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Original Article

Ophthalmology Section

Comparison of Dexamethasone Implant and Anti-VEGF Agents in the Treatment of Naive Diabetic Macular Oedema: A Prospective Cohort Study

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ABSTRACT

Introduction: Diabetic Retinopathy (DR) is one of the common microvascular complications of diabetes. In patients with DR, the most frequent cause of vision loss is Diabetic Macular oedema (DME). In the present era, anti-Vascular Endothelial Growth Factor (anti-VEGF) agents are the mainstay of treatment for managing DME. A majority of patients show a good response to multiple doses of these agents administered by a pro re nata regimen at regularly spaced fixed intervals. However, the tendency of DME to become chronic and resistant to these agents, as well as the burden of repeated injections, necessitates considering alternative treatment options with similar or better efficacy. As steroids can address these drawbacks of anti-VEGF treatment, the present study compared the efficacy of anti-VEGF agents with dexamethasone implant in the treatment of naïve DME.

Aim: To compare the effectiveness of dexamethasone implant with anti-VEGF agents in the treatment of naïve DME.

Materials and Methods: A prospective cohort study was conducted in the Department of Ophthalmology at Kalinga Institute of Medical Sciences and Pradyumna Bal Memorial Hospital, Bhubaneswar, Odisha, India from September 2020 to September 2022. A total of 100 eyes with DME, newly diagnosed patients aged 18 years and above, without other macular oedema-causing diseases, were included. A total of 50 eyes in each group were treated with an anti-VEGF agent (Group A) or dexamethasone implant (Group B), and Best Corrected Visual Acuity (BCVA) and Central Foveal Thickness (CFT) were monitored for six months. For statistical analysis, paired t-test and independent t-test were used for within-group and inter-group analysis, respectively. A p-value <0.05 was considered statistically significant.

Results: In both groups, post-treatment BCVA showed marked improvement, but there was no significant difference in mean BCVA between the groups (p=0.89) at six months. However, the mean CFT showed significant improvement in Group B at six months. In Group A, the mean CFT reduced from 441.87±54.48 µm to 257.83±25.73 µm, and in Group B, the mean CFT reduced from 464±109.44 µm to 207±22.51 µm at six months (p<0.0001). Adverse events like cataracts and glaucoma were seen in patients treated with the dexamethasone implant and were managed by cataract surgery and topical anti-glaucoma medications, respectively.

Conclusion: Dexamethasone implant and anti-VEGF agents are equally effective in improving visual acuity; however, dexamethasone stands superior in reducing macular thickness. Needing fewer injections while treating with a dexamethasone implant improves compliance. The progression of cataract remains a major side-effect with the dexamethasone implant, which is not a concern when treating DME in pseudophakic eyes.

Keywords: Diabetic retinopathy, Microvascular complications, Ranibizumab, Vascular endothelial growth factor

INTRODUCTION

DME is the most common cause of visual loss in patients with diabetic retinopathy, especially among the working population in the developing world. It is characterised by capillary leakage, fluid accumulation, and retinal thickening. The prevalence of DME in patients with diabetic retinopathy is 2.7%-11%, but after 25 years of diabetes, its prevalence approximates 30% [1]. Chronic hyperglycemia, via various biochemical pathways, causes an increase in oxidative stress, inflammation, and vascular dysfunction, leading to the upregulation of VEGF and Tumour Necrosis Factor (TNF), which contribute to the breakdown of the blood-retinal barrier and the occurrence of DME [2]. Improved understanding of the pathophysiological mechanisms of DME has led to the development of effective therapies such as laser photocoagulation, anti-VEGF agents, corticosteroids, and vitreo-retinal surgeries [3].

