Dexamethasone Intravitreal Implant (Ozurdex) in the Treatment of Macular Edema: A Retrospective Study

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Research Article

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Abstract

Background*:* To evaluate the efficacy and safety of intravitreal dexamethasone implant (Ozurdex) in the management of macular edema (ME) of varied etiology, particularly in case of diabetic macular edema (DME).

Methods*:* This was a single-center, retrospective, observational, cohort study based on the data retrieved from the medical records of the patients with ME who were administered with dexamethasone intravitreal implant during 2013 to 2018. At baseline, a complete ophthalmologic evaluation, including measurement of visual acuity (VA), central retinal thickness (CRT), and intraocular pressure (IOP) was performed for all patients in the clinic. Descriptive statistics were used to summarize patients' demographic and disease related data. Data were analyzed using XLSTAT statistical software for descriptive analysis. Statistical significance was set at $p<0.05$.

Results*:* A total 114 patients with ME were included in this study. Diabetes mellitus (DM) was found to be the main etiology (80%; 91 out of 114 patients) and systemic comorbidity (92 out of 114) and those patients were considered as diabetic macular edema (DME) patients. All 114 patients received dexamethasone intravitreal implant and then followed up for next six months. Furthermore, 20.2% (23/114) and 0.9% (1//114) patients received the second Ozurdex injection alone or in combination with anti-VEGF, respectively, during the follow-up period on PRN basis. The CRT significantly reduced from baseline (480 μm) to 320 μm ($p=0.0001$) during six-month period with maximum reduction occurring in first three months. The pre-treatment mean VA (0.92 LogMAR) also significantly improved to 0.75 LogMAR ($p=0.01$) following three months of treatment. Mean pre-injection IOP increased from 15 mmHg to 21 mmHg in patients receiving dexamethasone implant. However, with the use of anti-glaucoma medication, the IOP was reduced to the baseline value.

Conclusions*:* Dexamethasone intravitreal implant can be considered as an effective and safe treatment modality for ME patients, particularly the DME patients.

Background

Macular edema (ME) is an important issue in retinal pathology as it damages macula, eventually affecting the central visual acuity (VA). This has significant impact on quality of life of the patients [1, 2]. ME occurs due to fluid accumulation in the retinal layers surrounding the fovea, leading to an increase in retinal thickness (edema). The vision loss associated with ME results due to the alteration of the functional cell relationship in the retina and activation of the inflammatory responses [2]. It can either be intracellular or extracellular. In intracellular ME, the blood-retinal barrier (BRB) remains intact with swollen retinal cells causing excessive accumulation of neurotransmitters. In extracellular ME, BRB is damaged and the tissue volume increases due to an increase in the retinal extracellular space [2].

ME occurs in various ocular complications, including vascular retinopathies, diabetic retinopathy, macular degeneration, uveitis, trauma, and intraocular surgery [3]. Diabetic retinopathy (DR) and ME are common

diabetes-related microvascular complications that cause deterioration of central VA and acquired blindness, in mostly working-age adults worldwide [4-6]. In diabetic patients, high blood glucose level impairs the small capillaries supplying blood to the retina and this causes leakage of blood and its solutes from capillaries in the extracellular space beneath the macula causing fluid accumulation, and this is referred to as diabetic macular edema (DME) [7]. Moreover, in diabetic patients, cataract surgery can lead to higher risk of complications with poor visual outcome compared to non-diabetics [3, 8, 9]. This occurs due to some histological changes in the retina that activates the inflammatory mediators and triggers endothelial cell death, causing damage of BRB, leakage, and accumulation of fluid and serum in the outer plexiform layer leading to DME [3].

Pathogenesis of DME is complex and multifactorial, including angiogenic, inflammatory and hypoxic processes, and vitreomacular traction [5, 10]. Inflammation is the main cause since the disruption of the BRB releases wide range of inflammatory mediators, such as vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and monocyte chemotactic protein-1, and leukostasis [7, 11, 12].

Traditionally, DME was treated with focal/grid laser photocoagulation and by controlling diabetes medically in past decades [11]. However, in recent years, the therapeutic landscape of DME had a remarkable change [13] with the emergence of new intravitreal pharmacological therapies, such as anti-VEGF agents and corticosteroids. These therapies are known to prevent visual loss and improve anatomic outcomes efficiently [6]. Three anti-VEGFs, aflibercept (Eylea®), ranibizumab (Lucentis®), and bevacizumab (Avastin®) are the widely used intravitreal VEGF inhibitors; among which aflibercept and ranibizumab received approval from the United States Food and Drug Administration (USFDA) and European Marketing Authorization (EMA) for the treatment of DME [4, 6, 13]. A significant proportion of eyes had failed to achieve reduction of central retinal thickness (CRT) and <10-letter improvement in best corrected VA (BCVA) after one or two years of treatment [14, 15]. The partial responders or non-responders then require additional or alternative treatments [16].

Corticosteroids are considered to be effective in treating eyes with DME and vision loss [16]. Intravitreal corticosteroids exert influence on multiple signal transduction pathways and prevent the action of VEGFs, prostaglandins, and pro-inflammatory cytokines and thus inhibit leukostasis [7, 17, 18]. Consequently, they decrease the damage of the BRB and retinal thickening [16]. Among different corticosteroids (e.g. dexamethasone, triamcinolone, and fluocinolone), dexamethasone seems to be the most effective to treat DME, both, from the functional and anatomical viewpoints [19, 20].

Dexamethasone intravitreal implant (Ozurdex®, Allergen, Inc, Irvine, CA, USA), a biodegradable device, is used to release dexamethasone slowly into the vitreal cavity. The chief advantage of this sustained release dexamethasone implant is that the anti-inflammatory action of dexamethasone remains for a period of about four to six months with the peak level of activity during the first two months [18, 21]. A study by Pacella et al (2016) reported a significant reduction of CRT after one (T1), three (T3) ($p < 0.001$) , and four months (T4) ($p< 0.05$) from implants, while at six months (T6), CMT values were not statistically

different from baseline demonstrating that the greatest efficacy of dexamethasone is obtained within the first three months [22]. USFDA had approved the use of dexamethasone intravitreal implant, releasing dexamethasone at a rate of 0.7 mg, for the treatment of DME and noninfectious uveitis affecting the posterior segment of the eye [13, 23, 24].

