical) outcomes particularly at end of 1 month in combination group compared to monotherapy group.[18] Aly MM et al

proposed considerable improvement in mean CMT in all eyes and improvement in visual acuity in 83.3% of eyes with persistent DME with a combined IVB and PSTA.[19] Wang YS et al compared single IVB with combined IVB-IVTA for DME and they found favorable effects with combined injection but significant effect was not permanent.[20]

Esfahani MR et al conducted a study in centre involving macular edema and compared the results of IVB given alone and combined IVB-IVTA injection. They reported a significant reduction in macular thickness in combined IVB-IVTA group but visual acuity enhancement was better in IVB alone. Combination therapy decreases the number of injections required.[21] Tsilimbaris MK et al found out major decrease in central macular thickness and superior best corrected visual acuity in group with combined IVB-IVTA and showed this therapy to be very effective.[22]

In all of these studies, results are comparable to our study supporting combined simultaneous use of bevacizumab with corticosteroids to be more favorable with better outcomes.

Cardillo et al did a comparative trial of intravitreal and posterior subtenon triamcinolone and found out IVTA more beneficial than PSTA in cases of diffuse DME in each eye of one patient. Study had limitations of small sample size.[23] Bonini filho et al compared both intravitreal and posterior subtenon triamcinolone injections in refractory DME and reported IVTA more approving than PSTA.[24] Both these studies differ from current study which showed both IVTA and PSTA were equally effective in treating refractory DME in term of anatomical and visual (functional) outcomes. PSTA was safer as compared to IVTA in terms of IOP elevation. This disparity could be due to relatively short follow-up in our study. Their results are also relatively non-comparable to current study because combined simultaneous injections were given in our study. More studies are needed long follow-up to confirm long term effectiveness and safety of combined simultaneous injections.

CONCLUSION

Combined simultaneous injections of IVB-PSTA and IVB-IVTA are cost effective and evenly beneficial in treating persistent refractory DME but in terms of safety, IVB-PSTA is considered to be less harmful with fewer to no complication or side effects.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board **(136/IREF/RMU/2018).**

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Authors Designation and Contribution

Ambreen Gul; Assistant Professor: *Concepts, Design, Literature search, Data acquisition, Data analysis, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.*

Fuad Ahmad Khan Niazi; Professor: *Concepts, Design, Literature search, Manuscript preparation, Manuscript editing, Manuscript review.*

Ali Raza; Professor: *Concepts, Design, Manuscript editing, Manuscript review.*