

# Intravitreal Dexamethasone Implant in the Treatment of Pseudophakic Cystoid Macular Edema or Irvine-Gass Syndrome

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## ABSTRACT

**Purpose:** To evaluate the effectiveness of intravitreal injections of dexamethasone (DEX) implant in patients with pseudophakic cystoid macular edema (PCME) or Irvine-Gass Syndrome (IGS).

**Material and Methods:** Patients with ME secondary to uncomplicated cataract surgery who underwent single intravitreal injections of DEX implant from January 2015 to January 2017 were retrospectively reviewed. The patients were examined at base-line and day 1, week 1, month 1, 3, 6 and 12 after intravitreal injection. All patients underwent a complete ophthalmic evaluation, including biomicroscopy, best-corrected visual acuity (BCVA), intraocular pressure by applanation tonometry, and central macular thickness (CMT) measurement with a spectral-domain optical coherence tomography (SD-OCT).

**Results:** Nineteen eyes of 18 patients were evaluated. The alteration of mean BCVA and CMT were statistically significantly better than baseline values at first, third, sixth and twelfth months ( $p < 0.001$ ). At 1st week, 1st month and 3rd month intraocular pressure (IOP) values significantly higher than baseline ( $p=0.001$ ,  $p=0.006$ ,  $p=0.001$ , respectively). At 6th month and 12th month IOP values not significantly different at baseline ( $p=0.506$ ,  $p=0.650$ ).

**Conclusion:** Both BCVA and mean CMT had significantly improved from baseline values after treatment with single doz intravitreal DEX implant in patients with IGS.

**Keywords:** Intravitreal Dexamethasone Implant, Irvine-Gass Syndrome, Pseudophakic Cystoid Macular Edema.

## INTRODUCTION

One of the main causes of decreased vision after an uneventful cataract surgery is the pseudophakic cystoid macular edema (PCME) in other words ‘Irvine–Gass syndrome (IGS)’.<sup>1-5</sup> This event usually occurs 4 to 12 weeks after the surgery.

The pathogenesis of the PCME is known to be multifactorial. However, inflammation appears to be the main source of the disease. After surgery, synthesis of inflammatory mediators such as platelet activating factor (PAF), leukotrienes and prostaglandins is stimulated.<sup>3, 5</sup> Thus, the blood-retinal barrier is disrupted and eventually, increased retinal permeability occurs, causing fluid retention within the retina. It shows that a clear consistency of the hypothesis as indicated by the induction of the

macular edema (ME) by the prostaglandin analogues and anti-inflammatory treatments performed in IGS.<sup>6-7</sup>

No randomized studies have been conducted over the last two decades to identify the best therapeutic options for IGS. The current first-line treatment is the off-label use of combination of different treatments that include the oral acetazolamide and the topical administration of non-steroidal anti-inflammatory drugs (NSAIDs).<sup>8-9</sup> The second-line treatment options include the other different off-label therapies; the intravitreal injections of anti-vascular endothelial growth factors (also called anti-VEGF) and steroids such as the triamcinolone (IVTA).<sup>10,11</sup> Intravitreal anti-VEGF and IVTA have not shown convincing results but still, they have been reported by a number of the authors.<sup>10-11</sup>

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Dexamethasone (DEX) is one of the most potent anti-inflammatory corticosteroids that have various proven ocular effects. DEX implants have been approved for the treatment and cure related to ME of retinal vein occlusion along with the posterior segment noninfectious uveitis.<sup>12, 13</sup> Recently, DEX implants have been approved in treatment of persistent ME in the diabetic retinopathy by the Food and Drug Administration.<sup>14, 15</sup> Therefore, the idea of using DEX implants in PCME appears to be convincing.

The main objective of this study is to evaluate the effectiveness of single dose intravitreal injection of DEX implant in patients with PCME.

## **MATERIALS AND METHODS**

Patients with PCME secondary to uneventful cataract surgery who underwent single dose intravitreal injection of DEX implant between January 2015 to January 2017 at a training and research hospital were retrospectively reviewed. The diagnosis of PCME was established by the identification of postoperative cystoid ME with fundus examination, spectral-domain optical coherence tomography (SD-OCT, RT 3000 Nidex) and fluorescein angiography. The main inclusion criterion was the presence of IGS with declined visual acuity (VA) after cataract surgery. Exclusion criteria included complicated cataract surgery, untreated and uncontrolled chronic glaucoma, use of topical prostaglandin analogues before or after cataract surgery, diabetes with or without retinopathy or diabetic maculopathy, periocular or ocular active infection, uveitis, epiretinal membrane, macular vitreoretinal traction syndrome that could prevent the improvement of VA, patients treated for retinal vascular diseases and any other previous intraocular surgery. Patient exposed to intracameral adrenaline injection, usage of iris hooks, and iris trauma during surgery were also excluded from the study group.

