Original Article

Efficacy of Intravitreal Dexamethasone implants in Diabetic Macular Edema Unresponsive to Anti-VEGF Therapy

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Abstract

Background: Diabetic retinopathy is a common microvascular complication of diabetes leading to Diabetic Macular Edema (DME)and visual impairment in the working age population[1]About one third of diabetic individuals had some degree of Diabetic retinopathy and less than 10% develop DME.

Intravitreal dexamethasone implant in cases unresponsive to anti VEGF therapy has a beneficial role in improving visual acuity and macular morphology. The possible mechanism of action could be resolution of edema that was resistant to anti VEGF agents

Aims and Objectives: To determine the efficacy of intravitreal dexamethasone implant for DME unresponsive to anti Vascular Endothelial Growth factor(VEGF)treatment

Methodology: A retrospective analysis of refractory 21 cases, 30 eyes of DME to primary anti VEGF treatment was performed to analyze the profile of presentation and treatment outcome to Intravitreal dexamethsone implants. Ranibizumab (0.5 mg) administered monthly and if, were unresponsive after 5-6 injection were switched to Intravitreal Dexamethasone implants (0.7 mg).

Failure to therapeutic response was characterized by increase in central macular thickness from baseline finding or no response to treatment. Intravitreal dexamethasone implant was administered every two months

Best corrected visual acuity,Intraocular pressure and central macular thickness was evaluated at baselines and following intravitreal dexamethasone impant.

Result: The mean age was 56.3± 5.9 years. The mean Intra ocular pressure was 17.3±2.7 mmHg.

The mean anti VEGF treatment sessions was 5.8±1.2. The mean BCVA improved significantly from LogMar 0.76 ±0.16 to 0.67 ±0.19 (p value=0.029) and CMT improved significantly from 431.6 ±100.9µm to 379.1 ±80.72µm (p value =0.0005).

Conclusion: Intravitreal dexamethasone is effective in refractory cases of DME unresponsive to anti VEGF therapy. Optimal evaluation and tailoring therapy with the therapeutic response will be beneficial.

Key Words: *Diabetic Macular edema, DME, Intravitreal Dexamethasone, Diabetic retinopathy*

Introduction

Diabetic retinopathy (DR) is the leading cause of visual impairment in the working age population worldwide.[1] Diabetic macular edema (DME) is macular thickening secondary to diabetic retinopathy. The global prevalence of DME is 6.8% and observed to be related to the duration of diabetes.[2-4]

Treatment of DME remains controversial among various centers and treating specialists. . Focal and grid photocoagulation had been treatment of choice in the past but had the limitation of little role in improving

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vision.[5] Improved understanding of the pathogenesis of DME has facilitated treatment be directed to the cause.

The pathogenesis of DME is complex with a possible role of hyperglycemia initiating capillary endothelial damage in the retina leading to angiogenesis and inflammation. Vascular endothelial growth factor (VEGF) also plays a key role in the pathogenesis.

Corticosteroids have been used to treat DME due to their anti inflammatory and anti angiogeneic effect with the added risk of cataract and raised intra ocular pressure.

Currently anti-VEGF agents are the most effective agents for improvement of visual acuity and macular morphology. Despite significant improvement in visual and anatomic outcome large numbers of patients remain unresponsive to anti VEGF treatment and fail to resolve macular edema. It may impose a burden for patient by frequent administration [6-8].

The Diabetic Retinopathy Clinical Research Network (DRCR Net) observed that about 40% of eyes treated with anti VEGF have central subfield thickness of 250µm at 2 years post treatment[9]. The role of inflammation in progression of DR is well documented and therefore the hypothesis of sustained release steroid implant is justified for anatomical improvement with the added advantage of reduced number of intravitreal injections compared to anti VEGF.

Several studies have observed beneficial role of intra-vitreal dexamethasone implant in cases unresponsive to anti VEGF therapy. The possible mechanism of action could be resolution of edema that was resistant to anti-VEGF agents[10-11]

Lack of large prospective Indian data evaluating the effectiveness of intravitreal dexamethasone and the strong need to address the clinical situation encouraged us to analyze our data and determine the efficacy of intravitreal dexamethasone implant for DME, unresponsive to anti VEGF treatment in patients attending Retina clinic and outpatients department in the Department of Ophthalmology at Vardhman Mahavir Medical College and Safdarjang Hospital.

Methodology

Medical records of patients of diagnosed Diabetic Macular Edema {DME} attending Retina clinic and Out Patient Department of Ophthalmology at VMMC and Safdarjung Hospital between January 2018 and December 2018 were reviewed. 21 patients and 30 eyes were evaluable during the study period.

Inclusion criteria were the age ≥ 18 years, diagnosed as DME, with prior anti-VEGF treatment, unresponsive or refractory to treatment after 5-6 injections administered monthly and thereafter switched to Dexamethasone impant at the discretion of treating physician were included in the study .Intra-vitreal Inj. Ranibizumab (0.5 mg) injections was administered monthly for six months duration. Unresponsive cases were switched to Intravitreal Dexamethasone implants (0.7 mg) which was administered every two months.

Demographic and treatment details of the patients were recorded includingVisual Acuity (Snellen), Intraocular pressure [IOP] and Central Macular Thickness (CMT). The Best Corrected Visual Acuity (BCVA) was converted from Snellen VA to logarithm of minimum angle resolution (LogMAR) VA using standard conversion chart. OCT was performed using Heidelberg Spectralis spectral domain OCT[Heidelberg Engineering, Heidelberg, Germany]. Failure to therapeutic response was characterized by increase in CMT baseline finding or non responsive to treatment or (CMT)≥350m(SD-OCT). The changes in the BCVA, IOP and CMT values were recorded at baseline, 3 months and 6 months after Intravitreal Dexamethasone Implantation.

