

Comparison of Suprachoroidal Injection of Triamcinolone Acetonide Versus Intravitreal Bevacizumab in Primary Diabetic Macular Edema

FAISAL ANWAR¹, ASAD ASLAM KHAN², TEHSEEN MAHMOOD MAJHU³, RANA MOHAMMAD MOHSIN JAVAID⁴, MUHAMMAD TAHIR GHAFFAR⁵, MUHAMMAD HASAN BOKHARI⁶

¹Department of Ophthalmology, Eye Unit 3, King Edward Medical University, Mayo Hospital, Lahore

²Professor of Ophthalmology Eye Unit 3, King Edward Medical University, Mayo Hospital Lahore

³Senior Registrar, Eye Unit 3, King Edward Medical University, Mayo Hospital Lahore

⁴VR Fellow, Eye Unit 3, King Edward Medical University, Mayo Hospital, Lahore

⁵Department of Ophthalmology, Eye Unit 3, King Edward Medical University, Mayo Hospital, Lahore

⁶Senior Registrar, Department of Ophthalmology, King Edward Medical University, Mayo Hospital, Lahore

Correspondence to: Faisal Anwar, Email: faisal.gemni@gmail.com, Cell: +92 03334865903

ABSTRACT

Objective: Present study aims to compare the efficacy of single dose triamcinolone acetonide suspension in suprachoroidal space and intravitreal bevacizumab in primary diabetic macular edema patients.

Study design: Prospective observational study

Study duration and settings: Study was conducted at department of ophthalmology, Eye Unit III, Mayo hospital Lahore (KEMU) from March 2020 to August 2020.

Material and methods: The WHO calculator was used to estimate a sample size of 136 patients (66 patients in each group). Non-probability sequential sampling was used to identify patients.. Intravitreal bevacizumab injections (2.5 mg/0.1 mL) were given to patients in Group A, and triamcinolone acetonide was given to patients in Group B, all at random. After one and three months, patients were reassessed.

Results: Total 135 patients were included in study. There were 71(52.2%) male and 65(47.8%) female. Mean age of patients was 41.1±6.9SD. BCVA improved 5 letters after 3 month was significantly high in TA group as compared to IVB (P=0.002). Moreover, CSF decreased at least 10% from baseline after one and three months was comparatively high in TA group (p=0.01 and p=0.04 respectively). Among all the patients in IVB group, 29.5% showed efficacy while in group TA, 37.5% showed efficacy (p=0.03)

Conclusion: Triamcinolone acetonide is an efficient drug for management of diabetic macular edema. Triamcinolone had long standing effect as compared to intravitreal bevacizumab on structural and functional outcome of the patients with primary diabetic macular edema. Both interventions are associated with limited complications.

Keywords: Triamcinolone acetonide, Diabetic macular edema, Intravitreal bevacizumab

INTRODUCTION

Diabetic macular edema (DME) is most frequent complication of diabetic retinopathy, globally¹. It is also associated with high visual impairment in working age group. Literature reported that 12% of patients with diabetic retinopathy develop DME and leads to 10000 ne blindness cases per year². Hakeem et al. reported 10.8% prevalence to diabetic retinopathy majority of them leading towards DME in Abbottabad, Pakistan³. Prevalence rate of DME is directly dependent upon type and duration of Diabetes mellitus. Patients with type I diabetes mellitus develop DME in first 5 years, however, the prevalence of DME reaches 40% within 30 years. Studies provide evidence of DME in type II diabetic patients at the time of diagnosis⁴.

Systemic risk factors of DME includes gender, high level of HbA1c, duration of diabetes, excessive use of diuretics, cardiovascular disorders and proteinuria. There is no evidence regarding thorough definition of DME pathogenesis⁵. However, some studies explained this complex process in terms of some contributing factors including hypercholesterolemia, advanced glycation end products, free oxygen radicals, chronic hyperglycemia and protein kinase C. Literature reported that high level of vascular endothelial growth factor (VEGF) leads to disrupt inner blood retinal barrier (BRB). Accumulation of subretinal and intra-retinal fluid, following BRB disruption alters the macular structure and function. Management of DME involve laser treatment, anti VEGF agents, intravitreal corticosteroids and pars plana vitrectomy⁶.