A sustained-release DEX 0.7 mg intravitreal implant (IDI; Ozurdex<sup>®</sup>, Allergan, Inc., Irvine, CA, USA), approved by the FDA in 2014, is indicated for retinal vein occlusion, posterior segment uveitis, and diabetic macular edema (DME). In our study, before injection of single dose DEX implant, written informed consent about off label drug use was obtained from all patients. The Local Ethics Committee approved the study protocol. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and all of the participants provided written informed consent.

DEX implant was injected via intravitreal route using its special applicator from the pars plana region, in the operation room under sterile conditions. After the injection, topical antibiotics were given five times a day for one week.

The patients were examined at baseline and on day 1, week 1 and months 1, 3, 6 and 12 after intravitreal injection. All patients underwent a complete ophthalmic examination including biomicroscopy, best-corrected visual acuity (BCVA), intraocular pressure (IOP) by applanation tonometry, central macular thickness (CMT) measurement with SD-OCT. Concomitant ocular findings of the eyes and early anterior and posterior segment findings after cataract surgery were recorded. Topical and systemic medications used consistently and systemic disorders were also recorded. BCVA was measured in Snellen decimals and converted to logarithm of the minimal angle of resolution (logMAR) for statistical analysis.

### *Statistical analysis*

Statistical analysis was conducted with the Number Cruncher Statistical System (NCSS 2007 Statistical Software (Utah, USA)). During the analysis of data, in addition to descriptive methods such as mean, standard deviation, interquartile range, Friedman test was used for comparison of repetitive measurements of multiple groups (different times) and Dunn's multiple comparison test was used for subgroup (different times) analysis. A p value  $p < 0.05$  was considered to be statistically significant.

## **RESULTS**

Nineteen pseudophakic eyes of 18 patients (6 female, 12 male) were evaluated. The mean age was  $63.24 \pm 5.62$  years with a range of 58-74 years. All patients had undergone uneventful phacoemulsification with posterior chamber IOL implantation (in the bag). The mean time period of cataract surgery was  $62.13 \pm 11.78$  day and the mean time period of decreased visual acuity was  $28.11 \pm 8.11$  day. All cases were followed up at least one year after the intravitreal injection. Patient did not have any history of ocular disease and chronic topical ophthalmic medication usage. When patients were questioned for systemic disease history, 7 patients had medically controlled systemic hypertension and 9 patients had anxiety disorders with irregular follow-up. All patients were prescribed topical steroid and antibiotic treatment for three week after cataract surgery. No adverse events were observed in control visits on day 1 and week 1 after cataract surgery.

After the diagnosis of IGS, the patients with  $CMT \leq 399 \mu$  (5 eyes, %26) were treated with topical NSAID and the patients with  $CMT \geq 400 \mu$  (14 eyes, %74) were treated with topical NSAID and oral acetazolamide at least one month. DEX implant was applied as a second-line treatment in 17 patients who failed to respond to topical or topical plus systemic treatments. In addition, 3 doses of intravitreal ranibizumab were injected at 1-month intervals prior to DEX implantation to two eyes with  $CMT \geq 400 \mu$  due to

unresponsiveness to topical plus systemic treatment and a family history of glaucoma. In these two cases, anti-VEGF therapy was switched to DEX implant due to insufficient response to treatment.

The anatomical and functional outcomes of patients were summarized in Table 1, Figure 1 and 2. Regarding these data the mean ± standard deviation (SD) of BCVA (Snellen) was 0.33±0.11 at baseline. The mean BCVA was significantly increased on months 1, 3, 6 and 12 after the DEX injection compared to the baseline values (0.78±0.18; p<0.001, 0.80±0.19; p< 0.001, 0.80 ±0.19; p< 0.001, 0.80 ±0.19; p< 0.001, respectively). The mean CMT was 469.63 ± 28.14 μ before treatment. Compared to

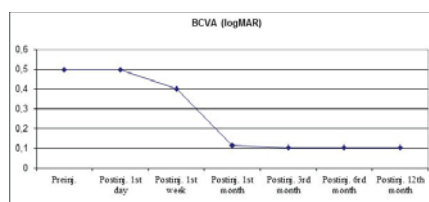
the baseline values, the mean CMT significantly decreased on months 1, 3, 6 and 12 after single dose DEX injection (234.58 ± 21.02; p<0.001, 232.47± 20.44; p<0.001, 230.79± 19.9; p<0.001, 231.05 ± 21.31; p<0.001). BCVA started to increase on week 1. This increase reached to statistically significance values on month 1 and the visual gain maintained throughout the study period (12 months). CMT values decreased significantly on week 1 and reached to the lowest level on month 3 and the decrease maintained for up to 12 months namely during the study period.

