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ORIGINAL ARTICLE

Comparison of Suprachoroidal Triamcinolone Injection with Intravitreal Bevacizumab Vs Intravitreal Bevacizumab only in Treatment of Refractory Diabetic Macular Edema

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ABSTRACT

Background: Macular edema due to diabetic retinopathy is among the most common causes of blindness in diabetics from working age group around the world . Diabetic macular edema which involves the center of the macula is among the major cause of visual decline in patients with diabetes mellitus. Intra-Vitreal Triamcinolone Acetonide with intravitreal Bevacizumab and intravitreal Bevacizumab only have been in practice as treatment options for cases not responsive to anti-vascular endothelial growth factor agents.

Objective: To compare safety and efficacy profile of suprachoroidal injection of triamcinolone acetonide with intravitreal Bevacizumav Vs intravitreal injection of Bevacizumab alone in management of resistant diabetic macular edema.

Patients & Methods: In this study, Fourty eyes of fourty patients who had resistant diabetic macular edema were randomly divided into two groups of 20 patients each (n=20) , our group A was injected with suprachoroidal triamcinolone acetonide 2 mg along with intravitreal Bevacizumab 1.25mg and the group B wasinjected with intravitreal Bevacizumab 1.25 mg only. Change in central macular thickness was observed after one month on Optical coherence tomography. Data was collected and analyzed by using SPSS software.

Results: The mean age of subjects in this study was 58.46±3.62 years (30-65 years) . Out of 40 patients 26 were male patients and 14 were female .The mean decline (change) in central macular thickness in comparison to baseline thickness on OCT in group A was 113±10microns and mean change in the central thickness of macula on OCT in group B was 83+-10 microns with a p value of 0.01.

Conclusion: Suprachoroidal triamcinolone acetonide with intravitreal bevacizumab is superior to intravitreal Bevacizumab alone in reducing central macular thickness among patients with resistant diabetic macular edema.

Keywords: Macular edema, Suprachoroidal triamcinolone , intravitreal Bevacizumab, Optical coherence tomography

INTRODUCTION

Diabetic macular edema(DME) is among the most common causes of blindness in the world among diabetics from the working age group . Diabetic macular edema which involves the center of the macula is one of the common cause of visual impairment. Intra-Vitreal Triamcinolone Acetonide and Argon grid laser have been in practice as an alternative treatment option for cases not responsive to anti vascular endothelial growth factors. Intra-Vitreal Triamcinolone has shown very promising results in refractory cases but with a downside of raised intraocular pressure. Recently Triamcinolone administered through suprachoroidal route has shown same efficacy with lesser incidence of raised intraocular pressure. Various studies have supported the fact that in subjects with type 2 diabetes or the non insulin dependent diabetes , the prevalence of diabetic macular edema raised from 3% to 28% within the first 5 years of diagnosis of diabetes mellitus till twenty years after the diagnosis of diabetes mellitus.[10] Diabetic macular edema which involves the central macula (fovea) is among the major causes of visual decline worldwide. From 1985 to 2010, retinal laser photocoagulation was the available method for treating center-involving diabetic macular edema. Various studies since 2010, including several large clinical trials have proven that intravitreal injections of various antivascular endothelial growth factor (Anti VEGF) agents injected into the vitreous (intravitreous injections) were superior as well as safer than argon laser photocoagulation in patients with center involving DME and visual acuity decline of of 20/32 or worse.[2]

Intravitreal injection Triamcinolone Acetonide have been used as a second line treatment for cases that are not responsive or resistant to anti vascular endothelial growth factor agents.[3] Although, Intra-Vitreal Triamcinolone Acetonide has very good effect in treating center involving diabetic macular edema and re-establishing as well as maintenance of compromised and leaky blood retinal barrier(outer and inner); its use is associated with various non-desirable effects like rise in intraocular pressure in steroid responders and early cataract development.[8] There is a need for repeated intravitreal injections of triamcinolone acetonide due to the waning effect of Intra-Vitreal Triamcinolone Acetonide over time which is limited by its intravitreal half life and reoccurrence of center involving diabetic macular edema after the duration of action of triamcinolone acetonide has been completed. Its documented complications include elevated Intraocular Pressure and cataract formation.[11]

Triamcinolone acetonide is a safe and effective as well as cost saving therapy in diabetic macular edema.[1] Central Macular thickness when documented by optical coherence tomography decreased after management with intravitreal injection of triamcinolone acetonide. Most patients who were treated with 4 mg of intravitreal injection of triamcinolone required early cataract surgery due to development of visually significant cataract. [8,6]