Ozurdex is effective for phakic and pseudophakic eyes showing inadequate response to anti-VEGF therapy, patients with severe edema, as well as for those who have undergone vitrectomy. Additionally, DME patients with glaucoma can receive corticosteroid treatment; however, intraocular pressure (IOP) needs to be controlled by one or two medications [25]. In addition to retinal thickness assessment, optical coherence tomography (OCT) helps to evaluate potential biomarkers related to other retinal abnormalities, for eg. integrity of outer retinal bands (the ellipsoid zone and external limiting membrane), disorganization of the retinal inner layers (DRIL), presence of hyper-reflective spots and subretinal fluid, that act as predictors of better visual outcome in DME patients administered with dexamethasone implant [26]. Even though dexamethasone intravitreal implant is considered as an effective treatment for DME, there is a scarcity of real-world data regarding the efficacy of this implant in DME patients. The objective of this study was to evaluate efficacy and safety of intravitreal dexamethasone implant (Ozurdex) in management of ME with varied etiology, particularly DME, in real-world clinical practice.

Methods

Study design

This was a retrospective, observational, cohort study based on the data obtained from the medical records of the patients with ME who were administered with dexamethasone intravitreal implant (Ozurdex) for the treatment of ME during 2013 to 2018. The medical records of the ME patients were retrieved from the computer system of Magrabi Eye Hospital, Jeddah, Saudi Arabia and used for analysis.

Inclusion-exclusion criteria

The patients' medical records from 2013 to 2018 were screened to identify patients who(1) were diagnosed with ME; (2) showed sub-optimal response to pan-retinal photocoagulation (PRP) and focal laser treatment or pharmacotherapy (intravitreal anti-VEGF agents, intravitreal triamcinolone, topical or systemic corticosteroids, and non-steroidal anti-inflammatory drugs); and (3) received intravitreal dexamethasone implant. Those who failed to complete the study follow-up of 6 months were excluded.

Data collection

The data related to etiology, comorbidities and previous therapies received by ME patients was collected from Magrabi Eye Hospital.

At baseline, all patients underwent a complete ophthalmologic evaluation including measurement of VA, measurement of CRT using spectral-domain optical coherence tomography (OCT) (Cirrus HD-OCT; Carl Zeiss Meditec Inc. Dublin, Calif., USA), and measurement of IOP. The patients were followed up in first

week of injection and then monthly for next six months and in each visit CRT and IOP were measured. Data collection form was designed in such a way that it captured all the relevant attributes of the patients.

Study outcomes

Primary efficacy outcome measures of the study were change in measurement of CRT, VA, and IOP from baseline to Month 6. Assessment was done in each month's follow-up. The reduction of CRT and improvement of VA following dexamethasone intravitreal implant would indicate its efficacy in the treatment of ME. Increase in IOP is an adverse effect of any corticosteroid treatment.

The secondary endpoints of the study included demographic characteristics of the patients, etiology of the disease, different comorbidities in the patients, and previous therapies for ME.

Statistics

Descriptive statistics were used to summarize patient's demographic and disease related data. Data were analyzed using XLSTAT statistical software for descriptive analysis. Visual acuity measures were converted to logarithm of the minimum angle of resolution (LogMAR) for all statistical analysis. Statistical significance was set at $p<0.05$.

Results

Study Population

There were total 114 patients identified from the electronic medical record (EMR) of the hospital with diagnosis of ME (**Table 1**). Of them, 92 (80.7%) were males and 22 were females (19.3%) with a mean (standard deviation [SD]) age of 55.88 (11.98) years (range 27-80 years). The number of right eyes treated were 63 (55.3%) and the number of left eyes treated were 51 (44.7%). There were 47 patients (41%) with distinct demographics of having differences in lens status7 (6%) had central retinal vein occlusion (CRVO), 9 (8%) had uveitis, and 2 (1.7%) had branch retinal vein occlusion (BRVO) (**Figure 1**). Majority of the ME patients in this study had DM as the etiological factor and were considered to be DME patients. Therefore, this study included 91 DME patients.

Different Therapies for ME

Patients had previously been exposed to a variety of treatments for ME that can be put broadly into two categories - Laser and Pharmacotherapy. The Laser treatment included focal laser and pan-retinal photocoagulation (PRP). PRP was used to treat 35 (30.7%) patients and focal laser photocoagulation was used to treat 61 (53.5%) patients. Pharmacotherapy included anti-VEGF injection, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs). Three (3) different anti-VEGF agents were used for treating ME prior to dexamethasone implant. Sixty-one (n=61) out of 114 (53.5%) patients received aflibercept injection, 50 (43.8%) received bevacizumab, and 25 (21.9%) received ranibizumab injections. Topical

steroids were administered in 38 (33.3%) patients, systemic steroids in 9 (7.8%) patients, and intravitreal triamcinolone acetonide (Kenalog) in 19 (16.6%) patients. Topical NSAIDs were received by 88 (77.2%) patients.

Dexamethasone intravitreal implant

All 114 ME patients, which included 91 DME patients received dexamethasone intravitreal implant and then followed up for next six months. Some patients received second dose of dexamethasone injection on occurrence of edema during the six month follow-up period on PRN basis. It was reported that 23 out of 114 patients (20.2%) and 1 out of 114 (0.9%) patients received the second Ozurdex injection alone or in combination with anti-VEGF, respectively.

Effects of dexamethasone intravitreal implant on CRT, VA, and IOP

Change in mean CRT

The mean CRT at the baseline was about 480 µm. The CRT was reduced to around 320-340 µm in first three months. A slight increase in CRT was observed in Month 4, followed by reduction in months 5^{th} and 6^{th}. Of note, this reduction in CRT was an after effect of the second Ozurdex injection (**Figure 2**). The mean change of CRT was found to be statistically significant ($p < 0.05$) at all time points compared to baseline (**Figure 3**).