Currently, anti-VEGF agents are the first-line treatment for DME [4,5]. A tremendous response is seen in the majority of patients with multiple injections of these agents administered at regularly spaced fixed intervals. They decrease the permeability of vessels and also reduce the concentration of unblocked VEGF to reduce oedema formation [1]. In chronic cases, their effect decreases and needs to be combined with steroids like the dexamethasone implant, which has a more comprehensive effect on the inflammatory cascade to reduce macular oedema. The steroid implant also employs the typical biphasic drug release by diffusion method, which allows the treatment to remain effective for up to six months by transitioning between an initial high-concentration phase and a second low-concentration phase, making it effective in persistent and refractory cases of DME [6].

Although anti-VEGF agents are the first-line treatment, the need for repeated injections and the failure or incomplete response in a subset of patients are major concerns [7-11]. These problems necessitate the search for alternative treatment options in naïve cases of DME. Both these drugs (anti-VEGF and dexamethasone) have been studied individually and also compared in persistent and refractory cases. The primary objective of the study was to assess changes in visual acuity (BCVA) in patients with primary DME treated with either of the modalities at six months. The secondary objectives were to assess changes in CFT, correlate changes in CFT with visual acuity (BCVA) following treatment, and also compare complications and treatment compliance between the two groups.

MATERIALS AND METHODS

A prospective cohort study was conducted at the Department of Ophthalmology in a tertiary care teaching hospital, Kalinga Institute of Medical Sciences and Pradyumna Bal Memorial Hospital, Bhubaneswar, Odisha, Eastern India between September 2020 and September 2022. The study was approved by the institutional review board (KIIT/KIMS/IEC/426/2020), and it adhered to the guidelines of the Declaration of Helsinki. Informed consent was obtained from all study participants.

Sample size calculation: The study included 100 eyes of 100 patients. The sample size calculation was based on the mean±SD values of CFT for both groups, which were 277.66±76.18 and 233.25±37.55. With a 5% level of significance, 90% power, and 95% confidence interval, the minimum calculated sample size for each group was 40, totaling 80. Accounting for a 20% attrition rate, the total sample size was set to be 96-100, with 50 in each group [12].

Inclusion criteria: Diabetic patients aged >=18 years diagnosed with DME, CFT >250 µm with spongy or cystoid oedema or serous detachment and the patients without other ocular co-morbidities that cause macular oedema were included in the study.

Exclusion criteria: The patients of DME with taut posterior hyaloid and vitreo-macular traction, those undergone previous treatment for DME, diagnosis of glaucoma/ocular hypertension or having a family history of glaucoma, mono-ocular patients were excluded from the study.

A total of 100 eyes from 100 patients who met the inclusion criteria were included in the study and were assigned to two groups, A and B, with 50 eyes in each group. Seven patients in Group A and three patients in Group B were lost to follow-up and were excluded from the final analysis at six months.

Study Procedure

After obtaining written consent, the demographic profile of all eligible patients was recorded. At the baseline evaluation, a detailed clinical history and thorough clinical evaluation were conducted, including visual acuity assessment using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, Intraocular Pressure (IOP) measurement using applanation tonometry, and anterior segment examination using a slit lamp to assess lens status. Posterior segment examination was conducted using indirect ophthalmoscopy to grade diabetic retinopathy and document macular oedema [13,14]. The ETDRS classification was used for grading DR [15]. Additionally, CFT and its morphology were assessed using Spectral Domain Optical Coherence Tomography (SD-OCT Heidelberg Engineering Spectralis) [16]. Fundus fluorescein angiography (FFA-Heidelberg Engineering Spectralis) was performed when necessary to confirm neovascularisation and rule out macular ischaemia. Naïve DME was defined as CFT greater than 250 µm within a 1 mm centered on the fovea in patients who had not received any treatment to date.

All patients received an intravitreal injection of either drug, depending on the patient's choice, after they were provided with a detailed explanation of both treatment modalities. Those who received anti-VEGF agents were grouped as Group A and received either an injection of ranibizumab (0.5 mg/0.1 mL) or bevacizumab (1.25 mg/0.1 mL) at monthly intervals until the resolution of oedema (CFT≤250 µm). Patients receiving a dexamethasone implant were grouped as Group B, and an implant containing 700 mcg of dexamethasone was used. The first dose was implanted at the time of inclusion and repeated at the fourth month if necessary.