One trial found that >50% improvement in central macular thickness was observed in 23% cases with modified grid laser and 46% cases with intravitreal Triamcinolone while ≥ 5 lines improvement in visual acuity was observed in 38% cases with modified grid laser and 55% cases with intravitreal Triamcinolone ($p<0.05$).[4] In another trial, improvement in central macular thickness was observed in 17% cases with modified grid laser and 32% cases with intravitreal Triamcinolone and gain in visual acuity was observed in 44% cases with modified grid laser and 22% cases with intravitreal Triamcinolone ($p<0.05$). This study did not indicate a long-term benefit of intravitreal injection of triamcinolone compared to grid photocoagulation by argon laser for patients with center involving diabetic macular edema . Most patients receiving 4 mg intravitreal injection of triamcinolone in the study were likely to require cataract surgery.[5]

The rationale of this study is to compare the outcome of Suprachoroidal triamcinolone injection in combination with intravitreal Bevacizumabin Vs intravitreal Bevacizumab only in

treatment of refractory diabetic macular edema. Literature showed conflicting results regarding the efficacy of both treatment protocols. There is also lack of local evidence and we are unable to decide whether which drug can be more beneficial in treating resistant diabetic macular edema among diabetics. So we wanted to conduct this local study to get the local evidence so that we can use the results of this study in local setting and can be able to implement the use of Suprachoroidal triamcinolone injection to avoid relapse and complication of diabetic macular edema in diabetics and help to protect their vision.

MATERIALSAND METHODS

This study was granted ethical approval by our local institutional ethical review board and study period of six months started after the approval of the ethical board. This study was conducted at the department of Ophthalmology, Eye Unit 1 at Services hospital Lahore from April 2021 to September 2021. During this time period forty eyes of forty three patients were selected with history of resistant diabetic macular edema which was defined as Diabetic macular edema not responding(Less than 50 percent decrease in thickness from the point of start of treatment) to at least 3 anti vascular endothelial growth factor injections given monthly or 2 different generations in last 12 weeks

Male and female patients between the age of 30-65 years of age were part of this study. Patients who agreed to participate in this study were informed about the time and duration of follow-up visits of twelve weeks, patients in the study signed a detailed written informed consent form both in English and in their local language. Patients with uncontrolled hypertension, ischemic heart disease, past history of stroke and myocardial infarction, previous history of pars plana vitrectomy , trauma ,Intra Ocular foreign body, systemic coagulation abnormalities and other systemic diseases were excluded from this study. In this study, Forty eyes of forty patients who underwent three port ROSO with 23 gauge port system were randomly divided into two groups of 20 patients each (n=20) , our group A was injected with suprachoroidal triamcinolone acetonide 2 mg along with intravitreal Bevacizumab 1.25mg and the group B wasinjected with intravitreal Bevacizumab 1.25 mg only.Change in central macular thickness was observed after one month on Optical coherence tomography.

The patients were given intravitreal injection of Bevacizumab1.25mg along with suprachoroidal injection of triamcinolone acetonide 2mg in group A and only ntravitreal Bevacizumab 1.25mg in group B. All intravitreal and suprachoroidal injections were injected using topical proparacaine eye drops. Procedure of intravitreal injection started with local aseptic techniques , the eyelids were scrubbed with a 10% povidone-iodine solution , and 5% povidone-iodine solution was instilled by drops in the conjunctival cul de sac. Then after 2 minutes, intravitreal injection was given. Povidone-iodine solution was applied to the conjunctiva directly over the intended injection site location. Bevacizumab(Avastin) (1.25 mg/ 0.05 cc) was injected in the intravitreal cavity using a 29-gauge 0.5-inch needle inserted through the region of pars plana in the inferotemporal quadrant , about 3.5-4.0 mm posterior to the limbus , similarly 2mg of triamcinolone acetonide (2mg in 0.05ml) was injectected by same technique into the suprachoroidal space . Patients were required to instill 1 drop of 0.3% ciprofloxacin into the conjuctical sac of the injected eye 4 times a daily for one week after the intravitreal injection procedure. All assessments were done by researcher. Then patients were followed-up in OPD weekly for 1 month. 1 month after injections, mean central macular thickness was noted by using optical coherence tomography(OCT) and change in the central macular thickness was quantified (as per operational definition).

Data was analyzed through SPSS version 21.0. Quantitative variables like age, duration of edema, pre and post-treatment central macular thickness and change in central macular thickness were presented as mean deviation and standard deviation. The qualitative variables like gender, laterality and diabetes was presented as frequency and percentage. Mean change in the central macular thickness was analyzed by paired sample t-test. The P-value of ≤0.05 was taken as significant.

RESULTS:

Mean age of patients in this study was 58.46±3.62 years (range 30-65 years) . Out of 40 patients 26 were male patients and 14 were female . Mean reduction in the central macular thickness from baseline on OCT in group A was 113±10 microns and the mean change in central macular thickness on OCT in group B was 83±10 microns with a p value of 0.01.