Triamcinolone acetonide (TA) is also an effective drug for managing primary diabetic macular edema along with anti VEGF injections. TA showed effective results in reversing macular edema and associated with well re establishment of compromised blood retinal barrier⁷. However, some studies reported cataract and increase intra ocular pressure as complications of TA due to repeated injection (Waning effect of TA) and rebound macular edema⁸. As shown by Tayab et al., there is a substantial difference between pre and after suprachoroidal triamcinolone acetonide

(SCTA) injection in BCVA and central subfield thickness. They also mentioned that SCTA is an effective and well tolerated drug that improves structural and functional outcomes in DME patients⁹. HULK trial also proved safety and tolerability of suprachoroidal injection of TA in patients with DME¹⁰. In Pakistan, there isn't enough information on this topic to draw any conclusions. Therefore, this study was done in Pakistan to improve our understanding of the drug's efficacy. In this trial, individuals with primary diabetic macular edema will be given either a single dose of triamcinolone acetonide suspension in suprachoroidal space or an intravitreal dosage of bevacizumab.

MATERIAL AND METHODS

A prospective observational study was conducted at department of ophthalmology, Eye Unit III, Mayo hospital Lahore (KEMU). Study duration was 6 months Study from March 2020 to August 2020. A sample size of 132 (66 in each group) patients was calculated using WHO calculator. Non-probability sequential sampling was used to pick patients. Ethics approval was granted by an internal ethics review body. A consent form was signed by each and every one of the participants. Inclusion criteria was based upon patients age ranging from 25- 75 years, both genders, diagnosed with both Type I and II diabetes mellitus, patients diagnosed with DME, patients with IOP<23 mmHg, patients with central macular thickness >300 micrometer, no history of laser, intravitreal steroid, pars plana vitrectomy or pan retinal photocoagulation and no history of glaucoma. Exclusion criteria was based upon patients already treated with intravitreal or periocular steroid injection at any age.

Preoperative history, visual acuity, refraction (subjective and objective), fundus examination, intraocular pressure and best corrected visual acuity was documented. Before the injection, the patients had been dilated. The fundus was examined immediately following injection using an indirect ophthalmoscope. We remove the branula and cut it so that just a small amount (around 1000um) of the insulin syringe is visible at the branula's border when it is in

place. The syringe was filled to the 0.1 ml mark with TA. For the eye painting, we employed a 10% povidone iodine solution, and 5% of that solution was injected into the fornices and allowed to rest for a period of time (30 seconds). It was wrapped like an intra-ocular technique to protect the eye in question; Group A underwent intravitreal bevacizumab injection (The 2.5 mg/0.1 mL) while group B underwent suprachoroidal triamcinolone acetonide. An insulin syringe of 30 gauge 1cc were utilized in our study. Moreover, other dispensable were triamcinolone acetonide (TA) 40mg/ml injection and intravenous branula of 24 gauge. Before the injection, the patients had been dilated. The fundus was examined immediately following injection using an indirect ophthalmoscope. We remove the branula and cut it so that just a small amount (around 1000um) of the insulin syringe is visible at the branula's border when it is in place. The syringe was filled to the 0.1 ml mark with TA. For the eye painting, we employed a 10% povidone iodine solution, and 5% of that solution was injected into the fornices and allowed to rest for a period of time (30 seconds). It was wrapped like an intra-ocular technique to protect the eye in question. Marking was done from limbus (3.5 mm) in supratemporal quadrant. TA (4 mg) was inserted in suprachoroidal space using a needle that is perpendicular to sclera. This needle should bevel point backward from limbus (3.5 mm) to said quadrant. The whole procedure was done in the presence of topical anesthesia. Efficacy of injection was measure at 1 and 3rd month after injection. DME patients who did not respond to anti VEGF injections spaced one month apart were considered treatment resistant. Spectral Domain Optical Coherence Tomography (SD-OCT) and BCVA were used to make the decision on failure to respond. Efficacy was measured as frequency of BCVA >5 letter improved from baseline on Early Treatment Diabetic Retinopathy Study (ETDRS) after one month of injection and by measuring frequency of decrease in central subfield thickness (CSF) 10% from baseline one month after suprachoroidal TA injection.

