Original Article

Long-term results of a single injection of intravitreal dexamethasone as initial therapy in diabetic macular edema

Santosh Kumar Mahapatra, Swati Kumari[1]

Purpose: To evaluate the long-term safety and efficacy of the intravitreal dexamethasone implant in the treatment of diabetic macular edema (DME) as initial therapy. **Methods:** A hospital-based prospective, non-comparative case study of recently detected DME patients was conducted between July 2016 and December 2017, in which30 eyes of 30 patients were studied. Presenting vision, age, gender, duration of diabetes, general and ocular examination, intraocular pressure, indirect ophthalmoscopy, fundus fluorescein angiography, optical coherence tomography (OCT), and blood sugar levels were noted. Patients with increased central macular thickness (CMT) received an intravitreal dexamethasone implant as initial therapy. All were followed up at 1 week, 1 month, 3 months, 6 months, and 1 year, and the findings were recorded and analyzed using SPSS software. **Results:** 30 eyes of 30 patients were studied which included 22 males and 8 females. The mean age of presentation was 58.7 ± 4.45 years. The mean decrease in CMT following intravitreal dexamethasone was 269.27 ± 112.002, 253.5 ± 108.294, and 286.73 ± 143.395 µm at the end of 3, 6, and 12 months, respectively, and the mean improvement in visual acuity (VA) was 2.27 ± 1.70 lines at 3 months, 2.27 ± 1.83 lines at 6 months, and 1.17 ± 2.00 lines at 12 months. Out of 30 cases, 4 had persistent DME and 6 had recurrence of DME at completion of 1 year of follow-up. **Conclusion:** Intravitreal dexamethasone as initial therapy in the treatment of DME is both safe and efficacious in the reduction of CMT and improvement of vision and can be considered as primary therapy for DME.

Key words: Central macular thickness, diabetic macular edema, diabetic retinopathy, intravitreal dexamethasone

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_620_19

Quick Response Code:

Diabetic retinopathy is a leading cause of vision loss in working-age adults and diabetic macular edema (DME) is the most common cause of vision loss in diabetes.[1] Within the last 5 years, the use of intravitreal anti-vascular endothelial growth factor (VEGF) agents have come into common clinical practice for the management of DME.[2-4] But, the treatment of DME remains difficult even with the availability of these new modalities of treatment, this is where comes the role of depot intravitreal steroids such as dexamethasone implant. Its effect is 6 times stronger than intravitreal triamcinolone acetonide[5] and 30 times more than cortisol.[6] Dexamethasone differs from triamcinolone acetate in pharmacologic activity and lipid solubility, as well as delivery requirements.[7] In previous studies, the dexamethasone implant has demonstrated efficacy in the treatment of persistent DME,[8,9] DME resistant to anti-VEGF treatment,[10] and DME in difficult-to-treat vitrectomized eyes.[11]

Though many studies are done on the use of intravitreal dexamethasone in recalcitrant or persistent DME, no study of intravitreal dexamethasone as initial therapy in patients with DME has been published in literature. Therefore, this study was designed to evaluate long-term results of a single intravitreal dexamethasone implant as initial therapy in patients with DME.

Methods

The institutional ethical committee's approval and informed consent were taken from all study subjects in accordance with the guidelines of Declaration of Helsinki.

The study included all the untreated patients with DME presented to a tertiary care eye hospital in eastern India between July 2016 and December 2017, which involves 30 eyes of 30 cases between the ages of 50 and 65 years.

Data were collected on a standardized form, which included age, sex, address, duration of diabetes, presenting vision, ophthalmic examination, investigations, number of follow-ups, squeal, complications, and final visual outcome. A detailed history was taken, and all subjects underwent comprehensive ophthalmologic examination. Best corrected visual acuity (VA) of each eye was recorded and categorized into severe visual impairment (20/200 ≥VA ≥20/400), moderate visual impairment (20/60 ≥VA ≥20/200), and mild or no

Chief Medical Officer and Vitreoretinal Surgeon, [1]Ophthalmology Resident, JPM Rotary Club of Cuttack Eye Hospital and Research Institute, Cuttack, Odisha, India

Correspondence to: Dr. Santosh Kumar Mahapatra, Chief Medical Officer and Vitreoretinal Surgeon, JPM Rotary Club of Cuttack Eye Hospital and Research Institute, CDA, Cuttack - 753 014, Odisha, India. E-mail: santu_k74@rediffmail.com

Received: 21-Apr-2019 Revision: 28-Aug-2019
Accepted: 16-Sep-2019 Published: 14-Feb-2020

