INTRAVITREAL TRIAMCINOLONE ALONE VERSUS COMBINED INTRAVITREAL TRIAMCINOLONE AND BEVACIZUMAB ON CENTRAL MACULAR THICKNESS IN DIABETIC MACULAR EDEMA

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ABSTRACT

Objective: To compare the effect of intravitreal triamcinolone (IVT) alone with combined intravitreal triamcinolone (IVT) and intravitreal bevacizumab (IVB) on central macular thickness (CMT) in patients of diabetic macular edema (DME).

Study Design: Randomized control trial.

Place and Duration of Study: Armed Forces Institute of Ophthalmology, Jun 2013 to Dec 2013.

Material and Methods: Eighty patients were included in the study through non probability consecutive sampling and were randomized to IVT alone or IVT + IVB group using random number table. Pre and post injection (12 weeks) CMT were recorded and intra and inter group comparison was performed.

Results: Both groups showed statistically significant reduction in mean CMT at 12 weeks ($p<0.05$). In Group A, mean CMT reduction at 12 weeks was 64.33 microns (SD=15.17) while in Group B it was 75.18 (SD=20.82). On comparison, IVT + IVB group was more effective in reducing CMT with statistically significant difference ($p=0.009$).

Conclusion: Intravitreal triamcinolone used in combination with IVB is more effective in reducing central macular thickness in diabetic macular edema (DME) than intravitreal triamcinolone alone.

Keywords: Bevacizumab, Central macular thickness, Diabetic macular edema, Traiamcinolone.

INTRODUCTION

Diabetes mellitus is a global health threat. Pakistan is 7th on the diabetes prevalence list with 6.9 million cases[1]. Diabetic macular edema (DME), a manifestation of diabetic retinopathy (DR)[2] is the commonest cause of visual impairment in diabetics. The macular thickness is increased in DME and optical coherence tomography (OCT) is used for assessment of macular thickness which correlates with reduced visual functions[3]. According to early treatment diabetic retinopathy study (ETDRS), focal / grid laser photocoagulation is the accepted standard treatment of DME[4]. Diabetic macular edema is a predominant cause of visual impairment in diabetic patients. The goal of any treatment modality is to reduce the macular thickness, thereby leading to visual improvement. The beneficial effects of both intravitreal triamcinolone and bevacizumab on DME had already been proven by various studies[5,6]. Recently combined effect of triamcinolone and bevacizumab on macular thickness in diabetics is being studied in various parts of the world[9,10].

Alternate treatment options for DME are currently under investigation. Intravitreal injections of triamcinolone, a corticosteroid, have shown to effectively improve visual acuity and reduce macular edema in DME[5] and is being used for the treatment of DME. Vascular endothelial growth factor (VEGF) is known to be a critical stimulus in DME[6]. Hence newer therapies like intravitreal anti VEGF agents are evolving for treatment of DME. Bevacizumab is an anti VEGF agent which is under extensive research and experimentation for intravitreal treatment of DME but is not yet approved by FDA. Its short term

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results are safe[7] and encouraging but long term safety and treatment recommendations are awaited, pending results of further research[8]. The purpose of this study was to determine whether combining the newer modalities like intravitreal anti VEGF agents (bevacizumab) with the tried and tested triamcinolone will be more effective in reducing macular thickness in DME than Triamcinolone alone.

MATERIAL AND METHODS

This randomized controlled trial was carried out at Armed Forces Institute of Ophthalmology from June 2013 to December 2013 after approval from the hospital ethical committee. Diagnosed cases of DME, more than 18 years of age, having CMT of more than 250 microns on OCT were included. Patients having vitreous haemorrhage, vitreomacular traction or history of vitrectomy were excluded. A total of eighty patients were enrolled through non probability consecutive sampling, after taking their informed written consent. Patients were randomly divided into two groups of forty each through random numbers table. Those receiving IVT alone were labeled as group A and those getting IVT + IVB were labeled as group B. Detailed Examination including unaided vision, pinhole vision, best corrected visual acuity (BCVA) testing using Snellens chart at 6 m, pupillary reactions, slit-lamp examination for studying details of cornea, anterior chamber, lens, vitreous and fundus using 90 D lens. Pre injection CMT was recorded using OCT. The values were recorded on a predesigned proforma.