Improvement in VA

The pre-treatment VA was 0.92 LogMAR. Following three months of treatment, the mean VA became 0.75 LogMAR, which was a statistically significant ($p = 0.01$) improvement (**Figure 4**).

Change in mean IOP

Mean pre-injection IOP was 15 mmHg. After first week of injection, IOP increased to 18 mmHg (mean change: 3 mmHg), and after Month 1, IOP was 19 mmHg (mean change: 4 mmHg). At Month 2 visit, IOP raised to 21 mmHg (mean change: 6 mmHg) and then IOP was reduced to 18-19 mmHg in Months 3, 4, and 5 (**Figure 5**). At the last visit (6 month follow-up), mean IOP was 16 mmHg (mean change: 1 mmHg). A statistically significant reduction in average IOP ($p<0.05$) was observed with the use of anti-glaucoma medication (**Figure 6**). No long-term increase in IOP was observed in this study.

Anti-glaucoma medication

Before starting dexamethasone implant injection, 37 out of 114 patients (32%) were using anti-glaucoma medication and after treatment, 65 patients (54.4%) were found to use anti-glaucoma medication (**Figure 7**).

Discussion

In the present retrospective observational study, dexamethasone intravitreal implant was administered in 114 ME patients who showed unfavorable responses to other traditional treatment modalities. Most of the ME patients (about 80%, 91/114) suffered from DM, which can be considered as the chief etiological factor for ME. Moreover, DM was the significant systemic comorbidity observed in these patients. The patients received previous treatment with anti-VEGF injection, and laser photocoagulation, without significant improvement in VA and CRT.

For DME patients, intravitreal anti-VEGF monotherapy or in combination with laser photocoagulation, is considered as the first-line treatment owing to high efficacy, minimal side-effects, and ease in administration [20]. However, this therapy may not be effective in all patients; because anti-VEGF drugs can typically reduce the level of free VEGF, but are unable to alter the levels of other pro-inflammatory molecules responsible for vascular permeability. A large multicenter study detected that 32-66% of eyes had persistent edema and lowered VA, even after receiving six monthly anti-VEGF injections [4, 16]. Another study noticed difficulty in treating DME patients with anti-VEGFs, steroids (triamcinolone), focal laser therapy, and PRP [18].

Additionally, anti-VEGF therapy has another limitation. It requires repeated monthly injections and follow-up in the first year of treatment [13]. A review by Kodjikian et al. (2019) detected the mean number of anti-VEGF injections in real life was 4.7, while in randomized controlled trials the mean number of these injections was more than 7. In fact, in real-life it becomes difficult to monitor and inject a diabetic patient on a monthly basis, particularly in the first-year of the DME management [13]. This may account for irregular ophthalmologic monitoring and reduced anti-VEGF administration, thereby affecting treatment outcome [5]. Moreover, laser photocoagulation is known to cause macular scars that can enlarge progressively, leading to secondary vision loss [13].

The second-line of treatment for patients with persistent DME is corticosteroid, since corticosteroids are known to reduce retinal thickening consistently [16]. In a retrospective study, eyes of 45 DME patients when subjected to three doses of ranibizumab injections, showed poor visual response in 66.7% patients and good response in remaining 33.3% patients. Upon switching to dexamethasone treatment, patients with poor response revealed a three-fold improvement in comparison to good visual responders. In addition, treatment with dexamethasone in good responders demonstrated added benefit and further improvement. Thus, dexamethasone treatment was beneficial to both good and poor responders. Therefore, early introduction of intravitreal corticosteroid treatment may result in optimal clinical outcomes in DME patients [27].

Sustained-release dexamethasone implant (Ozurdex) slowly releases dexamethasone for up to six months [28]; thus, the drug becomes available in therapeutic concentrations for a longer time [23]. Hence, frequent dosing requirements of anti-VEGF injections and associated injection-related complications can be reduced [20]. Corticosteroids are known to be effective in long-standing and refractory DME [25]. In the current study, dexamethasone intravitreal implant was administered in ME patients (mostly suffering from diabetes or DME) and followed-up for six months with a significant improvement in CRT and VA.

Similar to this real-life clinical practice data, another real-world study on eyes with early refractory DME (after three monthly anti-VEGF injections) revealed better visual and anatomical outcomes at 12 months when subjected to dexamethasone implant compared to those receiving continuous anti-VEGF treatment [29].

Moreover, this significant benefit was attained early in this study; maximum effectiveness of dexamethasone was observed between Months 1 to 3, when both CRT reduction and VA improvement were highest after which effectiveness gradually declined during Month 4 through Month 6. Results of several studies supported the findings of the present study. A study by Medeiros et al. (2014) detected that a peak effectiveness of dexamethasone implant occurred at Month 3 of the injection when mean foveal thickness (FT) reduction and BCVA improvement were highest [18]. A retrospective real-world study, CHROME indicated that the mean re-injection interval of Ozurdex in DME patients should be between 2.3 to 4.9 months [30, 31]. A randomized clinical trial determined that BCVA and FT of DME patients improved significantly after three months of dexamethasone drug delivery compared to the observational group. However, BCVA improvement was not found to be significant at Month 6 [10]. A study by Chatziralli et al. (2017) detected a significant improvement in VA in Month 1 with a peak in Month 3 after one injection, whereas significant reduction of CRT occurred in Month 1 and then gradually increased till Month 6, when another dose of injection was administered [32]. This observation suggested that it takes much longer for functional outcome (VA) to improve post CRT reduction (anatomical result). This might be because of time required for the restoration of photoreceptors that get damaged as a result of chronic edema-associated morphological changes. In this study, although there was symmetry between the VA and CRT curves, no significant correlation could be drawn between them. Thus, it was postulated that only CRT cannot predict the visual outcome and intraretinal alterations may contribute to this lack of association [32]. Similarly, our study showed significant VA improvement in first three months along with CRT reduction followed by reduction of VA and enhancement of CRT from Months 4 to 6. Some patients even required a second dose of injection after Month 3.

