Original Article

Effect of sustained-release long-acting intravitreal dexamethasone implant in patients of non-proliferative diabetic retinopathy undergoing phacoemulsification: A randomized controlled trial

Parul Chawla Gupta, Jagat Ram, Praveen Kumar-M[1], Aniruddha Agarwal, Vishali Gupta, Ramandeep Singh, Reema Bansal, Deeksha Katoch, Mangat R Dogra, Amod Gupta

Purpose: Cataract and diabetes, both being a major health care problem, an intervention evaluated for the combination of the two attains paramount importance. The purpose of the study was to determine the role of intraoperative intravitreal dexamethasone implant in patients with diabetic retinopathy with/without macula edema undergoing phacoemulsification. **Methods:** The study was a two-arm, single-center, randomized, assessor-blinded trial of 151 patients with type-2 diabetes mellitus and cataract. It had two groups: dexamethasone group (DEX) versus standard of care (SOC) group, i.e. phacoemulsification and intraocular lens (IOL) implantation without injection of dexamethasone drug delivery system (DDS). The number of rescue interventions required, central macular thickness by optical coherence tomography (OCT), Early Treatment Diabetic Retinopathy Study (ETDRS) score, laser flare meter (LFM) values, intraocular pressure (IOP), and grade of diabetic retinopathy (DR) were recorded until three months follow up. Macular thickness and number of rescue medications between the treatment groups were the co-primary outcomes. **Results:** A statistically significant interaction was present between treatment and time on OCT score ($P < 0.001$). The requirement of rescue interventions in the dexamethasone DDS group [40.2% (33/82)] was lesser as compared to the SOC group [49.3% (34/69)] at the end of 12 weeks [odds ratio (OR), 0.70 (0.36–1.33)] follow up although not statistically significant ($P = 0.343$). A statistically significant interaction was present between treatment and time on LFM score ($P = 0.003$). No statistically significant interaction was present between the treatment and time on visual acuity score ($P = 0.08$) and IOP score ($P = 0.375$). **Conclusion:** Dexamethasone implant may have potential as a valuable therapy for patients undergoing cataract surgery with DR with/without macular edema with effects lasting for at least three months.

Key words: Cataract, dexamethasone intravitreal implant, diabetic macular edema, phacoemulsification

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There is a worldwide increase in the prevalence of diabetes, with an estimated burden of 366 million patients by the year 2030.[1] Diabetic retinopathy (DR) is a leading cause of blindness and occurs due to progressive damage to retinal blood vessels, ultimately leading to blindness in 2% and visual handicap in 10%.[2] Among the plethora of conditions responsible for vision loss within DR, diabetic macular edema (DME) tops the list.[3]

There is a well-established association of cataract surgery with the progression of the disease and increase in DME undergoing surgery.[4–6] A range of medications, including intravitreal corticosteroids,[7] ranibizumab,[8] bevacizumab,[9] and aflibercept,[10] have been explored as adjuncts to improve visual results in these patients. Corticosteroids have been tried due to their anti-inflammatory effects, especially in patients undergoing cataract surgery.[11–14]

Dexamethasone is a potent steroid, and the use of the dexamethasone drug delivery system (Dexamethasone DDS–Ozurdex®) has been approved by the US-FDA for the management of DME. We have previously published a pilot study in which subjects with DR undergoing cataract surgery were randomized to receive Ozurdex implant compared to standard phacoemulsification. The study gave encouraging results and showed the potential use of Ozurdex along with cataract surgery in one sitting.[15]

In this study, we aimed to prospectively determine the role of intraoperative Ozurdex in a large sample of patients with background DR with/without DME undergoing phacoemulsification and IOL (intraocular lens) implantation.

Methods

The study was a two-arm, single-center, randomized, parallel design, an add-on to the standard of care study of dexamethasone DDS in patients of DR undergoing cataract surgery. The allocation

Departments of Ophthalmology and [1]Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Correspondence to: Dr. Jagat Ram, Department of Ophthalmology, Director, Postgraduate Institute of Medical Education and Research, Chandigarh - 160012, India. E-mail: drjagatram@gmail.com

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ratio was 1.2:1 between the dexamethasone DDS group and standard of care (SOC) group. Institutional Review Board (IRB) approved the study protocol, and the conduct was according to the principles laid down for research involving human subjects in the Declaration of Helsinki. Written informed consent was obtained from the patients before enrolling on the study.

This study included 151 eyes of 151 patients with type-2 diabetes mellitus and background DR with visually significant cataract enrolled in the Lens and Retina clinic of our tertiary care referral institute. The trail is registered in Clinical Trials Registry–India (CTRI) with registration number CTRI/2019/05/019407.

Inclusion criteria

Patients of either gender (age 30 years or more) with type-2 diabetes mellitus and mild/moderate or severe non-proliferative DR (NPDR) with/without DME, along with the presence of cataract requiring surgery.

Exclusion criteria

The presence of any one of the following resulted in exclusion: the presence of proliferative DR; ocular hypertension or glaucoma; neovascular glaucoma, retinal vein occlusions, uveitis; previous administration of any intravitreal/periocular agents (either as systemic or local administration) over the past 3 months; use of prostaglandin analogues, adrenaline or nicotinic acid or drug which can exacerbate DME; intraocular surgery/pars plana vitrectomy/laser photocoagulation in the last 3 months; and patients with media haze.

A simple randomization technique based on a computer-generated random sequence was used for randomization.

The two arms of the study were:

Dexamethasone DDS group: received injection dexamethasone DDS 0.7 mg intraoperatively during phacoemulsification and IOL implantation.

Standard of Care group (SOC): received phacoemulsification and IOL implantation without injection of dexamethasone DDS.