In our study the pre injection evaluation the mean CMT of the patients was 381.15±67.57 mm while post injection evaluation the mean CMT of the patients was 269.71±56.06 micron in group A and 298±45 microns in group B. This difference was taken as statistically significant i.e. p-value=<0.001. Mean age of patients was 58.46±3.62 years (range 30-65 years). Mean duration of sillicone oil temponade in patients was 6.25±1.52 months (range 5-11 months). In 62.20%(28) of patients there was no pain or discomforts (Pain analogue scale of less than 2), in 20%(9) there was mild(Pain scale of 2 to 3) and in 13.33%(6) of patients, moderate pain was observed(pain analogue scale of more than 3). Table 1.

Figure 1: Gender distribution of study participants

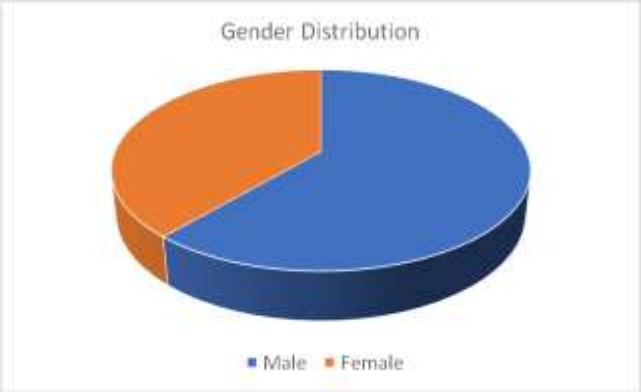

Table 1 Intra operative hemorrhage Pre and post comparison of CMT

		Pre	Post group A	Post group B	p-value
CMT	n	40	20	20	<0.001
	Mean	381.15	269.71	298	
	SD	67.57	56.06	48	

DISCUSSION

Bevacizumab is a humanized monoclonal antibody of 148kD and is inhibitor of all the isoforms of VEGF-A. VEGF which is responsible for the development of macular edema by breakdown of blood retinal barrier is released by retinal cells like muller cells, retinal ganglion cells, retinal pigment epithelial cells and photoreceptors in response to hypoxia by up regulation of HIF gene pathway and plays a vital role in the formation of macular edema ,vascular growth and angiogenesis as well as capillary leakage.

Bevacizumab injected into the vitreous cavity as an intravitreal injection is cleared by two major pathways in the eye: an anterior route which drains the drug through the anterior chamber via trabecular meshwork through the angle and a posterior segment route that passes across the neurosensory retina and bruchs membrane into to the choroid circulation.[14] Triamcinolone acetonide is injected in the suprachoroidal space whre it has a longer duration of action and acts on the inflammatory pathway to reduce the mechanisms that produce macular edema in diabetic retinopathy.

Clinical trials have documented that visual acuity improvement from baseline is associated with decline in the mean CMT from baseline among patients with diabetic macular

edema.[15,16] There was a significant level of ($P < 0.01$) correlation between the mean change in CMT of all study stages and the mean change in BCVA. One month after each injection, BCVA improved significantly, as a result of reduced macular edema and vascular leakage. These findings are in accordance with previous studies' results concerning the relationship between CMT and VA after ranibizumab.[13]

One study found that the mean decline in central macular thickness was 165.5±134.3µm (at presentation: 492.0±145.4µm and at 3 month: 326.5±95.4µm, $p<0.01$, n=134) with Single Dose Intravitreal Ranibizumab.[17,18] While another found that the mean reduction in central macular thickness was 112.6±5.1µm (at presentation: 421.9±23.1µm and at 3 month: 309.3±18.0µm, $p<0.05$, n=28) with Single Dose Intravitreal Ranibizumab.[8]

In HULK trial, 20 patients with diabetic macular edema were given suprachoroidal triamcinolone acetonide and 8.5 mean letter gain in visual acuity was noted on ETDRS chart after 6 months. Also,mean central sub field thickness was reduced from 473 um to 369 um after 6 months.[12]

In another recent study, 24 patients were assessed for safety and efficacy of suprachoroidal triamcinolone acetonide. Only one patient needed anti glaucoma medication for lowering intra ocular pressure and it returned to baseline after 3 months. The mean pre injection central thickness was 636.5 um and after 3 months of treatment it was noted to be 302.6 um. And the mean pre suprachoroidal triamcinolone injection best corrected visual acuity was 0.8 on ETDRS chart which became 0.45 after 3 months.[9]

CONCLUSION

This study concluded that the intravitreal injection of bevacizumab with suprachoroidal triamcinolone acetonide for macular edema is very effective and useful for the reduction in central macular thickness

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