In Group A, 34 eyes opted for Injection Bevacizumab, while 16 eyes opted for Injection Ranibizumab. In Group B, all eyes received a dexamethasone implant. Patients were followed up bimonthly following the dexamethasone implant injection and monthly following anti-VEGF agents for six months. Eleven patients (11 eyes) did not complete the follow-up, with seven from Group A and four from the dexamethasone group. Data were available for 89 eyes from baseline to six months of treatment.

Baseline BCVA, CFT, IOP, and lens status were documented. At the time of follow-up, changes in baseline parameters were documented and assessed, along with the number of injections and additional procedures such as cataract surgery. BCVA was documented in log MAR, and to calculate visual acuity differences between pre-injection and post-injection (at six months), ETDRS letter gain or loss was computed from the log MAR values.

STATISTICAL ANALYSIS

Data was coded and recorded in the MS excel spreadsheet program. Statistical Package for Social Sciences (SPSS) version 23.0 (IBM Corp.) was used for data analysis. Descriptive statistics, such as mean, Standard Deviation (SD), frequencies (n), and percentages (%), were used for categorical variables. Whenever possible, data were represented graphically using histograms, column charts, and pie-charts for categorical data, and bar graphs, line graphs, and pie-charts for continuous data. In bilateral cases, only one eye with naïve DME fulfilling the inclusion criteria was considered for analysis. A paired t-test was used for within-group analysis when the data had a normal distribution. An independent t-test was used for inter-group analysis. A p-value <0.05 was considered statistically significant.

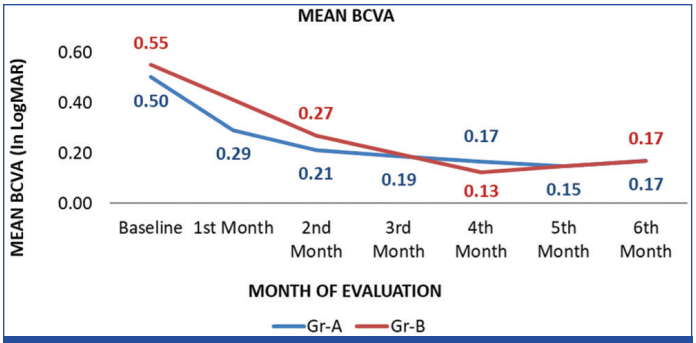
RESULTS

In the present study, [Table/Fig-1] displays the demographic characteristics and baseline parameters of the patients in each group, which were similar. The majority of patients in both groups were between 50 and 65 years of age. The maximum number of patients in either group had diabetes for 5-10 years. In the present study, 11 (22%) patients had mild Non-Proliferative Diabetic Retinopathy (NPDR), 20 (40%) had moderate NPDR, 9 (18%) had severe NPDR, and 10 (20%) patients had PDR in Group A. In Group B, 5 (10%) patients had mild NPDR, 30 (60%) had moderate NPDR, 5 (10%) had severe NPDR, and 10 (20%) patients had PDR.

		Group-A	Group-B (dexamethasone implant group)	p-value
Sample size (No. of eyes)		50	50	
Mean age (in years)		57.1±4.7	56.5±4.8	
Gender (male/female)		33/17	36/14	
Laterality (number of eyes)	Right eye	32	23	
	Left eye	18	27	
Duration of diabetes (in years)		8.6±4.0	9.4±3.8	
HbA1c (%)		8.77±0.90	8.98±1.16	0.25
Mean BCVA (logmar)		0.50±0.22	0.55±0.08	0.21
Mean CFT (in microns)		441.87±54.48	464±109.44	0.20
IOP (mmHg)		13.92±1.51	15.20±1.34	0.06
Lens status	Clear	11	12	
	Cataract	24	12	
	Pseudophakic	15	26	