All patients enrolled were subjected to routine detailed ocular examination that included the following parameters (preoperative data): best-corrected visual acuity (BCVA) using Early Treatment of Diabetic Retinopathy Score (ETDRS) chart; intraocular pressure (IOP) on Goldmann applanation tonometry (GAT); anterior chamber flare evaluation (performed one day before cataract surgery); fundus photography (FP) and fundus fluorescein angiography (FFA). For all the outcome measurements, the graders were masked to the group allotment.

Intervention

Standard phacoemulsification and IOL implantation were undertaken in all patients (eyes) by an experienced surgeon (JR) under peribulbar anesthesia. Both groups of patients received a similar standard of care, including routine care for diabetes. If the investigator considered it necessary, the patients were administered rescue interventions for DME. Criteria for interventions included a 100-μm increase in central macular thickness or CMT >350 μm on OCT.

Follow-up

Patients belonging to both groups had a similar follow-up schedule. Each patient was evaluated at day 1, one week, two weeks, four weeks, and 12 weeks after cataract surgery. The patients were followed up for a duration of 3 months from the time of cataract surgery.

Outcome measures

The co-primary outcomes of change in CMT as assessed by OCT and proportion of rescue medications required in the entire study between the dexamethasone DDS group and SOC group were considered. The rescue intervention is defined as administration of focal/grid laser photocoagulation or anti-vascular endothelial growth factor (VEGF-ranibizumab or bevacizumab) or dexamethasone DDS following administration of trial medication during the study period.

The secondary outcomes of this study included the following: change in the visual acuity as measured by ETDRS and LogMAR visual acuity scale at repeated intervals in the entire study; change in the grade of the DR, i.e. either a step up or a step down in the staging of the retinopathy, and change in the postoperative inflammation as measured by laser flare meter (LFM); and the number of patients with ocular hypertension post dexamethasone injection in the dexamethasone DDS versus SOC group. In addition, the number of rescue interventions required per patient between the two groups was compared. The patients with CSME at baseline (either diffuse or focal), diffuse CSME (center involving CSME), and focal CSME (non-center involving CSME) were separately assessed for ETDRS and number of rescue interventions required between the DEX and SOC groups were noted.

Sample size

Sample size estimation was based on the comparison of repeated measures of OCT at five different time points, namely, baseline, week 1, 2, 4, and 12, between SOC and dexamethasone DDS by two-way mixed model ANOVA evaluating for time-treatment interaction. The sample size was calculated using GPower software.[16] Since the option of two-way mixed model ANOVA was not present in GPower, the two-way repeated-measures ANOVA for within-between interaction was used for the determination of sample size. The effect size was kept at 0.15. The correlation among the repeated measures and non-sphericity correction were kept at 0.01 and 1, respectively. The alpha and beta error probabilities were kept at 0.05 and 0.10, respectively. This calculated to the total sample size of 138. Keeping a dropout possibility of 10%, the final sample size was calculated to be 151 patients. Based on the allocation ratio of 1.2:1 between the dexamethasone DDS group and SOC, this would amount to 82 patients in dexamethasone DDS group and 69 patients in SOC group.

Statistical analysis

We did an intention-to-treat (ITT) analysis. The analysis was conducted using R, Version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

The subgroup analysis was performed under 5 categories: focal and diffuse DME patients together, no DME patients, diffuse DME alone, focal DME alone, and patients requiring no rescue medications. The additional analysis included correlation analysis and comparison of categorical outcomes between continuous outcomes, and all 3 factored across the treatment groups.

Results

A total of 151 age and sex-matched patients (n = 82 in the dexamethasone DDS group and n = 69 in the SOC group) were recruited into this study between February 2015 and August 2018. Of the 151 patients, 143 (94.7%) completed the study. 8 (5.3%) patients did not complete the last follow up [Fig. 1]. The mean age of patients in the dexamethasone DDS group was 60.6 ± 7.7 years, and in the SOC group was

61.7 ± 7.5 years (P = 0.372). The demographic and baseline characteristics were comparable [Table 1].

A statistically significant interaction was present between treatment and time on OCT score (P < 0.001, Fig. 2A). Univariate analysis on OCT score between the treatment at each time point revealed no statistical difference at baseline (dexamethasone DDS 367.9 ± 141.3 vs SOC 347.8 ± 113.7, P = 0.355) and week 1 (345.6 ± 130.3 vs 380.8 ± 146.6, P = 0.126), and statistically significant difference at week 2 (332.9 ± 112 vs 416.1 ± 185.5, P = 0.001), week 4 (324.1 ± 96.3 vs 445.8 ± 179.3, P < 0.001), and week 12 (352.2 ± 121.8 vs 395.3 ± 130.5, P = 0.044). The requirement of rescue interventions in the dexamethasone DDS group [40.2% (33/82)] was lesser as compared to the SOC group [49.3% (34/69)] at the end of 12 weeks [Odds Ratio OR, 0.70 (0.36–1.33)] follow up although not statistically significant (P = 0.343). The absolute risk reduction (ARR) and number needed to treat (NNT) for the requirement of rescue intervention were 0.09 and 11, respectively. No statistically significant interaction was present between the treatment and time on ETDRS score (P = 0.082, Fig. 2B). Similarly, no statistically significant interaction was present between the treatment and time on LogMAR score (P = 0.08, Fig. 2C) and IOP score (P = 0.375, Fig. 2D).

A statistically significant interaction was present between treatment and time on LFM score (P = 0.003, Fig. 2E). Univariate analysis on LFM score between the treatment at each time point revealed no statistical difference at baseline (dexamethasone DDS 10.2 ± 10.2 vs SOC 11.2 ± 14.3 P = 0.611) and week 12 (dexamethasone DDS 10.7 ± 22.4 vs SOC 10.4 ± 8.3 P = 0.923), and statistically significant difference at day 1 (23.9 ± 18.2 vs 45.4 ± 63.2, P = 0.004), week 1 (14.7 ± 11.8 vs 27.1 ± 29.4, P = 0.001), week 2 (12.5 ± 13.5 vs 23.6 ± 27.5, P = 0.002), and week 4 (10.3 ± 9.7 vs 15.5 ± 14.3, P = 0.009).