Ozurdex has been found to cause higher VA improvement in DME patients with pseudophakic eyes compared to phakic eyes probably because of no effect on the lens indicating Ozurdex to be more reliable treatment of choice for pseudophakic eyes in DME [32, 33]. In agreement to these findings, our study had higher number of patients with pseudophakic eyes, who had responded well with dexamethasone implant injection.

Although dexamethasone implant showed success in the treatment of DME, the corticosteroids have two most common adverse effects: elevation of IOP and development or progression of cataracts. Due to these safety issues, there was a marked reduction in the use of Ozurdex in the last few years in the developing countries [18]. However, GENEVA study reported the safety profile of Ozurdex and its approval for the treatment of retinal vein occlusion [24]. Moreover, this dose-dependent IOP is transient and reversible with the use of medication [19, 34]. Accordingly, in this study, increase in mean IOP from baseline 15 mmHg to maximum 21 mmHg was observed within two months of dexamethasone intravitreal implant injection, followed by reduction of IOP (16 mmHg) close to the baseline value with the

use of antiglaucoma medication. No serious systemic and ocular adverse effects were detected in the patients receiving dexamethasone intravitreal implant.

In the present study, the anatomical and functional results are consistent with those that showed improvement in VA and CRT with no adverse side effects while assessing the efficacy of dexamethasone intravitreal implant in patients with DME in real-life situations [22, 33, 35-37]. Noteworthy, the efficacy of dexamethasone intravitreal implant reached its peak between months 1 to 3 and then gradually declined from months 4 to 6, when CRT is shown to increase [35].

Limitations

The study has several limitations. Firstly, this study was short-term, single-center, retrospective study because of which it was unable to predict long-term safety and efficacy of intravitreal dexamethasone implant in ME patients. Secondly, there was no control group in the study as treatment-naive patients were not included. Thirdly, the sample size was small. Finally, although it is known that systemic factors, such as hypertension and glycemic hemoglobin level (HbA1c) affect DME; yet no data on blood pressure level and HbA1c was collected during the follow-up.

Conclusions

In conclusion, the current study indicated that dexamethasone intravitreal implant with sustained therapeutic properties can be considered as a valuable treatment modality for ME patients, particularly with diabetes or the DME patients. Dexamethasone implant is effective in reducing CRT and improving VA and decreasing the burden of repeated monthly injections. Intravitreal dexamethasone implant was found to be well tolerated among all the patients studied and its benefits continues approximately through three to four months and then requires administration of second Ozurdex injection alone or in combination with anti-VEGF during the six month follow-up period on PRN basis. Significant treatment-emergent adverse effects were not observed indicating the safety and efficacy of the implant. Additional long-term trials with larger sample size and with administration of multiple dexamethasone injections are required to assess the safety and efficacy of multiple intravitreal injections for a longer period in DME patients.

Abbreviations

ME: Macular edema;; BRB: blood-retinal barrier; DME: Diabetic macular edema; DR: Diabetic retinopathy; VA: Visual acuity; VEGF: Vascular endothelial growth factor; ICAM-1: Intercellular adhesion molecule-1; FDA: Food and Drug Administration; EMA: European Medicines Agency; CRT: Central retinal thickness; IOP: Intraocular pressure; SRF: Subretinal fluid; IS/OS: Inner segment-outer segment; BCVA: Best corrected visual acuity; OCT: Optical coherence tomography; LogMAR: Logarithm of the minimum angle of resolution; DM: Diabetes mellitus; HTN: Hypertension; PRP: Pan-retinal photocoagulation; FT: Foveal thickness; BRVO: Branch retinal vein occlusion; NSAIDs: Non-steroidal anti-inflammatory drugs.

Declarations

Ethics approval and consent to participate: The research followed the tenets of the Declaration of Helsinki and written informed consent was obtained from all the patients. The institutional review board approval was obtained from the Magrabi Eye and ear Hospital prior to the beginning of the study.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Competing interest: The authors declare that they have no competing interests.

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Author's Contribution: Dr. Khairy has contributed the concepts, design, literature search, manuscript preparation and manuscript editing.

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Tables

Table 1: Patient Demographics and disease characteristics**.**

Attributes of patients	N (%)
Number	114
Age: Mean ±SD (Range in years)	55.8 ±11.98 (27-80)
Gender:	
Males	92 (80.7%)
Females	22 (19.3%)
Affected Eye:	
1. OD (Right eye)	63 (55.3%)
2. OS (Left eye)	51 (44.7%)
Lens status (pseudophakic)	47 (41%)
Systemic Co-Morbidities	
1. DM	92 (80.7%)
2. HTN	52 (45.6%)
3. Dyslipidemia	8 (7.0%)
4. Renal	1 (0.8%)
5. Autoimmune	1 (0.8%)
Duration of ME: Mean (Range in months)	6.33 (1-22)
1. Known	18 (15.8%)
2. Unknown	96 (84.2%)

Note: OD indicates oculus dexter (right eye), OS indicates oculus sinister (left eye), DM indicates diabetes mellitus, HTN indicates hypertension, and CME indicates cystoid macular edema.

