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Intravitreal Injection of Ozurdex as a Primary Mode of Treatment in Diabetic Macular Edema - One Year Follow Up

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1. Introduction

One of the leading causes of visual loss in diabetic patients with retinopathy is macular edema. Accumulation of fluid in the retinal layers causes disruption of blood retinal barrier in patients with diabetic macular edema (DME)[1]. Neurovascular damage in DME is due to various causes like high intracellular glucose levels, production of free radicals as a result of oxidative stress, activation of protein kinase C, Glycation end products seen in vitreous and vitreoretinal interface[2].

According to Early Treatment Diabetic Retinopathy Study the criteria for defining "Clinically significant macular edema" is as following:

- Thickening of the retina at or within 500microns of the center of the macula
- Hard exudates at or within 500microns of the center of the macula, if associated with thickening of adjacent retina.
- Retinal thickening at one disc area or larger at any part of which is within one disc diameter of the center of the macula.[3]

Role of sustained release of intravitreal ozurdex (0.7mg) implant is approved for the treatment of macular edema in various conditions like diabetic retinopathy, central or branch retinal vein occlusions and non-infectious uveitis.[4]

Role of steroids in DME is upcoming due to its anti-inflammatory and anti-edematous effects. It blocks the arachidonic acid pathway by inhibiting phospholipase A2. Thus it inhibits the synthesis of leukotrienes, prostaglandins and thromboxane's causing vasoconstriction and reduced capillary permeability. Thereby it reduces the synthesis of inflammatory mediators and VEGF, inhibits cell proliferation and stabilizes the BRB and lysozymes. Therefore it enhances the density and activity of tight junctions in the retinal capillary endothelium.

One of the major adverse effects of intravitreal steroid injections is raised Intra ocular pressure and cataract formation. Hence, its use is preferable in pseudophakic individuals who have recurrence of disease.[5]

The DEX implant contains micronized preservative free 0.7mg DEX in a biodegradable co-polymer of polylactic-co-glycolic acid. The advantage of this polymer is the release of active component within the vitreous cavity for about 6 months following IV injection. As a result, the frequency of injections is reduced and the complications of repeated injections like retinal detachment, endophthalmitis etc. is also significantly reduced.[6]

Various studies conducted regarding OZU DEX IV injection has confirmed a good safety profile with very less adverse effects like the progression of cataract is from 29.8% to 67.9%, an rise in IOP >10mmhg from baseline reported in a range of 15.4% and 27.7%.[7]

2. Materials and Methods

1) Aims

To evaluate the efficacy and safety of intravitreal dexamethasone implant Ozurdex in Diabetic macular edema.

2) Objectives

- To measure for best corrected visual acuity using ETDRS pre and post Ozurdex implant injection. (Primary outcome)
- To measure central macular thickness with SD- OCT pre and post Ozurdex implant injection (secondary outcome)
- Post- operative complications of Ozurdex injection like increased IOP, steroid induced cataract and infection.

3) Inclusion criteria

- Patients with diabetes mellitus.
- Central macular thickness (CMT) >250 μm as measured by spectral-domain optical coherence tomography (SD-OCT) at baseline examination.

4) Exclusion criteria

- Other associated retinopathies
- H/O trauma, glaucoma or IOP >21 mm Hg
- H/o hemorrhage disorder, active ocular infections, a recent history of myocardial infarction, uncontrolled hypertension or pregnant at the time of treatment.
- H/o usage of topical or systemic steroids in the past 3 months.
- Patients who have undergone ocular surgery (except cataract surgery) in the past, previous intravitreal injection

Intraoperative procedure of intravitreal dexamethasone implant

The implant was performed under sterile conditions, after preparation of the conjunctiva by using 5% povidone–iodine

solution, topical anaesthetic with paracain, and positioning of eye speculum. Sustained-release dexamethasone 0.7 mg intravitreal OZUDEX implant was injected into the vitreous cavity through the pars plana using a customized, single-use 22-gauge needle. Patients were treated with a topical antibiotic eye drops for 03 days after the injection.

Patients were asked to come for follow up for 12 months post injection.

