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Original Article

Effects of Intra-Vitreal Diclofenac in Refractory Diabetic Macular Edema

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ABSTRACT

Objectives: To see the effects of Intra-Vitreal Diclofenac injection (IVD) in refractory Diabetic Macular Edema (DME).
Study Design: Quasi-experimental study.
Place and Duration of Study: Retina Clinic, Al-Shifa Trust Eye Hospital, Rawalpindi Pakistan from Sep 2019 to Feb 2020.
Methodology: Patients included in the study having Clinically Significant Macular Edema (CSME) with Central Macular Thickness (CMT) of more than 300 microns not responding to three consecutive Intravitreal injections of Bevacizumab (IVB). Intravitreal Diclofenac injection (500µg/0.1 ml) was given by the same retina fellow with the same protocol across all patients. Each patient was evaluated based on Central Macular Thickness (CMT) before intravitreal Diclofenac injection and on follow-up visits one week and one month after injection.
Results: A total of 30 patients (30 eyes) were included in the study. Out of these, 11 were females, and 19 were males. The mean age of the patients was 57.87±4.424 years. Mean Central Macular Thickness (CMT) before injection was 439.67±110.45µm, after one week 398.47±110.55µm and 384.87±119.11µm after one month of intra-vitreal Diclofenac injection. Pre and post-injection central macular thickness (µm), which was clinically significant (p-value <0.001).
Conclusion: Intravitreal Diclofenac injection (IVD) is effective in diabetic macular oedema, not responding to intravitreal anti-VEGF (IVB) injections.

Keywords: Best Corrected Visual Acuity (VA), Central Macular Thickness (CMT), Intravitreal Bevacizumab (IVB), Intravitreal Diclofenac (IVD), Refractory Diabetic Macular Edema.

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INTRODUCTION

Diabetes Mellitus is a multi-organ disorder mainly affecting micro-vessels.[1] It can result in visual deterioration mainly due to micro-vascular leakage, thus resulting in retinopathy and diabetic macular oedema (DME).[2] This can ultimately lead to blindness.[3,4] Lack of treatment and poor diabetic control can lead to fluid accumulation at fovea centralis, which is the centre for sharpest vision. This macular swelling, i.e. diabetic macular oedema, causes blurred vision.[5]

Clinically significant macular oedema (CSME) is diagnosed clinically.[6,7] According to the Early Treatment Diabetic Retinopathy Study (ETDRS), it is defined as retinal thickening located 500µm of the centre of the macula or hard exudates which lie within 500 µm of the centre of macula centre accompanied by adjacent retinal thickening or retinal thickening of one or more disc diameters any part of which lies within one disc diameter of the centre of the macula.[8] It can be diagnosed by indirect ophthalmoscopy using an accessory lens with a slit- a lamp biomicroscopy. No investigations are needed to confirm the diagnosis, but OCT and FFA may be used to monitor the progress after treatment and to decide on the further management plan.

There are a few treatment modalities available for DME.[9] These include laser treatment, intravitreal anti-vascular endothelial growth factor (anti-VEGF), and corticosteroids in the form of injections or implants. In laser therapy, damaged areas of the retina are targeted and leaking blood vessels are sealed along with and prevention of neovascularization. Laser treatment can stabilize the current visual status. Multiple treatment sessions may be needed in case of severe disease. As already mentioned, there are two groups of injectable medications, i.e. anti-VEGF and corticosteroids. There are several subtypes available within each group. Anti-VEGF decreases the fluid leakage from the micro-aneurysms and micro-capillaries, thus reducing DME. Intra-vitreal steroids also reduce inflammation and DME and are used if there is no response to anti-VEGF therapy. With steroid therapy, there is an associated risk of cataracts and raised intra-ocular pressure (IOP). Recently, Intravitreal Non-Steroid Anti-Inflammatory Drugs (NSAIDs) such as Diclofenac (IVD) has shown promising outcome in the treatment of diabetic macular edema.[10] This study was carried out to find the best alternative and cost-effective treatment for

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refractory diabetic macular oedema, i.e., DME not responding to intravitreal Bevacizumab (IVB) and steroids, with minimal side effects.