Alterations in IOP values are summarized in Table 2 and Figure 3. Regarding these data, the IOP values were decreased significantly on the first day but from the first

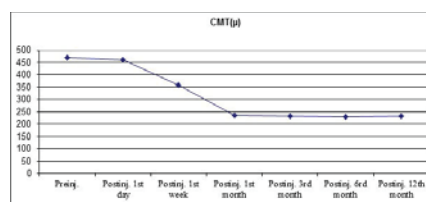
**Table 1. Alterations in BCVA and CMT during follow-up period.**

	BCVA(Snellen) mean ± SD	CMT(μ), mean ± SD
Pre-injection	0.33±0.11	469.63±28.14
Post-injection 1 <sup>st</sup> day	0.33±0.11	462.42±30.94
Post-injection 1 <sup>st</sup> week	0.41±0.12	358.53±39.2
Post-injection 1 <sup>st</sup> month	0.78±0.18	234.58±21.02
Post-injection 3 <sup>rd</sup> month	0.80±0.19	232.47±20.44
Post-injection 6 <sup>th</sup> month	0.80 ±0.19	230.79±19.9
Post-injection 12 <sup>th</sup> month	0.80±0.19	231.05±21.31
<i>P value</i>	<i>p&lt;0.001</i>	<i>p&lt;0.001</i>

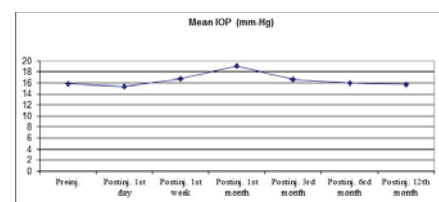
*BCVA: best corrected visual acuity, CMT: central macular thickness, p: significance level of intra-group analysis*



**Figure 1.** Alteration in BCVA during study period (BCVA: best corrected visual acuity, preinj: pre-injection, postinj: post-injection).



**Figure 2.** Alteration in CMT during study period (CMT: central macular thickness, preinj: pre-injection, postinj: post-injection).



**Figure 3.** Alteration in IOP during study period (IOP: intraocular pressure, preinj:pre-injection, postinj: post-injection).

**Table 2. Alterations in IOP during follow-up period**

	Mean IOP (mm-Hg)	p value
Pre-injection	15.89±0.66	
Post-injection 1 <sup>st</sup> day	15.32±0.95	0.01
Post-injection 1 <sup>st</sup> week	16.79±0.79	0.001
Post-injection 1 <sup>st</sup> month	19.00±4.38	0.006
Post-injection 3 <sup>rd</sup> month	16.68±0.48	0.001
Post-injection 6 <sup>th</sup> month	16.05±0.85	0.506
Post-injection 12 <sup>th</sup> month	15.79±0.85	0.650

*IOP: Intraocular pressure, P value: significance level of intra-group analysis*

week to month 6, the IOP values were higher than the baseline values. On week 1 and months 1 and 6, IOP values were significantly higher compared to the baseline values ( $p=0.001$ ,  $p=0.006$ ,  $p=0.001$ , respectively). Mean IOP levels showed no significant difference on months 6 and 12 compared to from baseline values ( $p=0.506$ ,  $p=0.650$ , respectively). The highest IOP values were recorded at first month of the treatment. Topical anti-glaucomatous therapy was initiated to 3 eyes (15.7%) due to an elevation of IOP  $\geq 22$  mmHg at the first month. Topical timolol + dorzolamide combination was applied in a patient with intraocular pressure value of 28 mmHg, while the other two eyes with the IOP levels of 22-27 mmHg received only topical brinzolamide medication. Topical anti-glaucomatous drops were stopped when the IOP levels returned to the normal values on month 6 in all 3 patients.

A significant pigment discharge was observed in the anterior chamber of 1 patient after injection. The anterior chamber was cleaned in 5 days without any treatment. In 3 cases (15.7%), a thin epiretinal membrane developed which did not affect the visual acuity. There was no recurrence of macular edema in any patient.

## DISCUSSION

While the spectacular advances in cataract surgery, macular edema may develop even in patients undergoing uncomplicated cataract surgery. Once it is developed after cataract surgery, there are limited treatment choices; for example, application of topical steroids, topical NSAIDs and systemic acetazolamide.<sup>8,9</sup> Here, we studied the effect of a single dose intravitreal DEX implant on the 19 eyes of 18 patients with ME developed after uncomplicated cataract surgery and found out that DEX implant has positive effects on BCVA and CMT despite mild side effects such as transient IOP elevation.

Nowadays, there are no sound evidence-based guidelines available for PCME therapy. For the reason that it can cause permanent damages to macula despite healing spontaneously, it might decrease the visual acuity continually. The current first-line treatment of PCME is the combination of oral acetazolamide and the topical administration of NSAIDs.<sup>16, 17</sup> There are certain side effects of using the systematic therapy with acetazolamide, such as asthenia, formication, cramps and renal colic, all which might create compliance issues for the patients.