Cite this article as: Mahapatra SK, Kumari S. Long-term results of a single injection of intravitreal dexamethasone as initial therapy in diabetic macular edema. Indian J Ophthalmol 2020;68:490-3.

visual impairment (VA > 20/60). Extraocular movements and pupillary reactions were checked using torchlight. Complete external examination was done by slit lamp biomicroscopy, intraocular pressure (IOP) was measured by using rebound tonometer (I-care). Fundus was evaluated using 90 D Volk lens and by indirect ophthalmoscopy with 20 D lens. The eye with DME was selected and was taken for fundus fluorescein angiography and optical coherence tomography (OCT). Glycosylated hemoglobin (HbA1c), fasting blood sugar, postprandial blood sugar, complete blood count, lipid profile and renal profile were done for every patient. Depending on the HbA1c, the blood sugar control was divided into good control (≤7%), fair control (7.1–8.9%), and poor control (≥9%).

All the primary cases of DME with no prior treatment were included in the study. Patients who have received prior intravitreal anti-VEGF or laser treatment, steroid responders, patients with any ocular infection, diagnosed case of glaucoma or ocular hypertension, patients with uncontrolled blood sugar and patients with diabetic nephropathy were excluded. Steroid responders are defined as any patient who had a rise of IOP more than 10 mm Hg from baseline after use of prednisolone acetate 1% eye drops 3 times daily for 2 weeks.

Under aseptic conditions, patients underwent intravitreal dexamethasone implant (0.7 mg) in the operating room under topical anesthesia using the 22 G sutureless applicator device. Topical antibiotics were given for a week following the injection. All patients were monitored for local or systemic adverse effects related to the implant for the duration of the study. Demographic data of the pooled patients, duration of DME, and previous treatments were recorded. Patients treated with intravitreal dexamethasone implant were called for follow-up visits at 1 week, 1 month, 3 months, 6 months, and 1 year, when best-corrected VA, IOP, slit-lamp examination, indirect ophthalmoscopy, and OCT were done.

All data were analyzed using SPSS software version 24.42 (IBM SPSS Statistics 24.42, www.spss.co.in) for Windows OS. Statistical analysis was done and the significance of correlation for each parameter was calculated using Chi-squared test and descriptive statistics. Percentages and frequencies were calculated for demographic variables as well as clinical parameters. Tables and graphs are used to present the results.

Results

Out of 30 cases, 22 (73.3%) were males and 8 (6.7%) were females. Majority of them were in 60–65 years age group with a share of 63.3%. The age group of 50–54 years and 55–59 years had 7 and 4 cases, respectively. The age distribution across males and females do not differ significantly ($P = 0.674$).

In this study, 2 patients presented to us with good VA, 4 cases with mild visual impairment, 14 cases with moderate visual impairment, and 10 cases with severe visual impairment. Following intravitreal dexamethasone implant, at 1-week follow-up the number of cases with severe and moderate impairment of VA decreased from 10 to 6 and 14 to 8 cases, respectively. At 1 month follow-up, severe visual impairment reduced to 4 and moderate cases were reduced to 4. Thereafter at 3 months, 6 months, and 1 year, there was no improvement in the proportion of severe and moderate visual impairment. Marginal homogeneity test recorded some significant improvement, that is, the proportion of severe and moderate impairment of VA between first visit and 1-week follow-up ($P = 0.001$), 1-week and 1-month follow-up ($P = 0.005$). Thereafter, there was no further improvement between 1 and 3 months ($P = 0.317$), 3 and 6 months ($P = 0.317$), 6 months and 1 year ($P = 0.059$). The VA at 1 year shows significant improvement ($P = 0.059$).

The mean lines of improvement was 1.27 ± 1.14 lines on the 1st week following intravitreal dexamethasone implant and this improved to 2.07 ± 1.65 at 1-month and 2.27 ± 1.70 at 3-months, 2.27 ± 1.83 at 6 months, and 1.17 ± 2.00 at 1-year follow-ups. The trend shows that there is a consistent and significant improvement between 1 week and 1 month ($P = 0.000$), 1 month and 3 months ($P = 0.031$) and after that it is maintained at 6-months follow-up and at 1 year except in 6 cases [Fig. 1].

The mean CMT at presentation was 437.00 ± 120.66 μ which decreased to 269.27 ± 112.00 μ at 3 months and further decreased to 253.50 ± 108.29 μ at 6 months. One of the representative cases is shown in Fig. 2. However, at 1-year follow-up, the mean CMT was increased to 286.73 ± 143.40 μ [Fig. 3].