Efficacy Assessment: By

1) Increase in mean BCVA using ETDRS SCORE and
2) Decrease in mean CMT using SD-OCT

Safety Assessment: By

1) Measuring IOP ,
2) Checking for lens opacity under slit lamp using LOCS II grading and looking for signs of infections during each follow up.

Re-treatment is considered when the CMT values worsen than the baseline values or CMT greater than 500 µm and drop in visual acquity, provided IOP is >21 mm Hg.

Re-injection criteria

1) Starting from the 4th month, in patients with recurrence/persistence of Macular edema as documented by slit lamp bio microscopyand spectral-domain OCT by measuring central macular thickness, thetreating surgeons were free to decide about the readminstration of injection.

3. Results

Patient selection

This was a prospective study of consecutive patients affected by Diabetes mellitus and DME.

The study included 10 patients (18 eyes), 06 males and 04 females. The mean age was 65.30, and the duration of DME in months is 60 and 240 in right eye 56 and 240 in left eye.

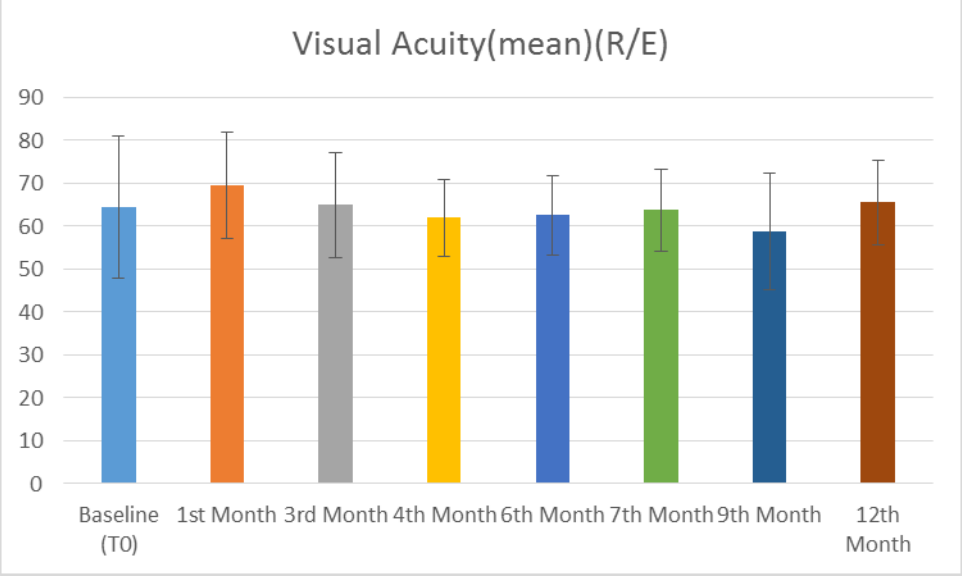
Descriptive Statistics	N	Minimum	Maximum	Mean	Std. Deviation
Age	10	60	72	65.3	5.143
Duration of DME R/E	10	60	240	92.7	83.803
Duration of DME L/E	10	56	240	105.5	71.48

Baseline values of clinical measurements

Medical histories of 10 patients were reviewed and baseline characteristics were recorded. The duration of study period is 1 year only in all cases. Before injection of the intravitreal dexamethasone implant, all the 18 eyes included in the study had a significant edema of the retina. The average thickness of the retina at baseline was 518.3, the mean BCVA was 65, and mean corrected intraocular pressure was 15.2mmHg. No intravitreal treatments other than DEX implants were administered to any eye during the study. All patients are seen at 1, 3, 4,5,7,9 and 12 months of follow-up

Visual acuity measured with Early Treatment Diabetic Retinopathy Scale after intravitreal dexamethasone implant

The BVCA was measured using the Early Treatment Diabetic Retinopathy Scale (ETDRS) score. Baseline Visual acuity and 4th month visual acuity data were statistically significant p =0.040.There is an slight decrease in visual acquity at the end of 12 th month in left eye due to patients Ischemic macular parameters