There were 21 patients who had no DME at baseline [dexamethasone DDS - 14 (66.7%) and SOC - 7 (33.3%)]. Out of this at the end of 3 months, 2 patients were changed to non-center involving and 0 patient was transformed to center involving DME in the dexamethasone DDS group, and none of the patients was transformed to center involving/non-center involving DME in SOC group (P = 0.533). Similarly, there were 39 patients who had mild non-proliferative diabetic retinopathy (NPDR) at baseline [17 (43.6%) in dexamethasone DDS and 22 (56.4%) in SOC]. Out of this at the end of 3 months, 1 (5.9%) patient was changed to moderate and 1 (5.9%) patient was transformed to severe NPDR in the dexamethasone DDS group, and 1 (4.6%) patient was transformed to moderate NPDR in SOC group (P = 0.722).

The number of rescue intervention required per patient in dexamethasone DDS group (Median 2; IQR: 2,3) was lesser as compared to the SOC group (Median 2; IQR: 2,4) at the end of 12 weeks follow up although not statistically significant (P = 0.067). Analyzing the rescue interventions individually, additional dexamethasone DDS was required in 4 (4.9%) in dexamethasone DDS group and in 16 (23.2%) in SOC group (P = 0.002); ranibizumab was required in 1 (1.2%) in dexamethasone DDS group and 3 (4.4%) in

Table 1: Baseline demographic characteristics in the Dexamethasone DDS and Standard of Care group

	Dexamethasone DDS (*n*=82)	Standard of Care (*n*=69)	*P*
Sex, *n* (%)			0.777
Males	45 (54.9)	40 (58)	
Females	37 (45.1)	29 (42)	
Eye, *n* (%)			0.544
Right	42 (51.2)	31 (44.9)	
Left	40 (48.8)	38 (55.1)	
Lens type, *n* (%)			0.32
Single piece	41 (50)	41 (59.4)	
Three piece	41 (50)	28 (40.6)	
Cataract type, *n* (%)			0.456
PSC	6 (7.3)	7 (10.1)	
NS	8 (9.8)	9 (13)	
CC	1 (1.2)	0 (0)	
PSC + NS	39 (47.6)	31 (44.9)	
NS + CC	11 (13.4)	5 (7.2)	
PSC + NS + CC	6 (7.3)	2 (2.9)	
PSC + CC	11 (13.4)	15 (21.7)	
Hypertension, *n* (%)	30 (36.6)	39 (56.5)	0.022
Nephropathy, *n* (%)	5 (6.1)	3 (4.3)	0.728
Neuropathy, *n* (%)	2 (2.4)	2 (2.9)	1
CAD, *n* (%)	8 (9.8)	11 (15.9)	0.371
Insulin, *n* (%)	28 (34.1)	26 (37.7)	0.777
Oral anti-diabetic drug, *n* (%)	81 (98.8)	67 (97.1)	0.593
Fasting blood sugar (in mg/dl), Median and IQR	102 (89, 122)	107.5 (94.5, 120.8)	0.256
HBA1C, Median and IQR	7.6 (7.2, 8.4)	7.8 (7.2, 8.5)	0.63
Duration of diabetes (in yrs.), Median and IQR	12 (10, 20)	12 (9, 15)	0.811

PSC-posterior subcapsular, NS-Nuclear sclerosis, CC-Cortical cataract, CAD-Coronary artery disease