Figures

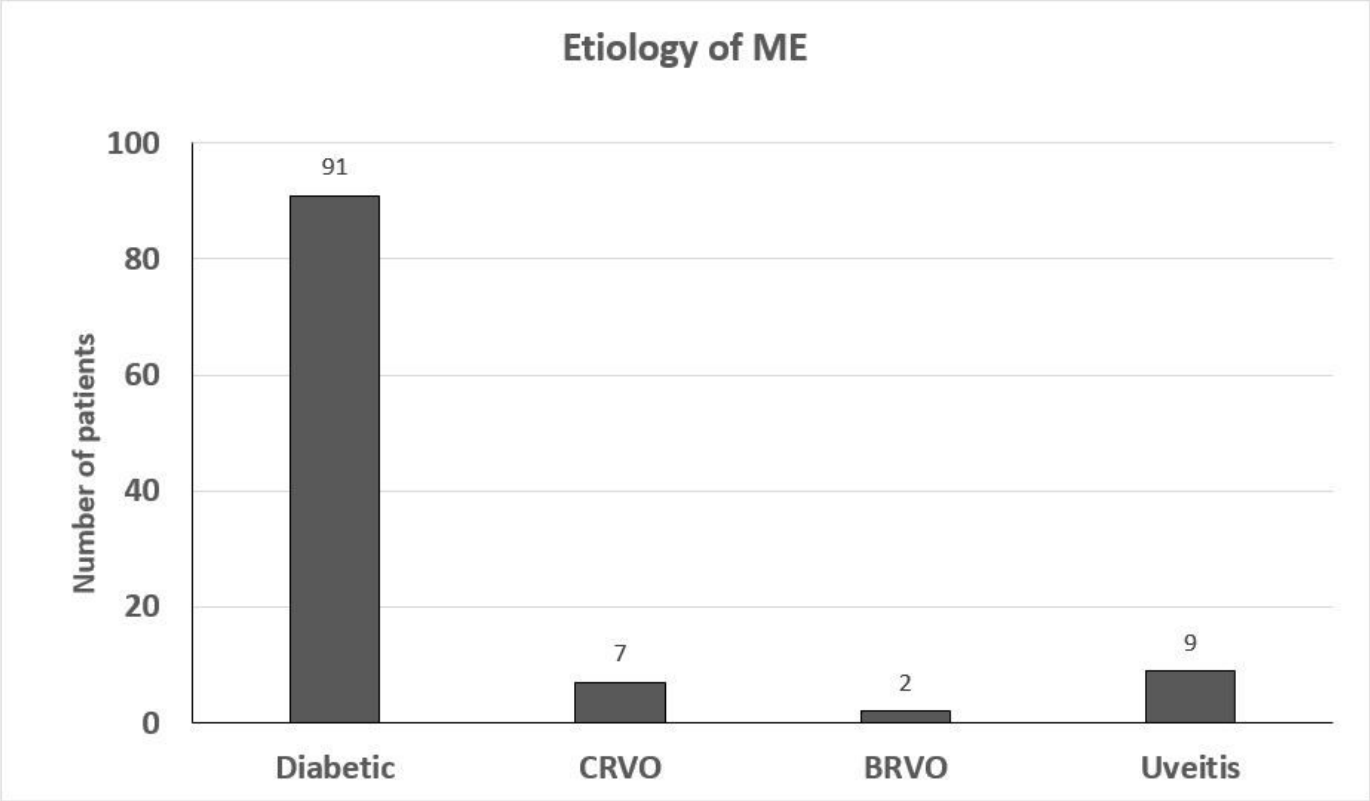

Figure 1

Different etiological factors for ME. Note: ME indicates Macular edema, CRVO indicates Central retinal vein occlusion, BRVO indicates Branch retinal vein occlusion.

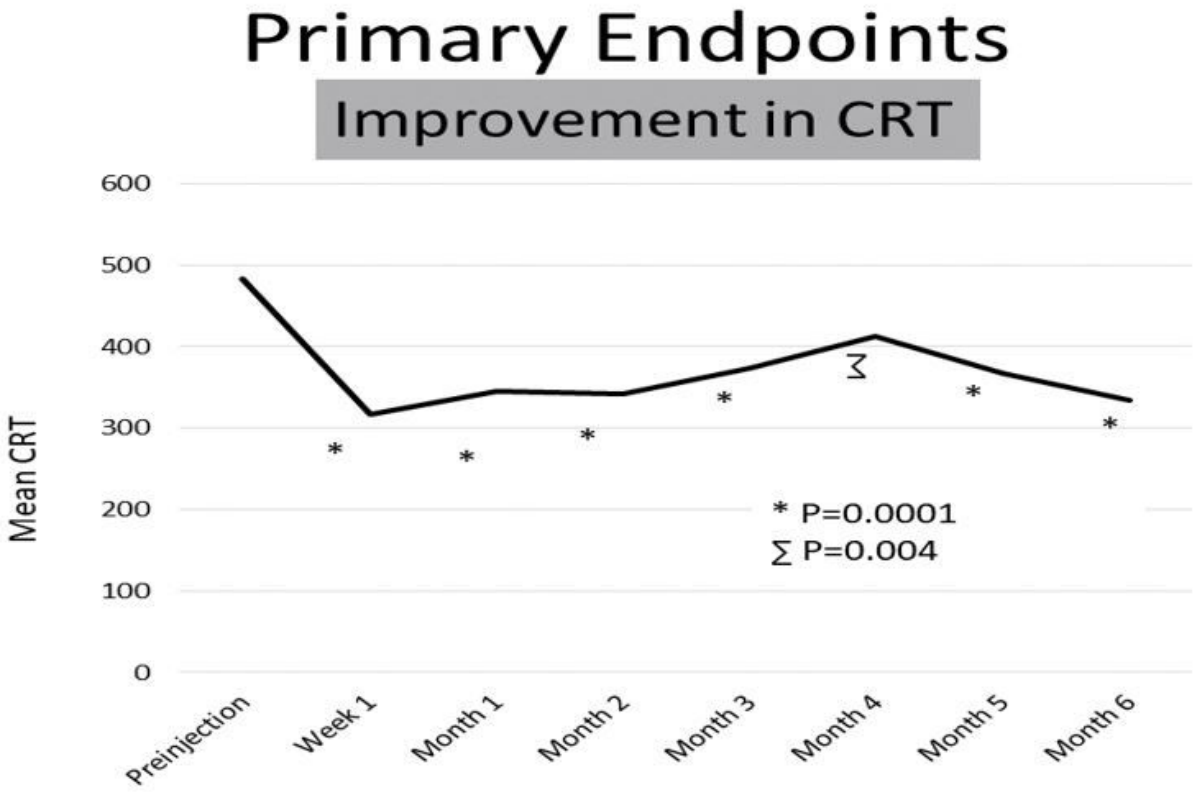

Figure 2

Primary endpoint: Improvement of Central retinal thickness (CRT) with the administration of dexamethasone intravitreal implant from baseline to Month 6 (p=0.0001).