METHODOLOGY

This study was conducted at Retina Clinic, Al-Shifa Trust Eye Hospital, Rawalpindi Pakistan, from September 2019 from February 2020 after IERB approval (Certificate No. ERC-56/AST-20). The sample size was calculated using the WHO sample size calculator.[11]

Inclusion Criteria: Patients with clinically significant macular oedema (CSME) were included in the study.

Exclusion Criteria: Patients younger than 18 years, with any history of ocular surgery (within the last six months) or another ocular disease such as glaucoma, uveitis, retinal vascular disease or any other chorioretinal disease, were excluded from the study. In addition, subjects with previous laser treatment (focal, grid or panretinal photocoagulation) or previous intravitreal Diclofenac injections (IVD) were not included in the study.

A total of 30 subjects (30 eyes - 18 right eyes and 12 left eyes) with clinically significant macular oedema (CSME) were included through consecutive sampling. Subjects had a Central Macular Thickness (CMT) of more than 300 microns that did not show improvement with Intra-Vitreal Bevacizumab (3 consecutive injections). If CMT did not decrease by >30 microns after ≥3 consecutive IVB injections or if there was increased CMT after 1-2 IVB injections, CSME was considered refractory.

Screened patients were received in the retina clinic OPD after their visual assessment and slit-lamp examination by an optometrist and an ophthalmologist, respectively. Any patient with Central Macular Thickness (CMT) of more than 300 microns which did not show improvement with three consecutive IVB injections, was included in the study. For the measurement of Central macular thickness (CMT), "Carl Zeiss Meditec Stratus OCT" was utilised. After detailed counselling regarding the procedure, informed written consent was obtained from all patients. Under sterile conditions, each subject was administered an intravitreal Diclofenac injection (500 µg/0.1 ml). After the injection, antibiotic eye drops were prescribed for five days (four times per day).

Patients were called for follow-up one week and one month after the injection in Vitreo-Retina Department, Al-Shifa Trust Eye Hospital, Rawalpindi Pakistan. On each visit, central macular thickness measurements were obtained by Carl Zeiss Meditec Stratus OCT. All the data was recorded according to a structured pre-designed Proforma.

Statistical Package for Social Sciences (SPSS) version 20:00 was used for the data analysis. Qualitative variables were summarized as frequency and percentages while mean and standard deviation were calculated for numerical variable, i.e., age and central macular thickness at presentation and on follow-ups. Paired sample t-test was used to compare the pre and post-injection central macular thickness. The p-value lower than or up to 0.05 was considered as significant.

RESULTS

A total of 30 patients (30 eyes) were included in this study. The mean age was 57.87±4.424 years. Out of 30 patients, 19 were males, and 11 were females. There were 18 right eyes and 12 left eyes.

The mean central macular thickness before IVD injection was 439.67±110.45 µm. One week after injection, it was 398.47±110.55µm and 384.87±119.11µm after one month (Table-I).

Table-I: Descriptive Statistics of Central Macular Thickness (µm) (n = 30)

Parameters	Central Macular Thickness
Before Intra-Vitreal Diclofenac Injection	439.67±110.45µm (246-611)
One Week Post-Injection	398.47±110.55µm (259-594)
One Month Post-Injection	384.87±119.11µm (232-610)

Paired sample t-test of pre and post-injection central macular thickness (µm) showed the clinical significant (*p*-value <0.001) (Table-II).

Table II: Pre and Post Injection Central Macular Thickness (µm) (n=30)

Parameters	Intra-Vitreal Diclofenac Injection		*p*-value
	Before Injection	One Month Post Injection	
Central Macular Thickness (µm)	439.67±110.45	384.87±119.11	<0.001

DISCUSSION

One of the most common causes of visual loss in subjects with diabetic retinopathy is diabetic macular oedema (DME).[12] Prolonged and poor glycemic control is a major risk factor.[13] Some other medical conditions, such as uncontrolled hypertension and diabetic nephropathy can increase the risk of DME.[14] Any stage of

diabetic retinopathy can present with DME. Initial treatment options include laser therapy and intravitreal Bevacizumab, and corticosteroid injections.[15] When there is no improvement with initial treatment, it is considered refractory DME.[16] Several studies have shown the promising outcome of intravitreal Diclofenac injection in refractory macular oedema due to other etiologies.[17]

In our study, we assessed the effect of intravitreal Diclofenac injection (IVD) on Central Macular Thickness (CMT) in patients with DME, and the results are comparable with the previous studies. Overall improvement was observed in CMT at the end of 1 month.