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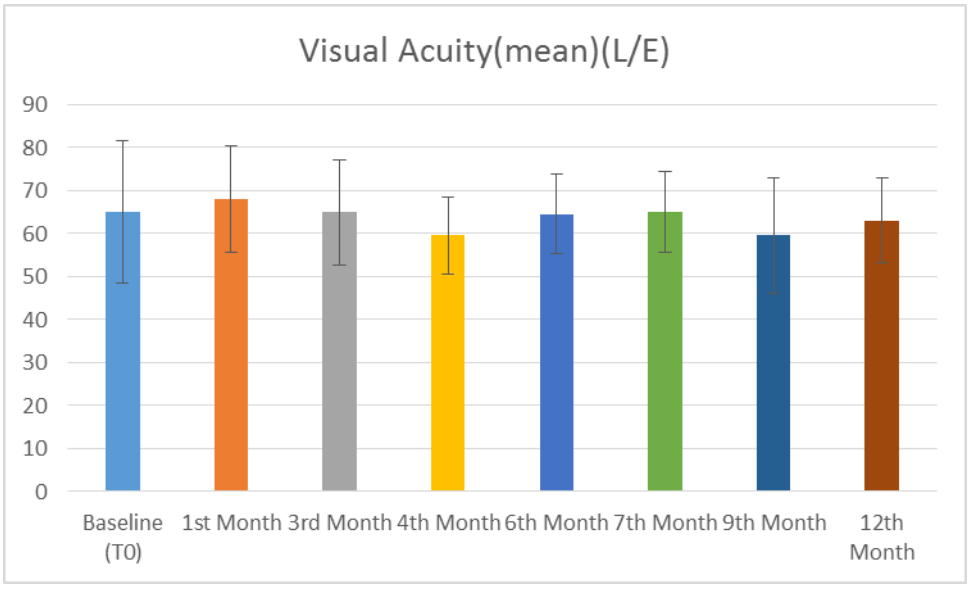
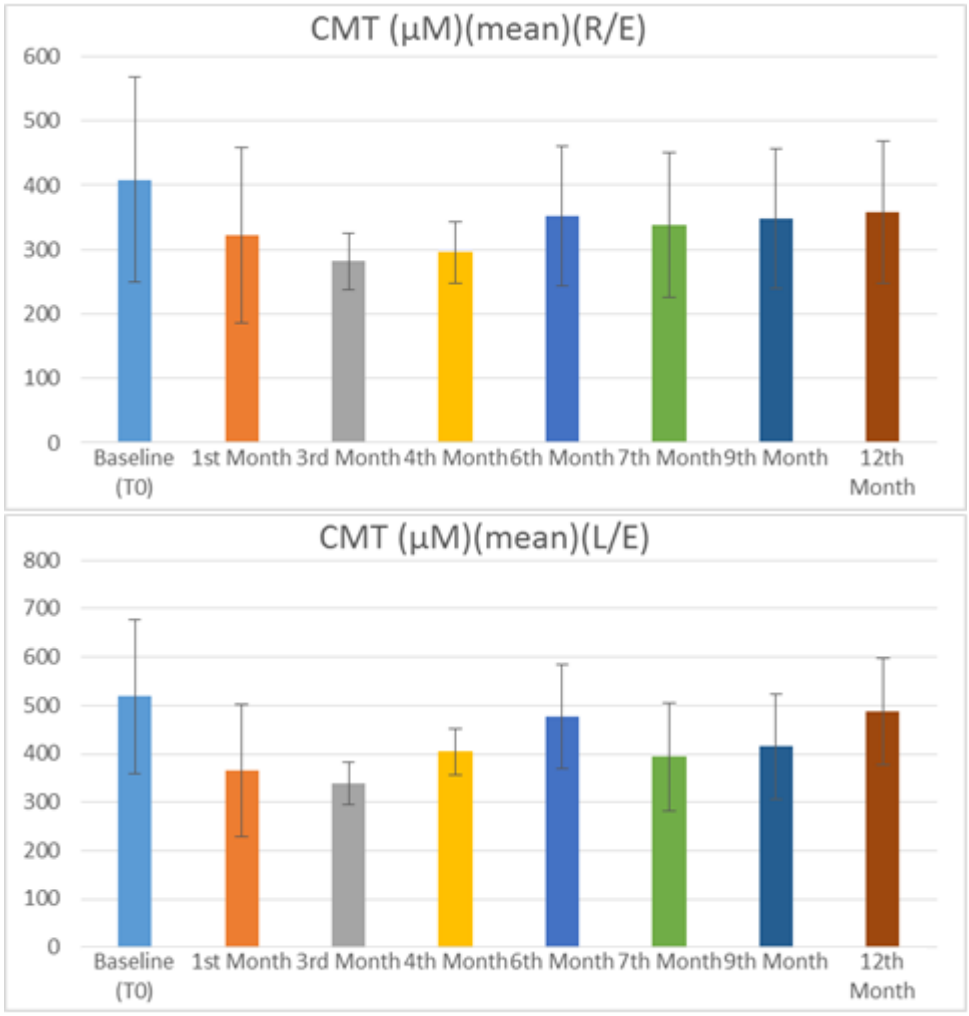