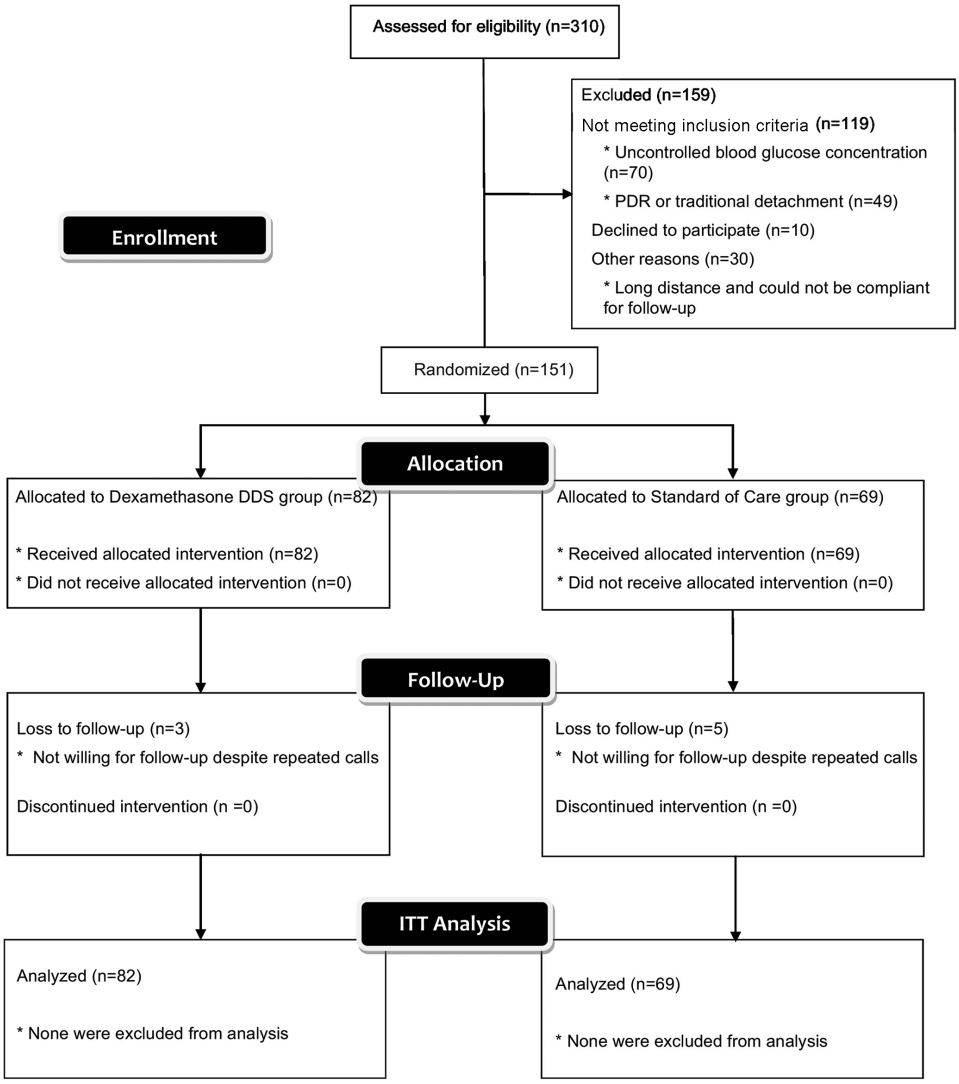

Figure 1: CONSORT diagram demonstrating the flow of study patients across the trial period

SOC group (P = 0.332); bevacizumab was required in 20 (24.4%) in dexamethasone DDS group and 20 (29%) in SOC group (P = 0.651); focal/grid laser photocoagulation was required in 17 (20.7%) in dexamethasone DDS group and 18 (26.1%) in SOC group (P = 0.56). The subgroup analyses were conducted as planned, and the results of subgroup analysis can be found in Table 2.

Additional analysis

A scatter plot representing the trend between ETDRS score vs OCT and LFM vs OCT at different time points for dexamethasone DDS and SOC group is represented in Fig. 3A and 3B, respectively. The trendline was similar between the two groups for ETDRS score vs OCT. The trendline of LFM vs OCT diverged between dexamethasone DDS and SOC group at week one and week 4, with greater divergence at week 1. The ρ between ETDRS score and OCT for dexamethasone DDS was − 0.07, −0.38, −0.42, −0.40, and − 0.43 at baseline, week 1, 2, 4, and 12, respectively; SOC was − 0.32, −0.41, −0.50, −0.62, and − 0.51 at baseline, week 1, 2, 4, and 12, respectively. The ρ between LFM and OCT for dexamethasone DDS was 0.11, 0.11, −0.01, −0.04, and 0.20 at baseline, week 1, 2, 4, and 12, respectively; SOC was 0.04, 0.28, 0.20, 0.42, and 0.30 at baseline, week 1, 2, 4, and 12, respectively.

Percentage of patients in different categories of visual acuity [Fig. 4A], anterior segment evaluation for the cells (0, 0.5, 1, 2, 3, 4 cells; Fig. 4B), posterior segment evaluation (mild, moderate, and severe NPDR; Fig. 4C), and CME (center involving, non-center involving, and no CSME; Fig. 4D) assessed at each time point for dexamethasone DDS and SOC are represented in Fig. 4.

Safety analysis

Ocular hypertension has been defined as an intraocular pressure of 25 mmHg or more at each visit or an increase by at least 10 mmHg from baseline.[17] However, this is usually found to be temporary and can be treated with topical treatment. Considering the definition of 10 mm of Hg increase from baseline as ocular hypertension, on postoperative day 1 [dexamethasone DDS group 8 (9.8%) vs SOC group 9 (13%)], week 1 [1 (1.2%) vs 1 (1.5%)], week 2 [0 vs 0], week 4 [2 (2.4%) vs 1 (1.4%)], and week 12 [5 (6.4%) vs 1 (1.6%)] had ocular hypertension. If we consider absolute value of intraocular pressure of 25 mmHg as ocular hypertension, then at day