Elbendary *et al*.[11] did a study to assess the effect of intravitreal Diclofenac compared to intra-vitreal triamcinolone acetonide for treating DME. Thirty-two eyes with DME were randomly divided into two groups, i.e. Group-1 (16 eyes) treated with intravitreal injection of 4mg/0.1ml of triamcinolone and Group-2 (16 eyes) treated with 500µg/0.1ml of intravitreal Diclofenac injection. In both groups, CMT was decreased significantly, i.e., triamcinolone (p-value = 0.02) and Diclofenac (p-value = 0.01). In addition, the difference between the results of the two groups was non-significant. Significant visual improvement was achieved only in Group-1, i.e. Triamcinolone Group (p-value = 0.05). This study demonstrated similar results to our study, i.e. intravitreal Diclofenac injection (IVD) has comparable efficacy to intra-vitreal Triamcinolone Acetonide in reducing CMT.

Soheilian *et al*,[18] in their randomized clinical study, compared the efficacy of intravitreal Diclofenac (IVD) injection with intravitreal Bevacizumab (IVB) injection in the treatment of refractory diabetic macular oedema (DME). A total of 57 eyes from 57 patients were randomly divided into the IVD Group (30 eyes) and the IVB Group (27 eyes). There was a significant improvement in best-corrected visual acuity in the IVD group, more than in the IVB group (p-value = 0.033). However, changes in macular thickness were more in the IVB group, but not significantly. These results contradict the results of our study. We did not compare the effect of IVD versus IVB and did not analyse the effect of treatment on best-corrected visual acuity.

In another such study, Ghanbari *et al*,[19] compared the efficacy of a single combined intravitreal injection of Bevacizumab and Diclofenac, i.e. 1.25mg ± 300µg/0.1ml (IVB/D) with 1.25mg/0.1ml of intravitreal Bevacizumab (IVB) alone for treating naive DME. The results showed that CMT was significantly reduced in both groups. The mean reductions in CMT were 82.43±160.09 in the IVB alone group and 153.26±163.85 in the IVB/D group. Furthermore, when the results of both groups were compared, it was observed that the IVB/D group reduced CMT more than the IVB Group (p-value = 0.04). Like our study, these results show the promising outcome of IVD in the treatment of DME, but in our study, we admini-stered IVD (500µg/0.1ml) alone, not in combination with Bevacizumab.

In another study by Faghihi et al,[20] the effects of IVD and IVB were compared in the treatment of refractory DME. Thirty-two patients (64 eyes) with refractory DME in both eyes were randomly divided into two groups, i.e. IVB and IVD. Follow-up was done at 1, 3, and 6 months post injections. Results showed that CMT was significantly reduced in both groups, and also the difference between both groups was insignificant. It was also noted that IVD reduced the intraocular pressure (IOP), unlike intravitreal steroid injections in which raised IOP is a common and sight-threatening complication. This study supports the results of our study, i.e., IVD can be a good alternative treatment option for refractory DME, and the results are comparable to that of IVB.

Chidambara *et al*,[21] conducted a study to assess the efficacy and safety of IVD injection. In their study, they administered 450µg/0.1ml of IVD injection in a 61-year male with refractory DME. On the first follow-up day after injection, inner retinal toxicity was reported along with splitting of the internal limiting membrane (ILM) from the retinal nerve fibre layer (RNFL). However, it resolved in one-month after injection, and macular oedema was completely resolved during this period. Our study did not evaluate the side effects associated with IVD injections.

There are many strengths as well as limitations in our study. Many treatment options are available for the treatment of persistent diabetic macular oedema. Our study aimed to choose an effective and safe option with minimal complications. Although further studies are required to confirm the safety of IVD injections compared to intravitreal anti-VEGF (IVB) or intravitreal steroids therapy, until now, studies have shown that IVD injection has fewer complications as compared to other therapies mentioned above.

CONCLUSION

Intra-Vitreal Diclofenac (IVD) injection can be used in persistent diabetic macular oedema that shows a poor response to intravitreal anti-VEGF (IVB) or intravitreal steroids therapy.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SHM: Conception, Study design, drafting the manuscript, approval of the final version to be published.

IS & US: Critical review, approval of the final version to be published.

NZ & SZ: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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