SPSS version 24 was used to analyse the data. For quantitative data, the mean and standard deviation were computed; for qualitative data, the percentage and frequency were used. The stratification of effect modifiers, such as age and gender, was used. The following day after stratification Fissure exact tests were used in conjunction with Pearson chi square. P values of less than 0.05 were regarded as noteworthy.

RESULTS

There were a total of 135 participants in the study. There were 71 males and 65 females in the group. It was found that patients mean age of patients was 41.1±6.9SD. There was no significant difference in pre injection BCVA (p=0.965). However, BCVA was significantly higher in TA group as compared to IVB (P=0.03) as shown in table 1. Significant post injection difference in CSF thickness was found in both group (p=0.05) as shown in table 2. BCVA improved 5 letters after 3 month was significantly high in TA group as compared to IVB (P=0.002). Moreover, CSF decreased at least 10% from baseline after one and three months was comparatively high in TA group (p=0.01 and p=0.04 respectively) as shown in table 3.

Among all the patients in IVB group, 29.5% showed efficacy while in group TA, 37.5% showed efficacy (p=0.03) similarly, in group IVB 45.6% reported intervention as safe with minimum complications while in TA group 47.1% showed drug as safe (p=0.746) as shown in table 4.

Table 1: Comparison of BCVA in both interventional groups before and after surgery

Groups	N=136	Pre Injection BCVA Visual acuity (Log Mar)	P value
Group A (IVB)	66	1.09±0.3	0.965
Group B (TA)	66	1.03±0.3	
		Post injection BCVA visual acuity (Log Mar)	
Group A (IVB)	66	0.83±0.2	0.03
Group B (TA)	66	0.62±0.1	

Table 2: Comparison of central sub field thickness in both interventional groups

Groups	N=136	Pre Injection sub central field thickness	P value
Group A (IVB)	66	410.2±12.3	0.05
Group B (TA)	66	423± 12.7	
		Post injection sub central field thickness	
Group A (IVB)	66	377.3±11.2	0.965
Group B (TA)	66	344.8±10.3	

Table 3: Comparison of clinical outcomes in both interventional groups

Outcomes		Group		Total	P value
		Group A (IVB)	Group B (TA)		
BCVA improved 5 letter after 1 month of injection	No	16(11.8%)	8(5.9%)	24(17.6%)	0.07
	Yes	50(36.8%)	62(45.6%)	112(82.4%)	
BCVA improved 5 letter after 3 month of injection	No	23(16.9%)	8(5.9%)	31(22.8%)	0.002
	Yes	43(31.6%)	62(45.6%)	105(77.2%)	
CSF Decreased at least 10% from baseline after 1 month	No	41(30.1%)	28(20.6%)	69(50.7%)	0.01
	Yes	25(18.4%)	42(30.9%)	67(49.3%)	
CSF Decreased at least 10% from baseline after 1 month	No	43(31.6%)	28(20.6%)	71(52.2%)	0.04
	Yes	23(16.9%)	42(30.9%)	65(47.8%)	

DISCUSSION

A retinal invasion by inflammatory cells and metabolic alterations as a result of hyperglycemia are linked to diabetic macular edema development¹¹. Laser photocoagulation is an important part of focal macular edema management. Other strategies include steroids triamcinolone acetonide (TA) and bevacizumab (anti-VEGF) injection or their combination with laser photocoagulation¹².