Repeated courses of the topical therapy and the observation might become quite troublesome for active individuals. VEGF is released during the surgical procedures, and it can be inhibited by using the intravitreal injection of anti-VEGF. Many publications have shown the positive impacts

of using bevacizumab (Avastin, Genentech) or ranibizumab (Lucentis, Novartis) for treating IGS.<sup>11</sup> These drugs have shown positive anatomical and functional benefits in these studies with a small sample size, however, this improvement can be achieved by several intravitreal anti-VEGF injections. In our study, no significant improvement in ME was noted in participants that use topical NSAIDs alone or in combination with oral carbonic anhydrase inhibitors. In addition, we did not experience regression of ME in 2 cases when we administered intravitreal 3-dose ranibizumab as second-line treatment.

There are some postulated hypotheses about the development of ME after cataract surgery.<sup>5,6,7,18</sup> The most relevant hypothesis within the physiopathological context is that the inflammatory mediators cause an inflammatory response when they are released during and after the surgery.<sup>6,18</sup> This causes a disruption in the blood-retinal barrier.<sup>6,18</sup> The release of the arachidonic acid is blocked by the corticosteroids and they may have a potential therapeutic role in the treatment of IGS. Corticosteroids can also act on VEGF and interleukins to help resorption of ME. Intravitreal injections of the triamcinolone (IVTA) for treatment of IGS in three cases have been attempted by Benhamou et al.<sup>19</sup> and revealed successful results. However, they have also reported that relapse was seen in two cases of ME in the first 6 months despite two injection of IVTA. Intravitreal triamcinolone has some disadvantages such as a shorter duration of action and some side effects containing increase in IOP, floater-like symptoms and sterile endophthalmitis.

The DEX implant is a biodegradable intravitreal implant which delivers 700  $\mu\text{g}$  of the corticosteroid dexamethasone into the vitreous and the retina. The benefits of using DEX implant in the treatment of 9 PCME patients were shown by Dutra Medeiros et al.<sup>20</sup> In this study, they stated that significantly improvement in CMT and VA has been obtained with a single dose of DEX implant during follow-up of six months. These results were in agreement with those reported by Bellocq et al.<sup>21</sup> showing a decrease in the CMT and improvements in the VA in a study of 50 patients. In this study, 49% of patients had received a second injection within 12 months and similar anatomical and functional response and safety profile was demonstrated with the first injection of DEX implant in these patients.<sup>21</sup> The anatomical and the functional effectiveness was observed in our study with a single dose of intravitreal DEX implant. A significant improvement in BCVA and a decrease in CMT was achieved by month 1 and maintained up to months 3, 6 and 12.

The IOP elevation is the common side effect of DEX implants and it can be controlled by the use of local anti-

glaucomatous therapy with up to 3 agents.<sup>22</sup> Three eyes of the patients (15.8%) showed an increase in IOP, which was controlled by topical anti glaucomatous treatments. In all of these cases, the treatments were discontinued due to measurements of the normal IOP level during the controls. No endophthalmitis or iatrogenic retinal detachment was observed during follow-up.

An increase in inflammatory mediators is seen after cataract surgery, which may be due to local surgical stress. Consequently, we were cautioned that we had panic attacks in half of our patients suggesting that systemic factors may also affect this condition. As it is well known, stress causes an increase in adrenaline-noradrenalin and cortisol release by activating the adrenomedullary system and hypothalamic-pituitary-adrenocortical (HPA) axis. Negative emotional reactions prevent the HPA axis working properly. Particularly, stress causes a decrease in cortisol secretion by HPA desensitization and thus induces an increase in the number of inflammatory cytokines.<sup>23,24</sup> Panic attack, a stress disorder, disabling several metabolic functions in affected patients may contribute to inflammation that causes ME.<sup>23,24</sup> It is also important to remember that every patient may experience a surgical stress similar to a panic attack at some point. Though there is no predisposing factor for PCME in our study, the fact that 50% of our cases are panic attacks with irregular treatment may have a role in the development of ME. Thus, a good investigation of the panic attack and other systemic factors with broader prospective studies may enlighten the systemic risk factors and their prophylaxis of PCME.

The limitation of this study is the small sample size and there has also been a lack of comparative arm for this study. The adverse effects such as vitreous hemorrhage, retinal detachment, and endophthalmitis could not be detected due to the small size of the sample.

## CONCLUSION

The use of intravitreal injection of the DEX implant could be a good alternative treatment for IGS according to the results of our study. Even a single dose application, it reduces CMT and improves VA in patients with IGS and prevents its recurrence for up to one year with a good safety profile.

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