Patients treated within 6 months prior with intravitreal or sub-Tenon's injections of steroids, focal/grid macular laser photocoagulation, panretinal photocoagulation, cataract surgery, or pars plana vitrectomy, or in whom the macular edema was secondary to a cause other than diabetes were excluded from the study.

Statistical tests were 2 tailed, paired tests (using SPSS 24.0) were used for parametric paired variables.

Results

Thirty eyes of 21 patients were considered as per inclusion criteria. Demographic details have been

tabulated in Table1. The mean age of the group was 56.3± 5.9 years with a slight male preponderance. The mean number of anti VEGF injections and Intravitreal dexamethsone were 5.8±1.2 and 2.8±0.9 respectively.

The mean LogMAR VA was 0.67±0.19 and mean CMT was 431.6±100.9µm at baseline prior Intravitreal Dexamethasone implant.

At 3months of implantation, the mean BCVA improved significantly from LogMar 0.76±0.16 to 0.75 ±0.17 (p value = 0.05) and CMT improved from 431.6 ±100.9 µm to 409.6 ±77.6µm (p value =0.08). [Table-2]

At 6 months of implantation, the mean BCVA improved significantly from LogMar 0.76 ±0.16 to 0.67 ±0.19 (p value=0.029) and CMT improved significantly from 431.6 ±100.9µm to 379.1 ±80.72µm (p value =0.0005). [Table-2]

There was mean reduction of CMT (52.5 µm) from baseline values . IOP values did not change significantly from baseline 17.3 ±2.7 to end of 6months 18.6±2.9 (p value =0.44) [Table 2]. Four patients required topical anti Glaucoma medications during the course of the study.

Table1: Demographic Details

	Mean +SD(Standard Deviation)	Unit
Age	56.3+ 5.9	Years
Visual Acuity	0.67+ 0.19	LogMAR
IOP	17.3+ 2.7	mmHg
Anti VEGF (Ranibizumab)	5.8+ 1.2	Number of injections
Intravitreal Dexamethasone Implant	2.8+ 0.9	Number of injections
Gender	Male -12	57.14%
	Female-9	42.86%
Eye	Right 18	60%
	Left-12	40%

Table 2: Effects of Intra-Vitreal Dexamethasone Implant in Anti VEGF unresponsive Eyes

	Best Corrected Visual Acuity(BCVA)		**Central Macular Thickness(CMT)**		**IOP**		**Eyes**
	Mean+ SD	**P value**	**Mean+ SD (µm)**	**P value**	**Mean+ SD**	**P**	**n**
Baseline	0.76+0.16		431.6+100.9		17.3+2.7		30
3 months	0.75+0.17	0.05	409.6+77.6	0.08	19.3+2.1	0.31	30
6 months	0.67+0.19	0.029	379.1+80.72	0.0005	18.6+2.9	0.44	30

Discussion

The present study was intended to evaluate effectiveness of Intravitreal Dexamethasone implants in DME unresponsive to anti VEGF treatment. Vascular endothelial growth factor(VEGF) is an important mediator in the pathogenesis of DME. It has been established that Intravitreal anti-VEGF injections are the mainstay of treatment for DME.

The Diabetic Retinopathy ClinicalResearch Network (DRCRnet) Protocol I showed that 52%of patients treated with Anti VEGF (ranibizumab) failed to achieve more than 2 line improvement in BCVA and 40% of eyes treated with anti VEGF have central subfield thickness of 250µm at 2 years post treatment. [9] Several studies have observed that patients treated with previous Ranibizumab injections may demonstrate tachyphylaxis or diminished therapeutic response [12,13]

Hence it is logical to switch from anti VEGF agents. Intravitreal Dexamethasone has the advantage of reducing inflammation and also decreases frequency of intravitreal administration.

Lim et al. reported visual and anatomical improvements after switching to aflibercept who had refractory DME to bevacizumab and ranibizumab injections[14]. Bahrami et al showed a improved response with aflibercept injections in patients refractory to previous Bevacizumab injections.[15]Wood et al demonstrated only anatomical improvements in a prospective study with aflibercept injections in poor response patients with ranibizumab injections. [16] Though it seemed that there was greater visual improvement after switching to aflibercept injections it was proven to be not statistically significant. Switching to intravitreal steroids like Dexamethasone implants is a logical option in case of failure to treatment of DME with other anti-VEGF injections.[17]

Both anti VEGF and steroid injections have different pharmacological properties and side effects. Steroids have anti-inflammatory, anti-permeability, and angiostatic effects in DME.[18]

In our study , there was significant improvement in BCVA and central macular thickness at the end of three and six months post intra-vitreal implantation with Dexamethasone. This finding is in line with the similar study.[19]

A transient initial rise in IOP though not statistically significant was observed as a side effect to dexamethasone implantation. This observation concurred with other studies reported earlier.[21]

The morphological improvement was more significant than BCVA, and this incongruity between morphological and functional improvements can be explained on the basis of irreversible damage of photoreceptors due to prolonged edema in the retinal layers, whereas the CMT is reduced due to clearing of edema from the retinal layers.[22]

Given the limitation of small sample size and retrospective design of the current study, the findings emphasize the beneficial role of Intravitreal Dexamethasone in refractory DME.

Conclusion

Intra-vitreal Dexamethasone implants showed significant morphological improvements in CMT in comparison to BVCA and functional achievements . In addition to the advantage of fewer injections, Intravitreal Dexamethasone implant has a definite beneficial effect in switching from regular anti-VEGF in refractory DME.

Source of Funding: Nil

Conflict of Interest: None

Ethical Clearance: Taken from the Institute ethics committee of VMMC & Safdarjung Hospital.

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