In present study TA is found to be more effective as compared to IVB. For the treatment of DME, a single injection of triamcinolone may be as effective as two to three injections of bevacizumab. Triamcinolone injection-related problems are reduced and patient compliance is improved when there are fewer injections. Lim et al. showed that intravitreal triamcinolone is an effective method for reducing DME as compared to bevacizumab¹³. Song et al. reported that TA is extra effective in improving best corrected visual acuity as compared to IVB¹⁴. Isaac et al. reported that TA is more likely to be effective in age >40 years as compared to IVB¹⁵. However, Sutter et al. reported that IVB showed superiority as compared to TA for DME management¹⁶. Similarly, Paccola et al also reported contradictory finding¹⁷. Rensch et al. informed that no remarkable difference in TA and IVB is observed in improving visual acuity and macular thickness reduction¹⁸.

Some studies also consider the systemic risk factors including blood pressure, glycemic levels and neuropathies to affect the efficacy of drugs¹⁹. Kreutzer et al. reported that dose of injection is also a contributing factor in determine efficacy. They reported that single TA injection is more effective as compared to 3 injections of IVB²⁰. Another similar study reported that frequency of injection is associated with efficacy of treatment. A higher IOP is the most prevalent side effect of IVTA injection, with an incidence of 20% to 80%. Even in a small number of patients, significant IOP rises have been documented. Less number of TA injection leads to improve compliance of patients and reduce injection related complications²¹.

In present study, we found limited complications including development or progression of lens opacities. Shimura et al reported that intraocular pressure increase was most common complication of TA injection²². Marey et al. reported that CME reduction rate was 38% in TA group as compared to IVB group with minimum complications²³. Triamcinolone acetonide (TA) is also an effective drug for managing primary diabetic macular edema in all diabetic patients along with other treatment options like anti VEGF bevacizumab injections.

In our study results showed that early recurrences in the patients with diabetic macular edema treated with bevacizumab injections as compared to those patients who are treated with triamcinolone acetonide injections. Patients treated with bevacizumab need multiple injections to prolong the treatment efficacy. It was shown that DME is not only linked to VEGF release, but also to the release of a slew of other growth factors and cytokines associated with inflammation. This medication works by inhibiting the release of inflammatory mediators, lowering VEGF secretion, and preventing fluid accumulation in the extracellular space. Because of this, triamcinolone acetonide is preferable than bevacizumab, which merely lowers VEGF.

Conduction of study at single center limits generalizability of study. Cost of treatment was not evaluated in this study

CONCLUSION

Triamcinolone acetonide is an efficient drug for management of diabetic macular edema. Triamcinolone had long standing effect as compared to intravitreal bevacizumab. Both interventions are associated with limited complications. Further, in depth trials are required to understand cost effective analysis of both drugs.