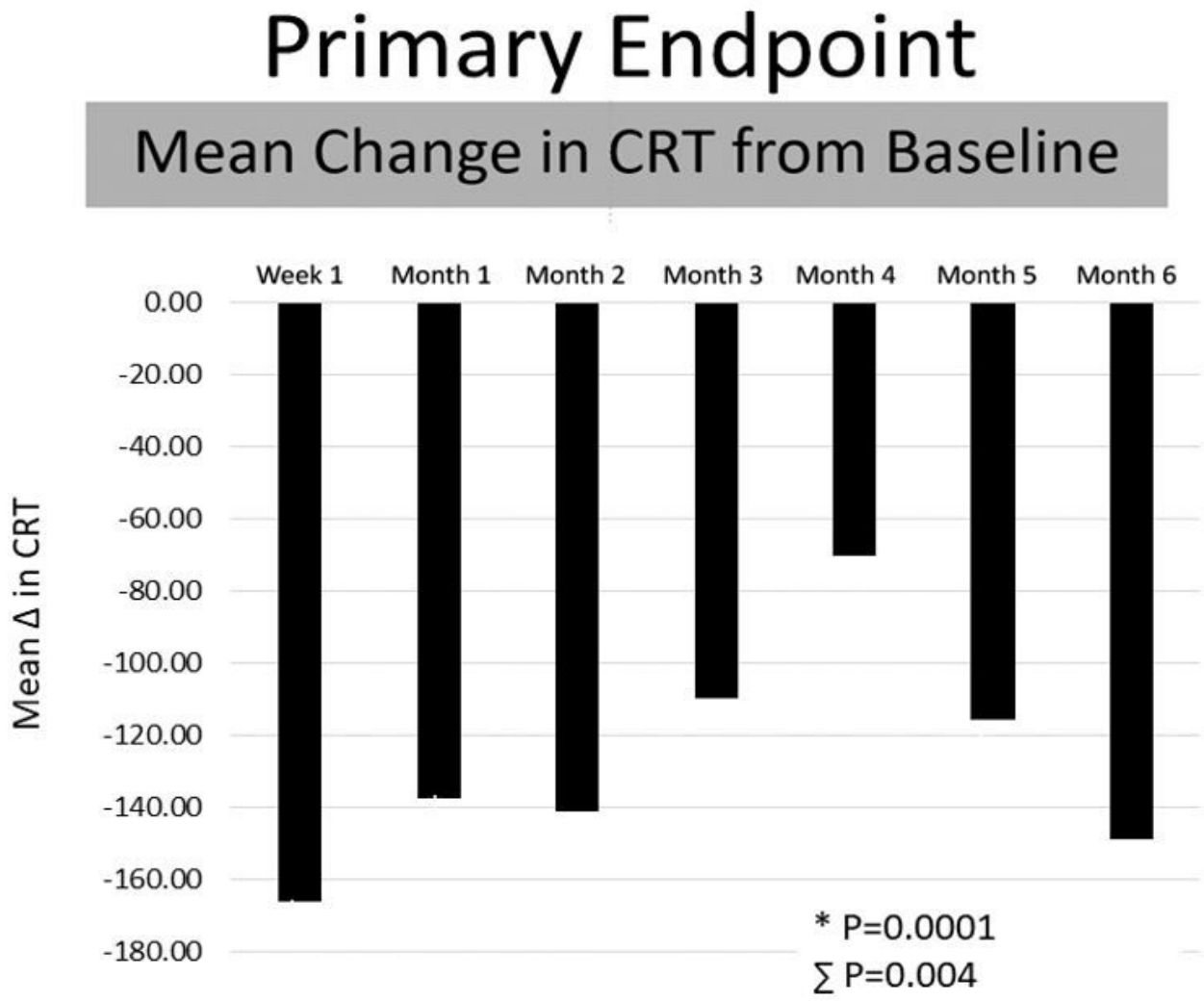

Figure 3

Mean change in Central retinal thickness (CRT) from baseline to Month6 in patients with dexamethasone implant injection.