The patients in both the groups received intravitreal injections. Preformed intravitreal injection of 2mg/0.05 ml triamcinolone alone was given to patients in Group A while cases in Group B also received 1.25 mg/0.05 ml bevacizumab in addition to IVT. The injections were carried out in the operating room under sterile conditions. After topical anesthesia, the ocular surface and the lids were disinfected with povidone iodine. We used a speculum, sterile gloves and a surgical drape. The injections were performed in the inferior or superior temporal quadrant 3.5–4.0 mm posterior to the limbus with a 30-gauge needle. The injection site was compressed with a cotton swab to avoid reflux when removing the needle. Topical drops of combined preparation of tobramycin and dexamethasone thrice daily along with levobunolol twice daily were prescribed for the following 2 weeks. All patients underwent OCT evaluation at baseline and 12 weeks during follow up.

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) version 20.0. Descriptive statistics were used to describe the results. The mean and standard deviation (SD) were calculated for age, number of diabetic years and difference in pre and post treatment central macular thickness at 12 weeks. Frequency and percentage were calculated for the type of diabetes, gender and presence or absence of hypertension. Independent sample t test was applied to compare the mean difference in CMT between Group A (IVT alone) and Group B (IVT plus IVB) at 12 weeks. Chi square and Paired samples t–test/Mann Whitney U test (where appropriate) were used depending upon the type and distribution of variables . *p*-value of < 0.05 was considered statistically significant.

Table: Comparison of *p*-value of change in central macular thickness between the patients of the two Groups.

Group of the Patient	Mean	Std. Deviation
A (n=40)	64.33	15.171
B (n=40)	75.18	20.820

RESULTS

Group A had 30 males (75%) and 10 females (25%) while group B had 33 males (82.5%) and 07

females (17.5%); (p=0.412). All the cases in both the groups were type 2 diabetics. Group A had 62.5% patients on oral hypoglycemics while in Group B there were 57.5% cases on oral hypoglycemic (p=0.648). There were 55% cases with co existent hypertension in group A while 47.5% had hypertension in group B (p=0.491). Mean age of group A was 62.15 ± 8.89 years while the mean age in group B was 59.13 ± 10.09 years (p=0.184). Hence, both the groups were comparable in terms of these demographic variables.

Mean duration of diabetes in group A was 22.03 ± 7.42 [Median (IQR)=22 (13)] years whereas that of group B was 17.98 ± 8.19 [Median (IQR) = 20(15)] years (p=0.021)

At baseline, mean CMT in group A was 356.88 ± 62.50 microns while in group B it was 375.90 ± 72. 20 microns. Hence, both the groups were comparable (p=0.211). Mean CMT, in group A was reduced to 292.55 microns (SD=53.119) at twelve weeks post intravitreal injection (p=0.00), showing a highly significant decrease ($p \leq 0.001$). Similarly, mean CMT was significally reduced to 300.18 microns (SD=63.306) at 12 weeks post treatment in Group B ($p \leq 0.001$) (fig).

Decrease in CMT in group B was higher as compared to group A (p=0.001) (table).

DISCUSSION

This study showed a highly significant effect of IVT alone in DME in terms of mean reduction of CMT at 12 weeks. The mean CMT reduced from 356.88 microns (SD=62.50) at baseline to 292.55 microns (SD=53.11) at 12 weeks. These results were similar to the Diabetic Retinopathy Clinical Research Network (DRCR. net) result[9]. It is a phase 2 randomized, multi-center clinical trial, conducted at 36 clinical sites in the United States that subjected the patients to five different treatment regimes for diabetic macular edema on 121 eyes (divided into 5 groups) with DME on the basis of central retinal thickness (CRT) and best-corrected visual acuity (VA). They showed a reduction in CRT to less than 250 microns in 37 (43%) eyes receiving 1 mg IVT and 45 (51%) eyes in 4mg IVT group at 3 year follow up.

Similarly, Ciardella et al[10] also found diminished foveal thickness at month 1 and 3 which increased at month 6 without reaching baseline levels.