The mean IOP at presentation was 16.53 ± 1.72 mm Hg. At 1 week the mean IOP increased to 18.73 ± 1.72 mm Hg and further increased to 20.17 ± 3.86 mm Hg at 1 month, and thereafter at 3 months and 6 months maintained the same level and decreased to 18.93 ± 3.15 mm Hg at 1 year [Fig. 4].

When blood sugar control was good and fair, the improvement was not significantly different but when blood sugar control was poor there was significant decrease in improvement ($P < 0.005$) at all follow-ups [Fig. 5].

At each follow-up, the mean CMT was lowest for good blood sugar level, bit higher for the cases with borderline blood sugar level, and highest for poor blood sugar control. It was found that 6 cases had recurrence of DME and 4 cases did have persistent DME.

In this study, we followed up 18 phakic patients for lens changes and found that none of the patients was showing any development or progression of cataract. No other adverse effects or significant complication such as endophthalmitis was seen in the study.

Discussion

This study was performed to investigate the safety and efficacy of a single intravitreal dexamethasone implant over time in patients with untreated DME. The results showed that intravitreal dexamethasone implant is a safe and efficacious

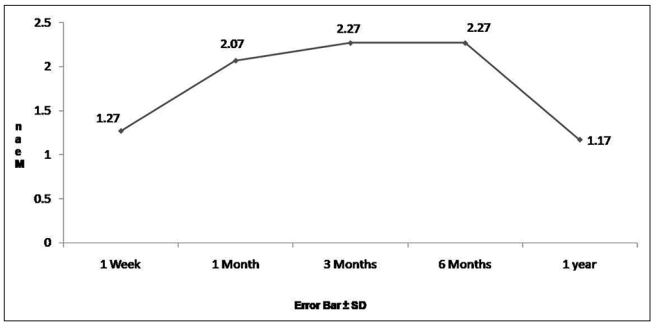

Figure 1: Average line of improvement over different follow-ups

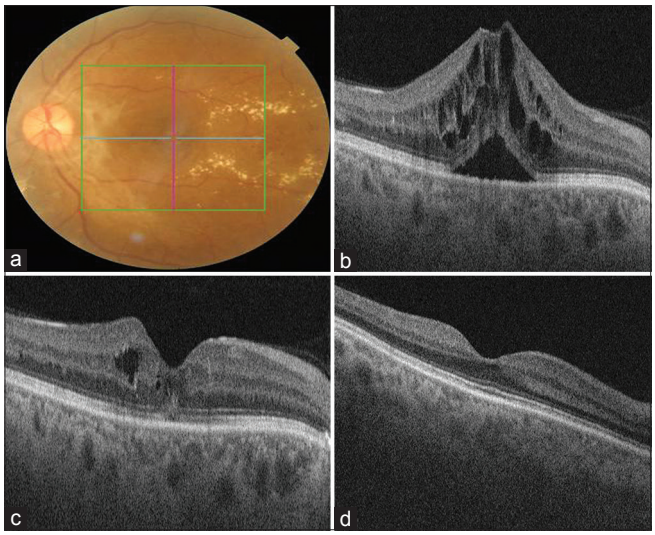

Figure 2: Fundus photograph (a), pre-injection (b), post-injection at 12 weeks (c) and post-injection at 24 weeks (d) OCT image of one representative case