CMT after intravitreal dexamethasone implant

* Baseline CMT and 1st month CMT values were statistically significant p=0.016, Baseline CMT and 3rd month CMT values were statistically significant p = 0.007, Baseline CMT values and 4th month CMT values are statistically significant p =0.010, Baseline CMT values and 7th month CMT values were statistically significant p = 0.034 and similarly baseline CMT values and 9th month CMT values were also statistically significant p = 0.019.



Efficacy

The efficacy of the treatment, as demonstrated by CMT and ETDRS values reported an effective rate of 100%.

Right Eye

Time Points	Visual Acuity (mean)	SD	CMT (µM) (mean)	SD
Baseline (T0)	64.38	16.57	408.5	159.35
1st Month	69.38	12.4	321.75	136.44
3rd Month	65	12.24	281.38	43.7
4th Month	61.88	8.83	295.25	48.2
6th Month	62.5	9.25	351.88	108.23
7th Month	63.75	9.54	338.25	111.83
9th Month	58.75	13.56	348	108.37
12th Month	65.53	9.79	357.38	110.6

Left Eye

Time Points	Visual Acuity (mean)	SD	CMT (µM) (mean)	SD
Baseline (T0)	65	12.47	518.3	296.21
1st Month	68	10.05	365.3	189.6
3rd Month	65	11.05	339	158.3
4th Month	59.5	11.41	404.6	215.5
6th Month	64.5	10.65	477.2	313.43
7th Month	65	6.67	394.3	205.4
9th Month	59.5	13.63	415.3	231.16
12th Month	63	18.88	487.7	308.0

Safety of intravitreal dexamethasone implant

The side effects correlated with intravitreal dexamethasone implant were monitored during the follow-up. Two patients were noted with an increase in intraocular pressure requiring medical treatment.

Retreatment

3 patients underwent a second injection at the end of the SIXTH month. In these patients, the HbA1c value was over 8%.

4. Discussion

This study was conducted to evaluate the efficacy of intravitreal dexamethasone implant (Ozurdex), as a primary modality of treatment in patients affected by DME. We evaluated the visual acuity and CMT during one year of follow-up period. On analysis of the results, during the follow up visits at 1, 3and 4 months after treatment there was a significant improvement in CMT and BCVAwhen compared to baselinevalues which is found to be statistically significant, suggesting that anatomical improvement preceded functional improvement in these cases. This result seems to be consistent with the findings of the Diabetic retinopathy clinical research network (DRCR) (8)

During the course of treatmentthere was an improvement in CMT and BCVA parameters with respect to baseline values, but CMT values and BCVA values at the end of 12 months are not statistically significant. The mean baseline CMT value and 3rd month CMT value was found to be 408.05and 281.38 in right eye and 518.03 and 339 in left eye. Hence, our results indicate that greatest effectiveness of DEX implant was found during the first 3 months following the first injection and then gradually decreasedquiet similar to another study onPreliminary results of an Intravitreal dexamethasone implant (Ozurdex) in patients with persistent diabetic macular edema, Where it showed baseline CMT value as 518.80 and 3rd month value as 346.95 (9). In our study at the end of the 6th month and 1 year slight increase in mean CMT values was noted as 351.88 and 357.38 in right eye and 404.06 and 487.7 in left eye. This can be explained by the decreased concentration of DEX in vitreous over time similar to study on pharmacokinetics and pharmacodynamics of sustained release intravitreal dexamethasone implant (10). The beneficial effects of DEX injection was seen within the first week as described by most of the studiesand this effect was found to be because of a strong anti-inflammatory and anti-edema property of the dexamethasone. Moreover, administration of steroids reduced the VEGF expression, attenuate leukostasis, vascular leakage and reduced the production of proinflammatory cytokines. (11, 12)