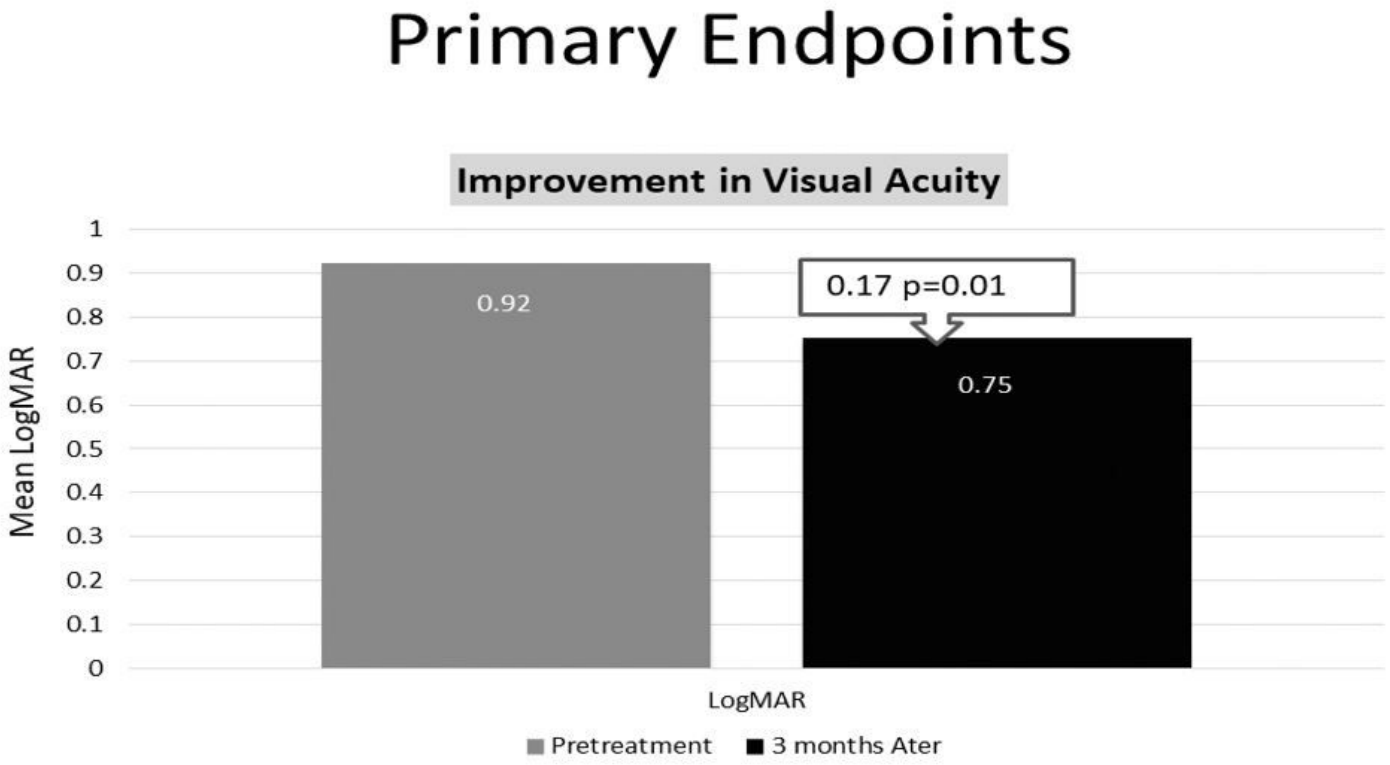

Figure 4

Improvement in Visual Acuity after dexamethasone intravitreal implant.

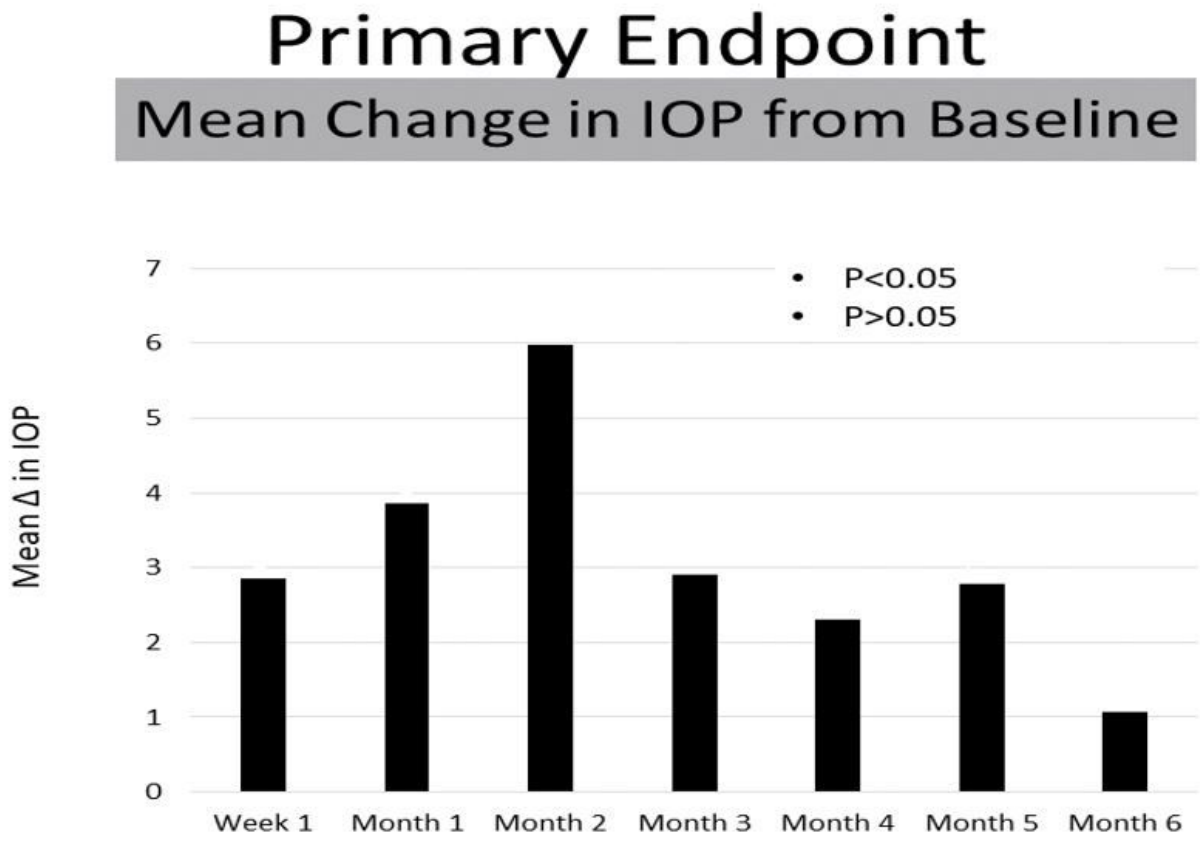

Figure 5

Change in Intraocular pressure (IOP) from baseline to Month 6 after dexamethasone implant injection.