Bevacizumab, an anti VEGF, has shown promising results in treatment of DME, when used alone or in combination with triamcinolone. In our study we found a statistically significant (p=0.000) reduction in CMT at twelve weeks, when combined IVT and IVB were used. The mean CMT reduced from 375.90 (SD=72.210) microns at baseline to 300.18 microns (SD=63.306) at twelve weeks. These results were similar to Wang Yu et al[11], who found that the central retinal thickness (CRT) reduced from (554.50 ± 169.05) μm at baseline to (292.76 ± 196.05) μm, (323.46 ± 164.05)

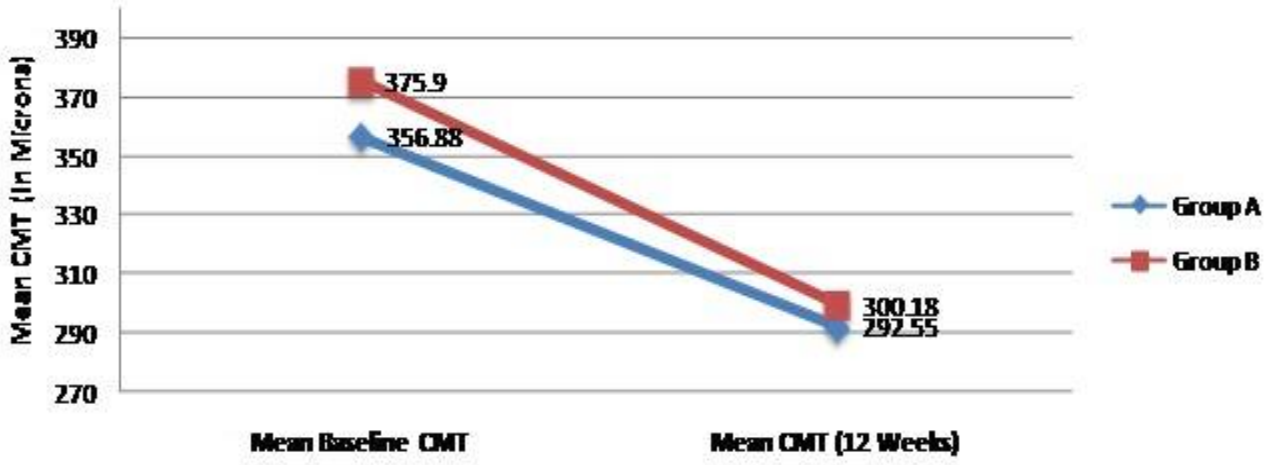

Figure: Comparison of mean control macular thickness between the two groups at baseline at 12 weeks.

μm and (426.38 ± 169.05) μm, at 4, 6 and 12 weeks respectively (p=0.009, p=0.014 and p=0.028, respectively).

We found that at the end of twelve weeks, the mean reduction in CMT from baseline in Group A was 64.33 microns (SD=15.17) while in Group B it was 75.18 microns (SD=20.82). It showed that IVT used in combination with IVB was more effective in reducing CMT at 12 weeks than IVT alone and the difference between the two groups was statistically significant (p=0.009). These results were similar to the results of Hatem M et al[12], in which there was a statistically significant (0.001) difference in reduction of CMT between IVT alone group and IVT + IVB group. They concluded that combined IVT and IVB had an upper hand in leading to maintained reduction in CMT at 12 weeks that couldn't be achieved with using IVT alone in DME.

However, another study conducted by Lim et al[13] showed completely different results. It was a randomized three arm clinical trial that evaluated one hundred eleven eyes with 12 month follow up. They found that although both IVT and IVB improved visual acuity and reduced CMT, no statistically significant difference was observed between the groups at 12 months. Hence, no beneficial effect of the combination injection was observed by them. These differences could be because of multiple factors. Firstly, it could be because of the difference in race as their study was carried out on Korean population. Secondly, our study was carried out on comparatively smaller group of patients. Thirdly, our study had a shorter follow-up of only twelve weeks while they determined the effects over a longer time frame of twelve months.

Hence, although this study shows that combined use of intravitreal triamcinolone and bevacizumab is effective in treatment of DME and the results are promising, it is a short term study with some limitations. The follow up of our study is still too short to make any specific treatment recommendations, or preclude any estimation of the long-term efficacy or safety of combined use of intravitreal Triamcinolone and bevacizumab. The number of patients evaluated was small and the results may be specific to our race. Evaluation in a multicenter randomized controlled clinical trial with longer follow-up is needed to evaluate the safety and efficacy of this treatment.

CONCLUSION

Combining intravitreal anti VEGF agent, bevacizumab with intravitreal triamcinolone is more effective in reducing CMT in patients of diabetic macular edema than intravitreal triamcinolone alone.

However, further clinical trials with larger sample size and longer follow-up are needed to determine the safety and long term efficacy of this treatment.

CONFLICT OF INTEREST

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

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