Scaramuzzi M1, Et al conducted a trial on 15 eyes **Repeated intravitreal dexamethasone implant (Ozurdex) for diabetic macular edema**. It concluded that Repeated intravitreal Ozurdex on an- “as needed” basis with a variable retreatment interval may produce long-term clinically meaningful benefits in the treatment of diabetic macular edema (13). At present, there is no specific protocol for use of DEX implants in DME patients, the effect of loading dose nor does the optimal interval between the doses still remain unknown.Most patients in**t**his study received only one injection. The mean number of injections per patient (1.44 in one year) was lower than that used in the BEVORDEX study (2.7 injections per year) (14) but similar to that used in a study by Callanan *et a (*15) and in the MOZART study (16) (mean rate of injections was 1.2 at 6 months with an average of 5. 4 months for re injection). The role of re-injection following first dose at the end of 4th month, may have helped to maintain the response, as there was a significant decrease in the beneficial effect of DEX implant at 3 months of initial therapy.The large number of patientstogether with the fact that thevision had not dropped to the baseline value despite ON-treatment, could give information about the importance of drug on inflammation in chronic DME and the durability of the effect of drug is to be a- the benefit of sustained release drug design**.**

In our study, we found that only three patients required a second injection at the end of six months since ETDRS and CMT values worsened than the baseline values. All these three patients had uncontrolled diabetes mellitus where the HbA1c values were above 8%. Hence, it can be concluded from the above results that inadequate monitoring and control of glycaemic levels, have led to the worsening of DME and needed for reinjection. Thus, retreatment in these patients is not only due to reduced concentration of the drug in vitreous, but also due to poor metabolic control.

MD David S. Boyer, et al from the MEAD study group conducted a Three-Year, Randomized, and Sham-Controlled Trial of **Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema**. (17). The study showed that DEX implant 0.7 mg and 0.35 mg met the primary efficacy endpoint for improvement in BCVA in patients with DME with ≥15 ETDRS letters from baseline at the end of

the study. In our study we found DEX implant of 0.7 mg showed an improvement in BCVA of >_10ETDRS lettersfrom baseline at the end of 3 months. Less than 5% of the whole sample showed BCVA worsening of at least 5ETDRS letters at the end of 3rd month.This proportion increased to 15% for the whole sample at subsequent visits.At the end of follow up, it was found that BCVA was the sole factor which showed persistent improvement in the first 3 months and as the drug effectiveness weans off, there is an decrease in visual acquityof ≥ 5 ETDRS letters noted at the end of 1 year of follow up when compared to baseline values and it might have been because of the differences in individual response and also due to natural course of the disease..

In recent days, compared to other treatment modalities, dexamethasone showed a significant structural improvement in the retina in individuals with DME (18, 19, and 20). In addition to this, the safety profile and compliance of dexamethasone is better compared to other therapeutic techniques as the risk of complications with repeated injections was avoided. The complications related to the implant or the drug itself was very minimal in accordance with other reports.(21,22,23) At the follow up period, only 2 eyes had a raised IOP which required medical treatment.

Limitation of our study, firstly there was no control group. Second, the total no. of eyes included in the study was relatively low with a short follow up period hence it is difficult to come to a conclusion. In order to study the therapeutic efficacy and pharmacokinetics of dexamethasone a greater cohort of subjects with longer follow up is required.

5. Conclusion

Our study demonstrates the efficacy and safety profile of the intravitreal dexamethasone implant with one year time frame. Our findings also suggest that patients with dexamethasone implant showed maximum efficacy at 3 months which then declined progressively, but is still better than baseline values at the end of follow-up, although individual response and metabolic state of the patient should be strictly monitored. In CONCLUSION, DEX implants in DME patients resulted in improved anatomical and functional parameters especially evident at early stages of treatment.Retreatment was used sparingly only when BCVA or CMT showed signs of reverting back to baseline values. In our study DEX implant doesn't show any clinically significant side effects which supports its use in most types of DME, as a primary mode of treatment.

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