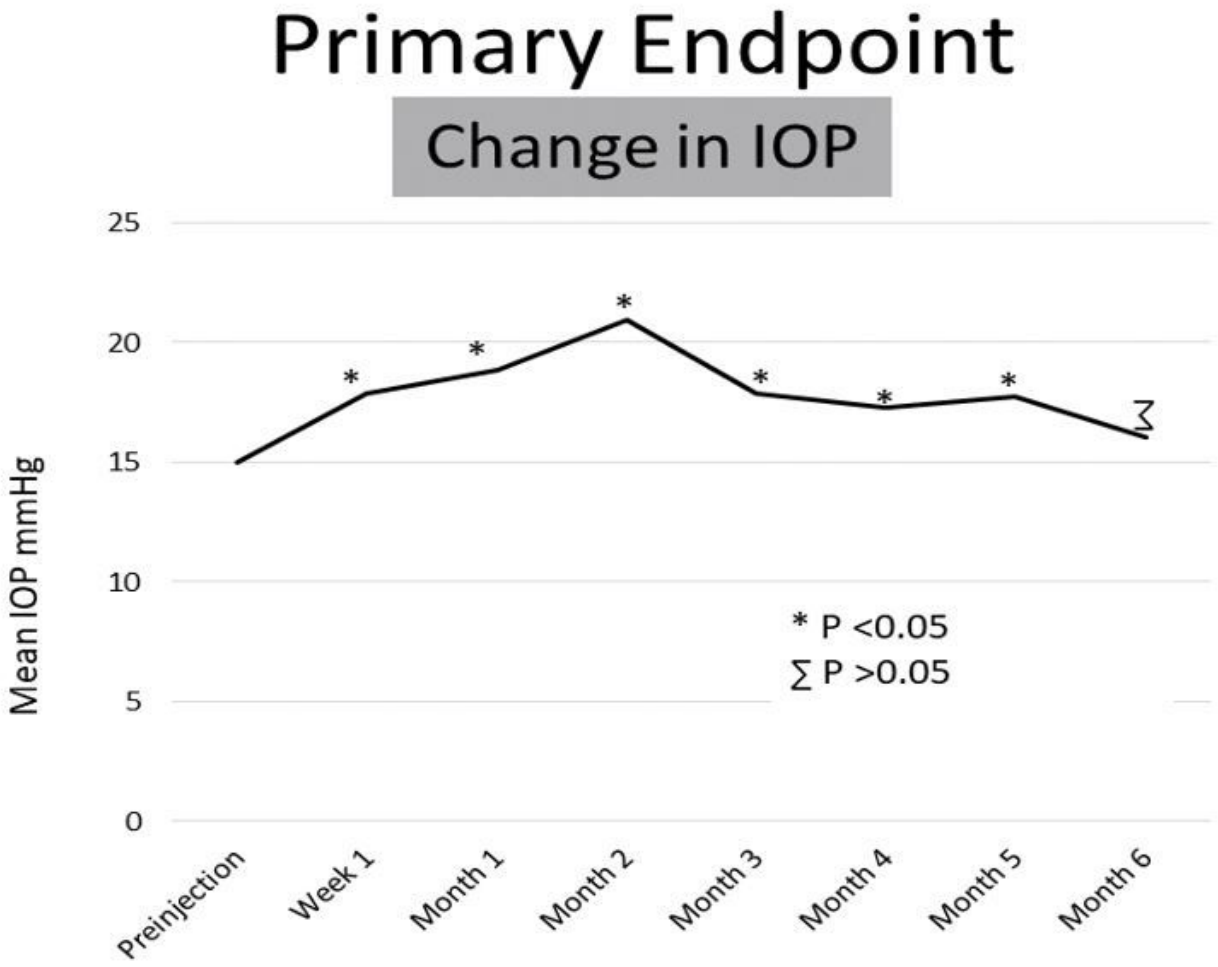

Figure 6

Mean change in Intraocular pressure (IOP) from baseline to Month 6.

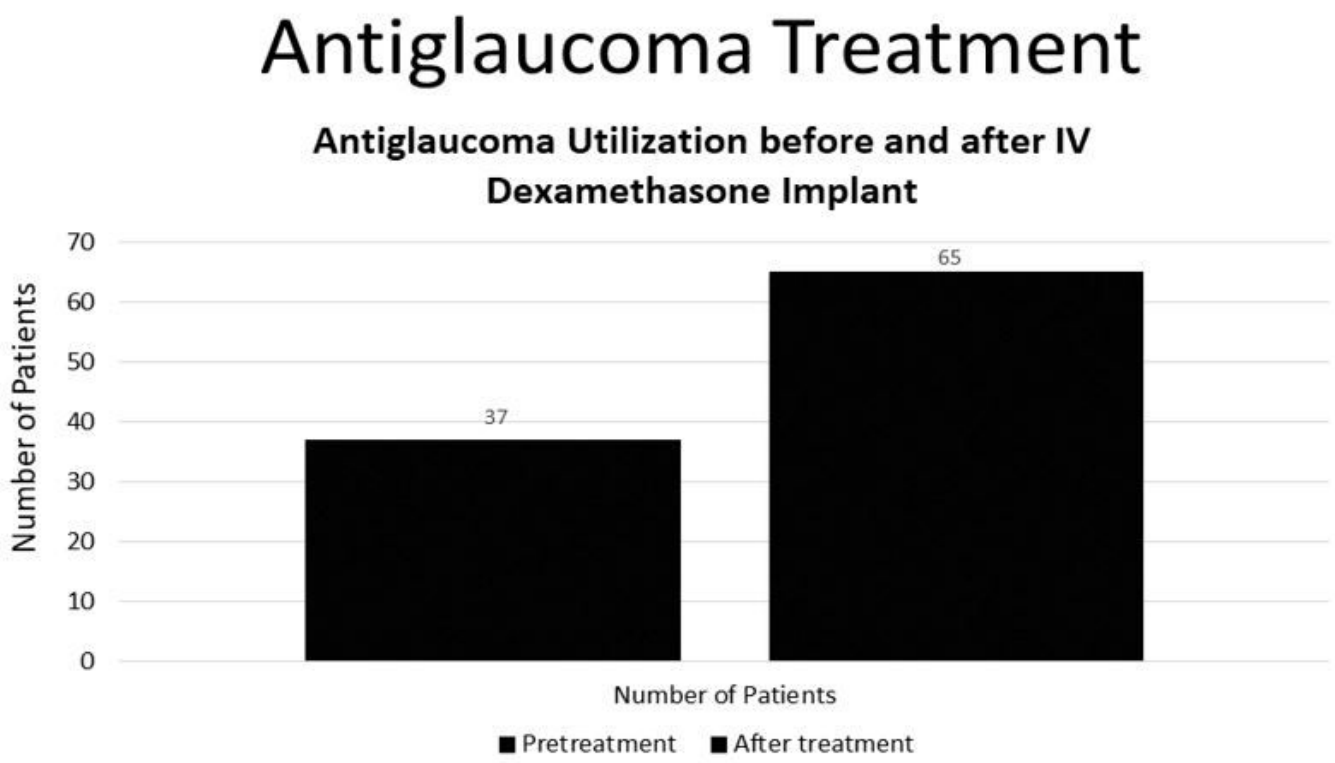

Figure 7

Use of anti-glaucoma medication before and after intravitreal (IV) dexamethasone implant.