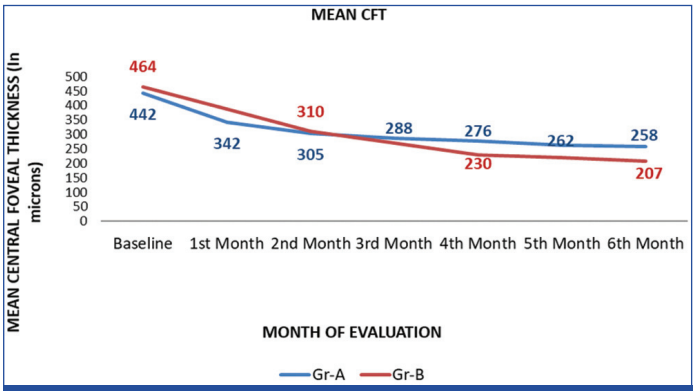
[Table/Fig-1]: Shows the baseline characteristics of the two groups.

The mean BCVA was 0.50±0.22 at baseline in Group A patients and 0.55±0.08 in Group B patients. At baseline, there was no significant difference in mean BCVA between both groups (p=0.21). The mean BCVA improved from 0.50±0.22 to 0.17±0.07 in Group A and from 0.55±0.08 to 0.17±0.03 in Group B at six months, which was a statistically significant improvement for each group (p-value <0.001). However, at six months following treatment, there was no significant difference in mean BCVA between the groups (p=0.89). [Table/Fig-2] displays the mean BCVA of the two treatment groups over the six months of follow-up.



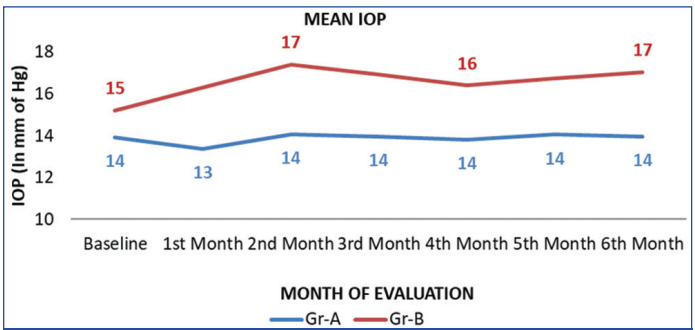
[Table/Fig-2]: Line graph shows the change in mean BCVA in Group-A and B upto six months of follow-up.

The mean CFT was 441.87±54.48 µm in Group A, while in Group B it was 464±109.44 µm at inclusion (p=0.20). The CFT reduced from 441.87±54.48 µm to 257.83±25.37 µm in Group A and from 464±109.44 µm to 207.39±22.51 µm in Group B at the end of six months. This was a greater and statistically significant reduction in macular thickness in Group B (dexamethasone implant) at the end of six months (p-value <0.0001). Also, in either of the groups, a significant reduction of CFT was observed from baseline to six months post-treatment (p-value <0.0001). [Table/Fig-3] displays the changes in mean CFT in Group A and B.



[Table/Fig-3]: Line graph shows the changes in mean CFT in Group-A and B upto six months of follow-up.

The average number of injections required was 5.12 in Group A patients over six months of treatment, while the average number of injections required was 1.4 in Group B. The mean IOP varied from 13.92±1.51 mmHg to 13.95±1.27 mmHg in Group A and from 15.20±1.34 to 17.04±3.31 mmHg in Group B at the end of six months [Table/Fig-4]. At baseline, there was no significant difference in mean IOP between the two groups (p=0.06). A significant increase in IOP was observed at the end of six months of treatment in Group B (p=0.0002). When both groups were compared at six months, the mean IOP was significantly higher in Group B than in Group A (p-value <0.0001). Ten patients had IOP >21 mmHg atleast once during their follow-up visits in Group B and were controlled by topical anti-glaucoma medications only. None of the eyes had cataract progression in Group A in subsequent follow-ups. Two eyes with pre-existing cataracts opted to undergo