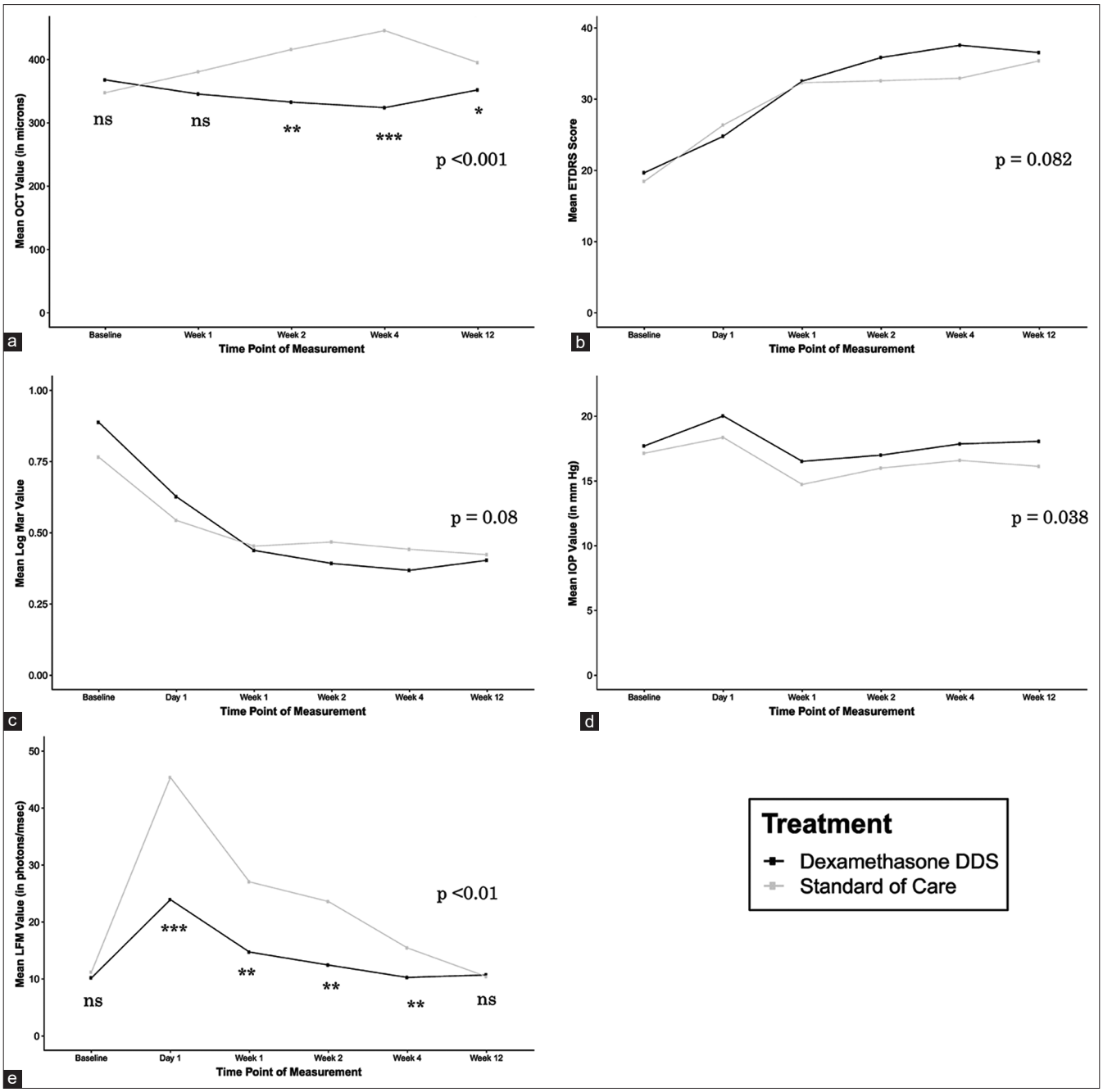

Figure 2: Line diagram representing the mean OCT (in μm), ETDRS score, Log MAR, IOP (in mmHg), LFM (in photons/msec) of the dexamethasone DDS and standard of care group assessed at different time points of study (baseline, day 1, week 1, week 2, week 4, and week 12 for all parameters except for OCT for which it is the baseline, week 1, week 2, week 4, and week 12). The *P* value mentioned represents the comparison of the interaction between time and treatment as assessed by two-way mixed-model ANOVA. For significant interaction (OCT and LFM), the results of univariate analysis between treatment at each time point are shown. * – $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, ns represents non-significant. OCT-Optical Coherence Tomography; ETDRS-Early Treatment Diabetic Retinopathy Study; Log MAR-Logarithm of the Minimum Angle of Resolution; IOP-Intraocular Pressure; LFM-Laser Flare Photometer; DDS-Drug Delivery System

1 [dexamethasone DDS 12 (15%) vs SOC 14 (20%)], week 1 [0 vs 0], week 2 [1 (1.2%) vs 0], week 4 [2 (2.4%) vs 0], and week 12 [4 (5.1%) vs 0] had ocular hypertension. For the management of the increase in IOP, patients were started on anti-glaucoma drugs like topical brimonidine or topical timolol and/or oral acetazolamide. No serious complications like retinal detachments, vitreous hemorrhage, or endophthalmitis were seen in either group.

Discussion

The treatment modalities approved for DME have several pitfalls: in laser photocoagulation, majority do not regain the lost visual acuity.[15] Ranibizumab requires a monthly injection for three years which is a huge deterring factor in its practical utility.[18,19] Main concern with the use of intravitreal triamcinolone acetonide (TA) is the need for repeat injections