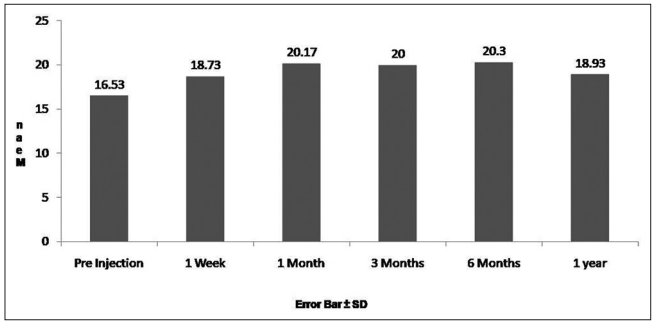

Figure 4: Average change in IOP at different follow-ups

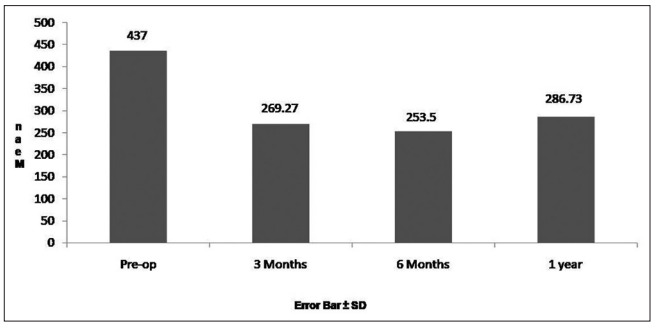

Figure 3: CMT on OCT over different follow-ups

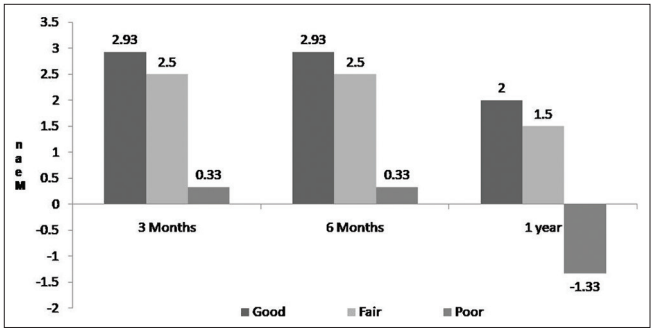

Figure 5: Visual acuity by diabetic control

treatment and can be used as initial therapy for DME as it showed significant improvement within 3 months and was maintained till the end of the study without any significant complications. We compared the findings of our study with the related articles to find out the similarities and differences with other studies and to derive conclusions from our results.

The mean age of presentation was 58.70 years, mean duration of diabetes was 10.40 ± 4.30 years, and mean HbA1c was 7.97 ± 1.39% in this study. VA at 5 subsequent follow-ups at 1 week, 1 month, 3 months, 6 months, and 1 year showed substantial improvements. Improvement in vision was noted after 1 week of placing the intravitreal implant but this improvement was highly significant between 1 week and 1 month (P = 0.000) and between 1 and 3 months (P = 0.031). Maximum improvement in vision was seen in the third month. This finding is consistent with Pacella *et al*.[9] and Kupperman *et al*.[12] Between 3 and 6 months the vision of the patient was stable without any significant change (P = 1.000). At the end of the study, 6 (20%) cases showed decrease in VA after initial improvement and 4 (13.3%) cases never showed improvement indicating treatment failure.

Patients with OCT were followed up at 3 months, 6 months, and 1 year to know the anatomical improvement in terms of CMT. Significant improvement was found in OCT done at 3 months (P = 0.000) and further improvement was seen in OCT done at 6 months (P = 0.142). Out of 30 cases, 6 (20%) cases showed decrease in CMT till 6 months but did not maintain it at 1 year and 4 (13.3%) cases did not show any improvement throughout the study period. Hence, the maximum effects of the dexamethasone implant were seen between 3 and 6 months after which there was a minute increase in CMT in 6 cases which never reached the baseline. This finding is in line with previous studies by Rishi *et al*.[13] Pacella *et al*.[9] Querques *et al*.,[14] and Zalewski *et al*.[15] showing that the improvement of all parameters already starts from day 3 of the intravitreal implant and decreases over time. This gradual decrease of the efficacy may be due to reduced concentrations of dexamethasone in the vitreous.

In patients with good glycemic control, the mean improvement was 2.93 ± 1.43 lines and in patients with poor blood sugar control the mean improvement was 0.33 ± 1.37 lines, which is a significant difference (P = 0.003). Patients with good systemic control of blood sugar had significant decrease in CMT at every follow-up and maintained it till the end of the study, whereas patients with poor control of blood sugar never improved as seen in 6 cases (13.3%) and this difference in CMT was highly significant (P < 0.05). Previous studies have suggested that intravitreal corticosteroid treatment may be more effective in pseudophakic eyes than in phakic eyes.[16,17] We divided the patients into two subgroups: pseudophakic and phakic and found no conclusive difference between the subgroups. All showed a similar positive response to dexamethasone implant with a pattern that is comparable to that found in other similar studies.[11,18,19] We did not encounter any significant complications such as subconjunctival hemorrhage, superficial punctate keratopathy, increased IOP, infection (involving anterior segment/posterior segment or both), cataract, vitreous hemorrhage, or retinal detachment in this study.

The IOP was measured at every follow-up starting at 1 week, 1 month, 3 months, 6 months, and 1 year following intravitreal dexamethasone implant. Out of 30 cases, 21 had transient elevation of IOP which did not require anti-glaucoma medication cases and it came back to baseline IOP after 6 months. Development or progression of cataract was not seen in any of the cases at the end of the study. This finding varies with Pacella *et al*.,[20] in which grade 1 nuclear sclerosis and cortical cataract were found in all the phakic patients treated with intravitreal dexamethasone implant. No other complications such as subconjunctival hemorrhage, endophthalmitis, vitreous hemorrhage, or serious systemic or ocular treatment-related adverse events occurred in any patient as found in other studies. Single injection of dexamethasone implant was preferred because of its longer duration of action, negating significant inconvenience to the patient in the form of repeated intraoperative room procedures, 7 days of topical use of antibiotics and repeated hospital visits. A total of 6 cases (20%) showed recurrence of DME at the end of the study with initial improvement in the ones who did not have good systemic control of blood sugar. A similar observation was also noted in Pacella *et al*.[9]

Two patients with good VA were also administered intravitreal dexamethasone as there was a center involving macular edema. On follow-up, their vision remained stable with resolution of macular edema. There was no significant rise in IOP, cataract development, or any other complications.