[Table/Fig-4]: Line graph shows the changes in mean IOP in Group-A and B from baseline to six months.

phacoemulsification with Intraocular Lens (IOL) implantation at the end of the 5th month in Group A. In Group B, 12 eyes had an increase in cataract density, and two eyes with clear lenses developed cataracts in subsequent follow-ups. Phacoemulsification with IOL implantation was performed for six eyes, among these 14 eyes after four months of the injection. No other significant adverse effects were noticed in the groups. In the present study, two eyes had subconjunctival haemorrhage following administration of anti-VEGFs intravitreally, while one eye had a similar adverse event in the dexamethasone implant group. Three patients complained of eye pain post-intravitreal injection in Group A, while one patient had similar complaints in Group B. No eyes had severe adverse events like vitreous haemorrhage or endophthalmitis in either of the groups. Systemic adverse events were also not seen in any of the study patients.

The anti-VEGF group showed visual improvement of >10 letters in 62% of patients, while the Dexamethasone group showed statistically significant improvement in 82% of patients at six months (p-value=0.041) [Table/Fig-5].

	Group-A		Group-B	
Gain at 6th month (post treatment)	<10 letter	≥10 letter	<10 letter	≥10 letter
Number of patients	12	31	5	41
Percentage (%)	24	62	10	82

[Table/Fig-5]: Visual outcome in terms of letters gained at the end of six months in Group-A and B.
Seven patients in Group A and three patients in Group B were lost to follow-up

DISCUSSION

The present study showed comparable efficacy of both molecules in their structural and functional outcomes, with a remarkable improvement in BCVA and CFT in both groups. The visual improvement in the anti-VEGF group at the end of six months was 62% in the present study. These results were comparable with the studies by Sharma A et al., which showed 50% of patients gaining >10 letters in the 6th month [12]. Gillies MC et al., in their study, showed 40% of patients gained >10 letters at the end of 12 months [17]. These visual outcomes in the anti-VEGF groups could be due to intensive treatment during the induction phase [18]. Sharma A et al., and Gillies MC et al., also observed that 60% and 41.3% of eyes receiving dexamethasone injections showed >10 letters improvement, respectively [12,17].

In the present study, a large number of eyes receiving dexamethasone showed an improvement in mean BCVA at the end of six months, with 82% of them showing >10-letter improvement. When comparing the two groups, a large percentage of patients in the dexamethasone implant group had better letter gain in the above studies and the present study. The present study showed a greater reduction in macular thickness in patients receiving dexamethasone implants (Mean CFT change 258.01 µm) compared to anti-VEGF (mean CFT change 184.04 µm) at the end of six months. In the INVICTUS study, the mean CFT change was 95.6 µm in the DEXA Group and 124.4 µm in the ranibizumab group [19]. In the BEVORDEX study, there was a mean change in CFT of 187 µm for the dexamethasone implants group and 122 µm for the bevacizumab group at 12 months [20]. In a study conducted in Spain, naïve cases showed better improvement in CFT at six months, around 245.9 µm [21]. This could be due to corticosteroids inhibiting the production of a broad spectrum of inflammatory molecules and modulating vascular permeability through anti-inflammatory effects, in addition to the suppression of VEGF production [22].

These improvements enhance the barrier function of vascular tight junctions, resulting in better control of DME and improved BCVA [23]. When comparing the change in CFT with the visual improvement, there was a consistent decreasing trend in CFT and an improving trend in BCVA in both groups. However, in the DEXA group, better

improvement in CFT couldn't be directly equated to improvement in BCVA at six months. This could be due to the side effects of steroid implants causing the progression of cataracts and the need for cataract surgery.