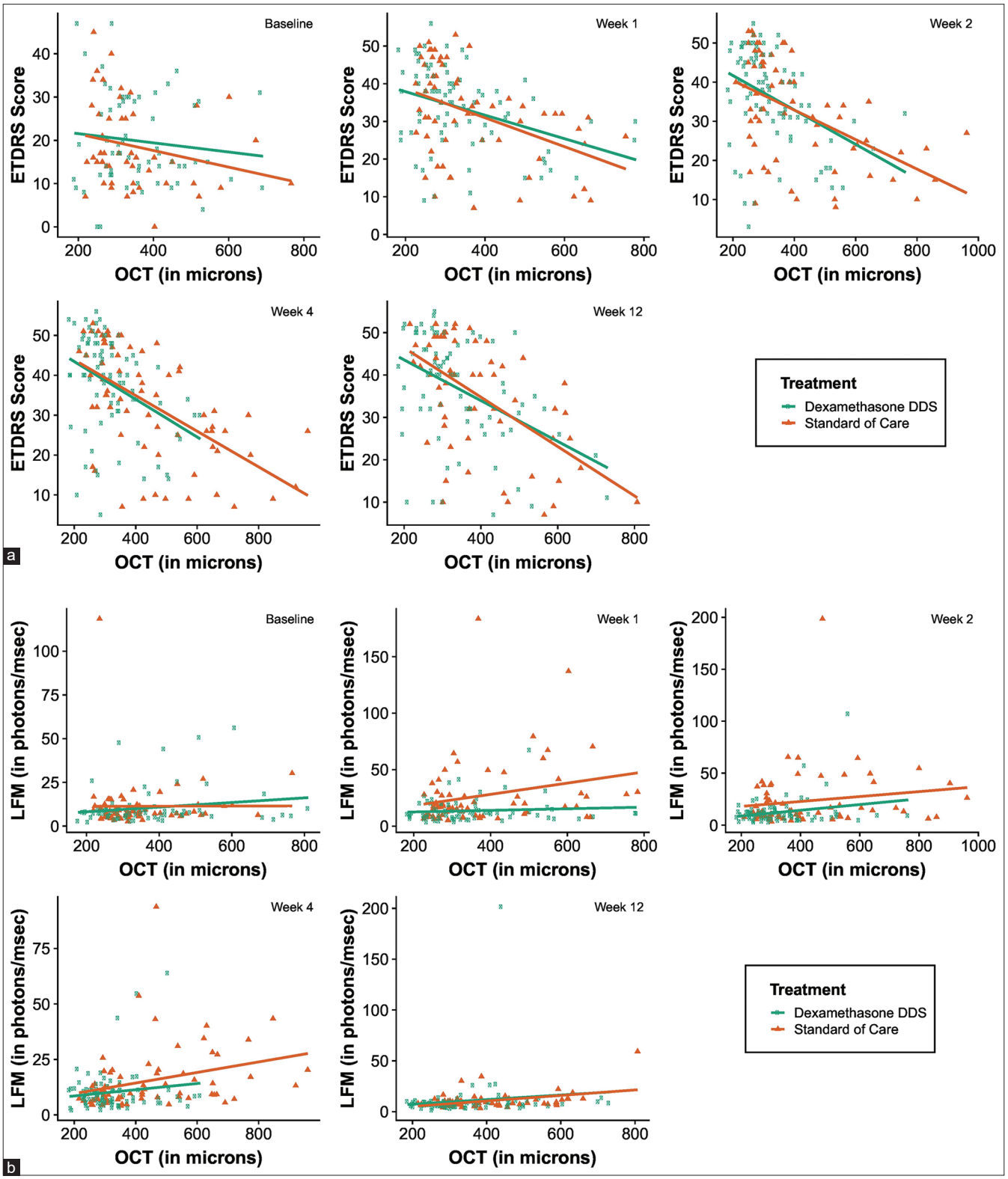

Figure 3: Scatter plot representing the trend between ETDRS score vs OCT (Figure 3A) and LFM vs OCT (Figure 3B) at different time points (baseline, week 1, week 2, week 4, and week 12) for dexamethasone DDS and standard of care group. The lines represent the trendline fitted according to linear regression methodology individually (green line–dexamethasone DDS group and orange line –standard of care group). The green dots represent the data points of dexamethasone DDS group, and orange dots represent the data points of standard of care group. OCT-Optical Coherence Tomography; ETDRS-Early Treatment Diabetic Retinopathy Study; LFM-Laser Flare Photometer; DDS-Drug Delivery System

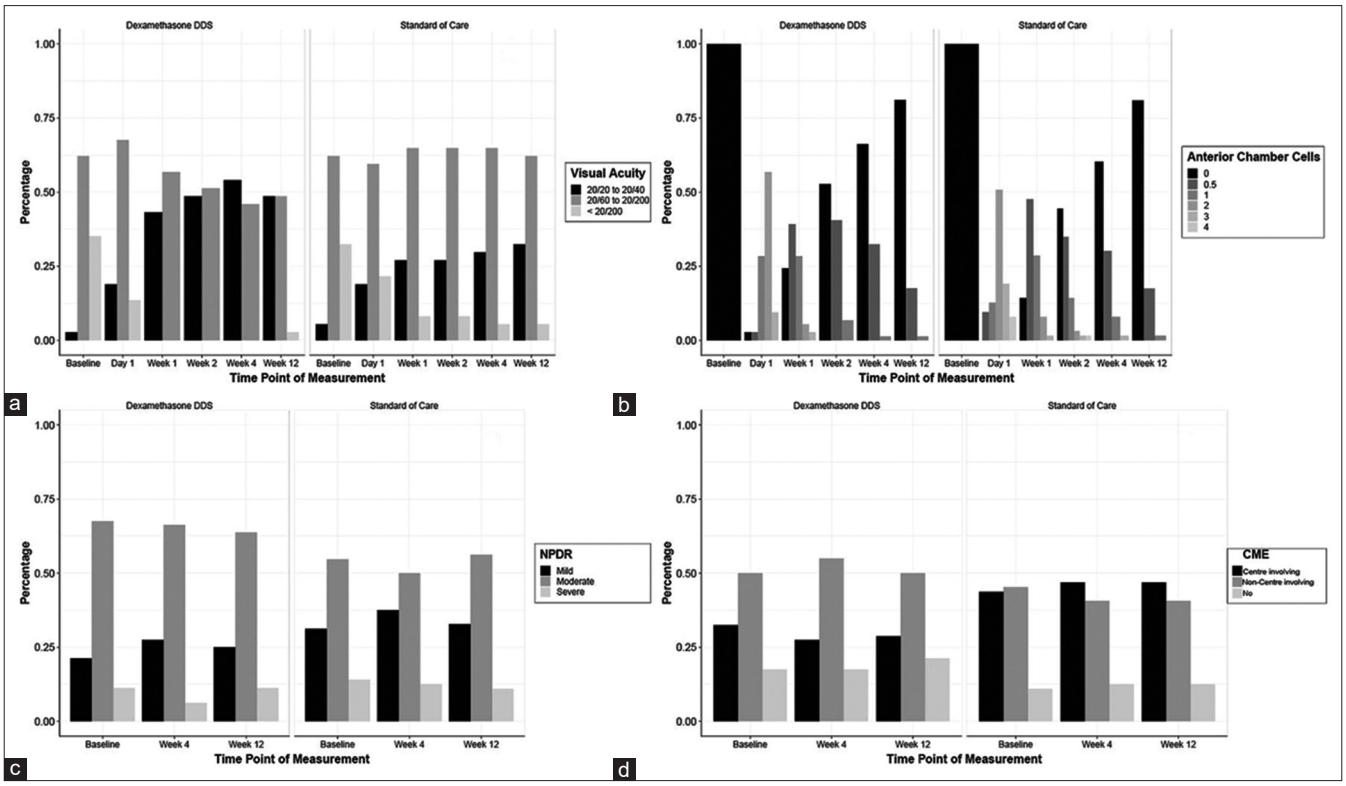

Figure 4: Dodged bar plot representing the percentage of patients in different categories of visual acuity (20/20 to 20/40, 20/60 to 20/200, <20/200; Fig. 4A), anterior chamber cells (0,0.5,1,2,3,4; Figure 4B), NPDR (mild, moderate, and severe; Figure 4C), and CME (center involving, non-center involving, no; Figure 4D) assessed at each time point (baseline, day 1, week 1, week 2, week 4, and week 12 for visual acuity and anterior segment evaluation; baseline, week 4, and week 12 for posterior segment evaluation and CME) for dexamethasone DDS and standard of care. The color represents the respective categories as mentioned in the legend of the figure. NPDR-Non-proliferative Diabetic Retinopathy; CME-Cystoid Macular Edema; DDS-Drug Delivery System

and recurrence of CME. However, the dexamethasone DDS (containing 700 µg of dexamethasone) releases the drug over a period of 180 days. In a proof-of-concept study by our group, Agarwal *et al*.[15] showed that a single injection of intravitreal dexamethasone DDS intraoperatively decreased CMT and increased the visual acuity. In the present study, we aimed to tackle both components of DME that is known to worsen after cataract surgery by focal/grid laser photocoagulation and dexamethasone DDS.