REFERENCES

- Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology*. 2018;115(11):1859–1868
- Zhang X, Zeng H, Bao S, Wang N, Gillies MC. Diabetic macular edema: new concepts in patho-physiology and treatment. *Cell Biosci*. 2016;4(3):27.
- Hakeem R, Fawwad A. Diabetes in Pakistan: Epidemiology, Determinants and Prevention. *JDiabetol*. 2017;1(3):3
- Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol*. 2019;54(1):1–32.
- Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of vitreous inflammatory factors with diabetic macular edema. *Ophthalmology*. 2016;116(1):73–79
- Bandello F, Pognuz R, Polito A, Pirracchio A, Menchini F, Ambesi M. Diabetic macular edema: classification, medical and laser therapy. *Semin Ophthalmol*. 2017;18(4):251–258
- Zhang X, Bao S, Lai D, Rapkins RW, Gillies MC. Intravitreal triamcinolone acetonide inhibits breakdown of the blood-retinal barrier through differential regulation of VEGF-A and its receptors in early diabetic rat retinas. *Diabetes*. 2018;57(4):1026–1033.
- Ghoraba HH, Leila M, Elgouhary SM, Elgemai EEM, Abdelfattah HM, Ghoraba HH, et al. Safety of high dose intravitreal triamcinolone acetonide as low-cost alternative to anti-vascular endothelial growth factor agents in lower-middle-income countries. *Clin Ophthalmol*. 2018;12(2):2383–2391
- Tayyab H, Ahmed N.C, Sadiq A.A.M. Efficacy and safety of Suprachoroidal Triamcinolone Acetonide in cases of resistant diabetic Macular Edema. *Pak J Med Sci*. 2020 ; 36(2): 42–47.
- Goldstein DA, Do D, Noronha G, Kissner JM, Srivastava SK, Nguyen QD. Suprachoroidal Corticosteroid Administration: A Novel Route for Local Treatment of Noninfectious Uveitis. *Transl Vis Sci Technol*. 2016;5(6):14.
- Fong DS, Ferris FL, 3rd, Davis MD, Chew EY. Causes of severe visual loss in the early treatment diabetic retinopathy study: ETDRS report no. 24. Early Treatment Diabetic Retinopathy Study Research Group. *Am J Ophthalmol*. 1999;127(2):137–141.
- Striph GG, Hart WM, Jr, Olk RJ. Modified grid laser photocoagulation for diabetic macular edema. The effect on the central visualfield. *Ophthalmology*. 1988;95(12):1673–1679.
- Lim JW, Lee HK, Shin MC. Comparison of intravitreal bevacizumab alone or combined with triamcinolone versus triamcinolone in diabetic macular edema: a randomized clinical trial. *Ophthalmologica*. 2012;227(2):100–106.
- Song HJ, Lee JJ, Lee SJ. Comparison of the Short-Term Effects of IVTA and Bevacizumab Injection for Diabetic Macular Edema. *Korean J Ophthalmol*. 2011;25(3):156–160.
- Isaac DL, Abud MB, Frantz KA, Rassi AR, Avila M. Comparing IVTA and bevacizumab injections for the treatment of diabetic macular oedema: a randomized double-blind study. *Acta Ophthalmol*. 2012;90(1):56–60
- Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology*. 2004;111(11):2044–2049.
- Paccola L, Costa RA, Folgosa MS, Barbosa JC, Scott IU, Jorge R. Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study) *Br J Ophthalmol*. 2008;92(1):76–80.
- Ophir A. Full-field 3-D optical coherence tomography imaging and treatment decision in diffuse diabetic macular edema. *Invest Ophthalmol Vis Sci*. 2014;55(5):3052–3053
- Kreutzer TC, Al Saeidi R, Kook D, Wolf A, Ulbig MW, Neubauer AS, Haritoglou C. Comparison of intravitreal bevacizumab versus triamcinolone for the treatment of diffuse diabetic macular edema. *Ophthalmologica*. 2010;224(4):258–264.
- Zhang XL, Chen J, Zhang RJ, Wang WJ, Zhou Q, Qin XY. Intravitreal triamcinolone versus intravitreal bevacizumab for diabetic macular edema: a meta-analysis. *Int J Ophthalmol*. 2013;6(4):546–552.
- Christoforidis JB, Carlton MM, Knopp MV, Hinkle GH. PET/CT imaging of I-124 radiolabeled bevacizumab and ranibizumab after intravitreal injection in a rabbit model. *Invest Ophthalmol Vis Sci*. 2011;52(8):5899–5903
- Shimura M, Nakazawa T, Yasuda K, Shiono T, Lida T, Sakamoto T, Nishida K. Comparative therapy evaluation of intravitreal bevacizumab and triamcinolone acetonide on persistent diffuse diabetic macular edema. *Am J Ophthalmol*. 2008;145(5):854–861.
- Marey HM, Ellakwa AF. Intravitreal bevacizumab alone or combined with triamcinolone acetonide as the primary treatment for diabetic macular edema. *Clin Ophthalmol*. 2011;5:1011–1016.