An increase in IOP has been the most common short-term complication in the DEXA implant group in many studies. In a study on the French population, fewer eyes (4/21) in the DEXA group developed a rise in IOP ≥25 mmHg or ≥10 mmHg rise from baseline [19]. The BEVORDEX study in 2014 showed that 26% of eyes (12/46) had a significant rise in IOP in the DEXA arm [20]. A study of newly diagnosed cases of DME in Indian eyes showed an IOP rise in 20% of eyes (4/20) atleast once during their follow-up visits in the DEXA arm only [12].

Similarly, in the present study, an IOP rise was seen in 10/43 patients treated with dexamethasone. Steroids may impact glucocorticoid receptors on trabecular meshwork cells by decreasing their cellularity and increasing extracellular matrix deposition, which increases aqueous outflow resistance and leads to increased IOP, which holds true for all these studies [24]. However, these effects remain temporary as OCT of the optic nerve head has shown no change in the thickness of the retinal nerve fiber layer at the seventh month of follow-up in a study by Shah SU et al., and were managed medically with topical IOP-lowering medications in all the studies [25]. Regarding the changes in lens status, this study's results were similar to those of the BEVORDEX study [20]. However, a few other studies, including persistent DME cases, showed a lower number of steroid-related cataracts [12,20]. This may be due to the fact that cataracts related to steroid use typically develop during the second year of steroid therapy, so the number of cases may vary in long-term follow-ups [25]. Although local adverse events are commonly seen with steroids, these need to be weighed against the potential for severe systemic adverse events associated with repeated anti-VEGF injection for a long duration. In the combined data from the RISE and RIDE studies, there was a dose-related increased mortality rate of 4.4% in patients treated with monthly Ranibizumab for two years, which increased to 6.4% at three years [8]. This aspect could not be assessed in the present study due to the short duration of the follow-up.

The repeated visits for re-evaluation and injections are considered a burden by DME patients due to the associated significant co-morbidities and the expenses of treatment and consultation [26]. To assess the burden, the mean number of injections and cases lost to follow-up were documented. The mean number of injections in the dexamethasone group was significantly lower due to the prolonged duration of action of dexamethasone. Additionally, only four patients were lost to follow-up compared to the seven patients in the anti-VEGF group in the present study. Similar experiences have been documented in many studies, regardless of the study duration [12,17,20,23,25].

Cho H et al., conducted a retrospective study comparing the cost-effectiveness of DME treatment in patients who were treated with anti-VEGF medications or a DEXA implant in a Korean-based population [27]. They found that the mean yearly eye-related medical expense of the DEX-implant group was much lower than that of the anti-VEGF group. This difference was primarily attributable to the DEX-implant group having decreased use of eye care-related injections. However, the authors needed to consider the additional expenses of cataract surgery in either group, though more so in the dexamethasone group.

The BEVORDEX study has also stated that when comparing cost-effective options, certain facts should be considered. This includes weighing the fewer injections and less frequent visits by those receiving dexamethasone against its cost and side effects, such as cataract progression requiring surgery [20]. These facts highlight that dexamethasone implants are a cost-effective alternative in pseudophakic eyes. However, in phakic eyes, considering the additional burden of cataract surgery, anti-VEGF agents still remain the first choice. To the best of the author's knowledge, there is a paucity of literature regarding the comparison of both these treatment modalities in the management of naive DME. Therefore, the present study intends to compare the effectiveness of these two treatment options in naive DME.

Limitation(s)

The sample size was small with a short duration of follow-up, so these results cannot be extrapolated to the general population. Subgroup analysis based on lens status should have been considered for visual outcome.

CONCLUSION(S)

Dexamethasone led to better resolution of macular oedema, though both were equally effective in improving visual acuity. Fewer injections and hospital visits led to better compliance in those receiving dexamethasone injections. IOP elevation following dexamethasone was manageable medically, but the progression of cataract requiring surgery adds extra expenses. Considering the benefits and drawbacks, dexamethasone implants could still be a cost-effective alternative for naive DME in pseudophakic eyes.

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- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

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