In this study, even though the difference in visual acuity was not significant, the authors found a greater proportion of patients with a good vision in dexamethasone DDS group.

The LFM values were significantly decreased in the dexamethasone DDS group as compared to the control group at first postoperative day 1, 1, 2, and 4 weeks but not significantly decreased at week 12 suggesting that the effect of dexamethasone DDS in decreasing the anterior chamber inflammation lasted for approximately one month and then it gradually weaned off.

The mean OCT thickness in the dexamethasone DDS group was lesser as compared to that of SOC group at all time points assessed post-intervention, even though at baseline, the SOC group had a lesser mean OCT thickness.

In a study by Boyer *et al*.,[20] taking 15 letter improvement and mean average reduction in central retinal thickness (CRT) during the study (baseline vs study end) as an outcome parameter, dexamethasone implant at both doses (0.35 and 0.70) showed a greater improvement in both the parameters as compared to that of sham with greater improvement in 0.70 mg dexamethasone implant. Dexamethasone DDS being a steroid, the decrease in inflammation was expected.

ETDRS score is negatively correlated in all, an obvious finding suggesting that better visual acuity has a lesser thickness of macula. The correlation is similar between the two groups for ETDRS score vs OCT. For correlation between LFM vs OCT in dexamethasone DDS group, the steroid is decreasing the inflammation, thereby decreasing both LFM as well as OCT, causing the correlation to be almost 0 at week 2 and week 4. It is established that more thickness has more LFM, but it being a predictor has not been mentioned in literature. But with our results, it is probable that high LFM is a predictor of increased thickness.

Adverse events that are of the greatest concern with corticosteroid therapy especially increase in IOP. Similar to the earlier study by Kuppermann *et al*.[21] in which increased IOP was demonstrated between day 91 and day 180 in 6% in dexamethasone DDS group and 0% in observational group, even in our study an increased IOP (6.4% in the dexamethasone DDS group and 1.6% in the SOC group) was noted at day 90. Topical/oral IOP lowering medications were used for the management of IOP in these patients, and advanced treatments like laser or surgical interventions were not required. No treatment-related cases of concern like retinal detachment, endophthalmitis, and vitreous hemorrhage occurred in the study. Patients were given rescue interventions for their

Table 2: Results of the subgroup analysis

Subgroup analysis	Outcome	Timeline	Time and Treatment Interaction (*P*)	Treatment Groups		*P*
				Dexamethasone DDS	SOC	
Focal/Non Center involving and Diffuse/ Center involving CSME together (Dexamethasone DDS - 68 patients and SOC-62 patients)	OCT Score, Mean±SD	Overall	P<0.001	-	-	-
		Baseline	-	387.7±142.8	354.7±118.2	0.167
		Week 1	-	364.1±134.4	389.3±150.7	0.323
		Week 2	-	348.6±114.9	429.7±191.3	0.004
		Week 4	-	337.7±97.6	462±181.8	<0.001
		Week 12	-	369.1±125.9	407.6±132.6	0.105
	Requirement of rescue intervention, *n* (%)	-	-	29/68 (42.6%)	32/62 (51.6%)	0.397
	ETDRS	Overall	0.175	-	-	-
	LogMAR	Overall	0.098	-	-	-
	IOP	Overall	0.098	-	-	-
	LFM score, Mean±SD	Overall	0.012	-	-	-
		Baseline	-	10.9±11	11.7±14.9	0.709
		Day 1	-	25.9±19.2	46.2±66.1	0.017
		Week 1	-	15.9±12.5	27.7±30.8	0.005
		Week 2	-	13.3±14.6	24.3±28.9	0.007
		Week 4	-	10.8±10.4	15.8±15	0.028
		Week 12	-	11.7±24.6	10.6±8.8	0.755
	Number of rescue intervention required per patient, Median (IQR)	-	-	2 (2, 3)	3 (2, 4)	0.079
No CSME group (Dexamethasone DDS - 14 patients and SOC - 7 patients)	OCT Score	Overall	0.241	-	-	-
	Requirement of rescue intervention, *n* (%)	-	-	4/14 (28.6%)	2/7 (28.6%)	1
	ETDRS	Overall	0.310	-	-	-
	LogMAR	Overall	0.686	-	-	-
	IOP	Overall	0.112	-	-	-
	LFM score, Mean±SD	Overall	0.005	-	-	-
		Baseline	-	6.9±3	6.7±5	0.916
		Day 1	-	14.7±7.7	37.8±27.3	0.007
		Week 1	-	9±4.2	21.4±9.8	0.001
		Week 2	-	8.4±4.3	17.3±8.7	0.005
		Week 4	-	7.6±3.9	12.2±4.2	0.021
		Week 12	-	6.1±1.9	8.8±2.2	0.010
	Number of rescue intervention required per patient, Median (IQR)	-	-	2 (2, 2.8)	2 (2, 2.5)	1
Diffuse CSME alone (Center involving CSME) (Dexamethasone DDS - 27 patients and SOC - 30 patients)	OCT Score, Mean±SD	Overall	<0.001			
		Baseline	-	443.6±145.8	401.8±141.3	0.290
		Week 1	-	400.2±127.6	437.3±159.3	0.358
		Week 2	-	396±126.5	482.5±197.4	0.062
		Week 4	-	369.8±98.7	515.5±171.4	0.001
		Week 12	-	395.4±119	435.8±125.5	0.235
	Requirement of rescue intervention, *n* (%)	-	-	12/27 (44.4%)	20/30 (66.7%)	0.155
	ETDRS	Overall	0.538	-	-	-
	LogMAR	Overall	0.241	-	-	-
	IOP	Overall	0.627	-	-	-
	LFM score, Mean±SD	Overall	0.026	-	-	-
		Baseline		13.8±14.3	14.3±20.6	0.913
		Day 1		28.5±19.3	45.3±37.7	0.045

Contd...