Conclusion

There are various treatment options available for the treatment of DME and intravitreal dexamethasone is one among them, but there is no data available regarding the use of this as initial therapy. This study demonstrates that intravitreal dexamethasone implant is a good option for DME as initial therapy in terms of improvement in VA and decrease in CMT with maximum efficacy between 3 and 6 months which can be maintained thereafter without any significant complications with best possible results obtainable and good glycemic control.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Moss SE, Klein R, Klein BE. The 14-year incidence of visual loss in a diabetic population. Ophthalmology 1998;105:998-1003.
2. Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB. Diabetic retinopathy clinical research network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010;117:1064-77.
3. Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, *et al*. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2011;118:609-14.
4. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, *et al*. The RESTORE study: Ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology 2011;118:615-25.
5. Martidis A, Duker JS, Greenberg PB. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002;109:920-7.
6. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, *et al*. Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology 2014;121:1904-14.
7. Edelman JL. Differentiating intraocular glucocorticoids. Ophthalmologica 2010;224(Suppl):25-30.
8. Haller JA, Kuppermann BD, Blumenkranz MS, Williams GA, Weinberg DV, Chou C, *et al*. Dexamethasone DDS Phase II Study Group. Randomized controlled trial of an intravitreous dexamethasone drug delivery system in patients with diabetic macular edema. Arch Ophthalmol 2010;128:289-96.
9. Pacella E, Vestri AR, Muscella R. Preliminary results of an intravitreal dexamethasone implant (Ozurdex) in patients with persistent diabetic macular edema. Clin Ophthalmol 2013;7:1423-8.
10. Lazic R, Lukic M, Boras I. Treatment of anti-vascular endothelial growth factor-resistant diabetic macular edema with dexamethasone intravitreal implant. Retina 2014;34:719-24.
11. Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li XY, *et al*. Ozurdex CHAMPLAIN Study Group. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina 2011;31:915-23.
12. Kuppermann BD, Blumenkranz MS, Haller JA, Williams GA, Weinberg DV, Chou C, *et al*. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. Arch Ophthalmol 2007;125:309-17.
13. Rishi P, Rishi E, Kuniyal L, Mathur G. Short-term results of intravitreal dexamethasone implant in the treatment of recalcitrant diabetic macular edema: A case series. Oman J Ophthalmol 2012;5:79-82.
14. Querques G, Lattanzio R, Querques L, Triolo G, Cascavilla ML, Cavallero E, *et al*. Impact of intravitreal dexamethasone implant on macular morphology and function. Retina 2014;34:330-41.
15. Zalewski D, Raczyska D, Raczyska K. Five-month observation of persistent diabetic macular edema after intravitreal injection of Ozurdex implant. Mediators Inflamm 2014;2014:364143.
16. Diabetic Retinopathy Clinical Research Network, Elman MJ, Qin H, Aiello LP, Beck RW, Bressler NM, *et al*. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: Three-year randomized trial results. Ophthalmology 2012;119:2312-8.
17. Blumenkranz MS, Haller JA, Kuppermann BD, Williams GA, Davis M. Correlation of visual acuity and macular thickness measured by optical coherence tomography in patients with persistent macular edema. Retina 2010;30:1090-4.
18. Lazic R, Lukic M, Boras I, Draca N, Vlasic M, Gabric N, *et al*. Treatment of anti-vascular endothelial growth factor-resistant diabetic macular edema with dexamethasone intravitreal implant. Retina 2014;34:719-24.
19. Haller JA, Dugel P, Weinberg DV, Chou C, Whitcup SM. Evaluation of the safety and performance of an applicator for a novel intravitreal dexamethasone drug delivery system for the treatment of macular edema. Retina 2009;29:46-51.
20. Pacella F, Ferraresi AF, Turchetti P, Lenzi T, Giustolisi R, Bottone A, *et al*. Intravitreal injection of Ozurdex implant in patient with persistent Diabetic Macular Edema. Ophthalmol Eye Dis 2016;8:11-6.