Table 2: Contd...

Subgroup analysis	Outcome	Timeline	Time and Treatment Interaction (*P*)	Treatment Groups		*P*
				Dexamethasone DDS	SOC	
		Week 1		20.5±16.8	28.3±19.8	0.122
		Week 2		18.8±21.8	23±18.2	0.429
		Week 4		14.7±15.2	15.4±11.3	0.858
		Week 12		17.7±38.9	10.4±5.8	0.327
	Number of rescue intervention required per patient, Median (IQR)	-	-	2 (2, 3)	3 (2, 4)	0.083
Focal CSME alone (Non-Center involving CSME) (Dexamethasone DDS - 41 patients and SOC - 32 patients)	OCT Score, Mean±SD	Overall	<0.001	-	-	-
		Baseline	-	351.4±130.2	310.8±68.6	0.125
		Week 1	-	342.4±135.3	344.4±128.9	0.951
		Week 2	-	317.8±96.2	378.7±173.6	0.065
		Week 4	-	316.5±92.1	411.9±179.3	0.004
		Week 12	-	352.3±128.8	380.3±135.7	0.389
	Requirement of rescue intervention, *n* (%)	-	-	17/41 (41.5%)	12/32 (37.5%)	0.919
	ETDRS	Overall	0.422	-	-	-
	LogMAR	Overall	0.407	-	-	-
	IOP	Overall	0.169	-	-	-
	LFM score	Overall	0.122	-	-	-
	Number of rescue intervention required per patient, Median (IQR)	-	-	2 (2, 3)	2 (2, 3)	0.8
Patient requiring no rescue medications (Dexamethasone DDS - 49 patients and SOC - 35 patients)	OCT Score, Mean±SD	Overall	<0.001			
		Baseline	-	345.5±125.9	302.1±66.8	0.079
		Week 1	-	317.9±104.9	325±109.9	0.770
		Week 2	-	310.8±89.9	336.3±124.8	0.287
		Week 4	-	307±79.3	384±150.8	0.003
		Week 12	-	341.1±115.6	375.7±137.8	0.228
	ETDRS	Overall	0.691	-	-	-
	LogMAR	Overall	0.624	-	-	-
	IOP	Overall	0.259	-	-	-
	LFM score, Mean±SD	Overall	0.027	-	-	-
		Baseline	-	11.0±11.8	9.7±5.1	0.533
		Day 1	-	23.8±18.8	42.8±51.1	0.021
		Week 1	-	14.7±10.4	24.5±26	0.019
		Week 2	-	11.1±5.9	20.3±17.1	0.001
		Week 4	-	9.4±4.4	13.4±9.6	0.012
		Week 12	-	8.5±5.1	10.9±9.8	0.148

macular edema if the investigator deemed it to be necessary. A higher number of rescue interventions were required in the SOC group as compared to that of dexamethasone DDS group (though not statistically significant).

Patients with preexisting DME had significantly lesser LFM values and OCT score in the dexamethasone DDS group which corroborated with the main group results in which patients with both DME as well as No DME at baseline were included.

In patients who did not have preexisting DME, the LFM score was significantly less in the dexamethasone DDS group versus the SOC group at all time points, indicating that intraoperative steroids cause significantly less inflammation and prove their usefulness in patients of diabetic retinopathy undergoing cataract surgery even without any preexisting DME. The macular thickness was not significantly different in this subgroup.

In patients who were not given any rescue medications, the overall LFM values and OCT score were significantly lesser in the dexamethasone DDS group as compared to the SOC group, which was similar to the results obtained in the main group in which patients with both DME as well as No DME at baseline were included. This established the role of intraoperative dexamethasone implant in patients with DME undergoing cataract surgery.

The limitations of the study include non-employment of sham surgery or placebo group and a short follow up of 90 days, thereby preventing long-term generalization of the results making it difficult to evaluate the impact on DR with corticosteroids as we can do with anti-VEGFs. The bias of non-employment of sham surgery group was mitigated by the fact that the examiners performing OCT and other

visual assessment and technician assessing visual acuity were masked to the treatment assignment. The patients were also asked to maintain the confidentiality of treatment administration in the study. Usually, IOP spikes are more likely between the 1st and 2nd month. By gathering data at week 4 and week 12, we may have missed higher IOP spikes in a greater number of patients.[22] Although this study is well powered, it is a single-center trial. Hence, further trials would be required for the generalizability of the trial findings. However, our study is the single largest study ever conducted to evaluate the efficacy of dexamethasone DDS in patients of NPDR undergoing cataract surgery. Cataract and diabetes, both being major healthcare problems, an intervention evaluated for the combination of the two attains paramount importance.

Conclusion

To conclude, in patients with diabetes, a major cause of visual loss is DME. The visual acuity was better, and the DME was significantly decreased in the dexamethasone DDS group. The number of interventions required, as well as the number of rescue interventions required per patient was also lesser in the dexamethasone DDS group as compared to the SOC group. This study highlights that dexamethasone implant is a potential, invaluable treatment option for this recalcitrant disease and advocates further exploration of its use in longer clinical studies with longer follow-up.

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Informed consent

Informed consent was obtained from all individual participants included in the study.

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Conflicts of interest

There are no conflicts of interest.

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