EFFECT OF INTRAVITREAL DICLOFENAC ON DIABETIC MACULAR EDEMA WHICH UNRESPONSIVE TO INTRAVITREAL BEVACIZUMAB

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ABSTRACT

Background: Diabetic retinopathy (DR) is the leading cause of blindness in working-age persons around the world. Visual impairment is the most commonly a consequence of diabetic macular edema (DME). The cause of DME is multifactorial. Blood vessel damage, vascular dilatation, inflammatory changes, increase in expression of ICAM-1 (intercellular adhesion molecule 1). Optical coherence tomography (OCT) has become the gold standard used to objectively assess and quantify DME, central macular thickness (CMT) is the most common OCT measurement used for comparative purposes in recent clinical trials. Objective: To evaluate the effect of intravitreal diclofenac in patients with diabetic macular edema which unresponsive to intravitreal bevacizumab.

Material and Methods: In this non comparative case series 14 eyes of 13 patients with diabetic macular edema which unresponsive to 3 intravitreal bevacizumab injections. All patients received intravitreal diclofenac 500 µg/ 0.1 mL into vitreous in the operation room via pars plana. Pre and post injection values of intraocular pressure (IOP), best corrected visual acuity (BCVA) and CMT (central macular thickness) were compared after injection at 3 months. Results: The mean age of 13 (7 female, 6 male) patients was 62.6 ±10.2 years old. Pre and post injection mean BCVA were 1.03 ± 0.59; 1.18 ± 0.55 logarithm of the minimum angle of resolution (logMAR), (p= 0.146), respectively. Pre and post injection mean values of CMT were 431 ± 71 µm; 397 ± 110 µm (p= 0.161), respectively.
**Conclusion:** Intravitreal diclofenac has no significant effect on visual acuity and central macular thickness in patients with diabetic macular edema which unresponsive to 3 intravitreal bevacizumab injections.

**Key words:** central macular thickness, diabetic macular edema, intravitreal diclofenac.

**INTRODUCTION**

Diabetic retinopathy (DR) is the leading cause of blindness in working-age persons around the world. Diabetic retinopathy can be categorized into two broad groups. Group 1: nonproliferative diabetic retinopathy (NPDR), group 2: proliferative diabetic retinopathy (PDR). Within NPDR, retinopathy classified as mild, moderate, and severe. In a recent meta analysis of 35 population-based studies pooling data from the USA, Europe, Asia, and Australia found that in individuals with Diabetes mellitus (DM) the prevalence of any type of DR is 35 %, with diabetic macular edema (DME) present in 7.5 % and PDR present in 7.2 % of individuals. DME is secondary to breakdown of blood-retinal barriers. Center involving diabetic macular edema (ciDME) is also now commonly used to describe DME in which the central macula is involved. Visual impairment is the most commonly a consequence of diabetic macular edema.

Diabetic macular edema occured secondary to blood vessel damage, vascular dilatation, inflammatory changes, increase in expression of ICAM-1 (intercellular adhesion molecule 1).

More recently, optical coherence tomography (OCT) has become the gold standard used to objectively assess and quantify DME, central macular thickness (CMT) is the most common OCT measurement used for comparative purposes in recent clinical trials. Laser photocoagulation and pharmacological intravitreal agent injection are modalities of the treatment in patients with macular edema.

The goal of focal macular laser photocoagulation is preservation of VA and prevention of severe VA loss ( 3 snellen lines) over the long term. Visual acuity gains from focal laser treatment are frequently modest.

Pharmacological intravitreal treatment for DME included corticosteroids, anti-vascular endothelial growth factor (VEGF) agents and recently diclofenac. Main outcomes of this study were evaluated in IOP, BCVA and CMT.
MATERIALS AND METHODS
All patients who had central involved diabetic macular edema which did not resolved despite 3 intravitreal bevacizumab (IVB) injections. Bevacizumab injection (1.25 mg/0.05 mL) was performed with one month intervals. All patients had type 2 diabetes mellitus. The patients with retinal vein occlusion, optic atrophy, ischemic maculopathy were excluded. The injections were performed after the lid speculum inserted, povidone-iodine 5% were instilled and irrigation with saline solution, 500 µg/0.1 mL diclofenac injected inferior temporal area at 3.5 mm from the limbus used a 27 gauge insulin needle in the operating room. Topical antibiotic drop 4x1/day for 7 days used after injection in all patients. Measurements of IOP, BCVA and CMT was recorded after 1 month last IVB injection and after 3 months intravitreal diclofenac (IVD) injection. All procedures were performed in accordance to declaration of Helsinki. Approval of the local ethic committee was obtained and all patients gave written consent form. Paired t test was used for comparison of pre and after injection values of intraocular pressure (IOP) best corrected visual acuity [(BCVA), in logarithm of the minimum angle of resolution: logMAR)] and central macular thickness (CMT). A p value <0.05 was considered statistically significant.

RESULTS
This study included 14 eyes of 13 (female: 7, male: 6, mean age: 62.6±10.2 years, range: 39-75). Mean glycosylated hemoglobin (HbA1c) was 7.2 ± 1.3. Follow up time period was 2.9 ± 0.1 month after intravitreal diclofenac injection (Table 1). Mean BCVA was 1.03 ± 0.59 logMAR before IVD injection, mean BCVA was 1.18 ± 0.55 logMAR after injection at 3 months (p=0.146). Mean CMT was 431 ± 71 µm before injection and 397 ± 110 µm after IVD injection (p= 0.161), (Table 2). BCVA improved in 3 (21.4 %) eyes, did not change in 6 (42.8 %) and decreased in 5 (35.7 %) eyes.

Table 1: The values of age, gender and follow up time

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (mean ± SD)</td>
<td>62.6 ± 10.2 (39-75)</td>
</tr>
<tr>
<td>Gender (female/man)</td>
<td>7/6</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.2 ± 1.3</td>
</tr>
<tr>
<td>Follow up time (month)</td>
<td>2.9 ± 0.1</td>
</tr>
</tbody>
</table>

SD: Standard deviation, HbA1c: glycosylated hemoglobin
Table 2: The measurements of pre and after IVD in BCVA, CMT and IOP.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Preinjection (mean ± SD)</th>
<th>Post injection (mean ± SD)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA (logMAR)</td>
<td>1.03 ± 0.59</td>
<td>1.18 ± 0.55</td>
<td>0.146</td>
</tr>
<tr>
<td>CMT</td>
<td>431 ± 71</td>
<td>397 ± 110</td>
<td>0.161</td>
</tr>
<tr>
<td>IOP</td>
<td>15 ± 3.2</td>
<td>15.8 ± 3.0</td>
<td>0.999</td>
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</table>

*Paired t test. BCVA: best corrected visual acuity. logMAR: logarithm of the minimum angle of resolution. CMT: central macular thickness. IOP: intraocular pressure, SD: Standard deviation

DISCUSSION
Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed classes of medication. Because they are potent inhibitors of cyclooxygenase (COX) enzymes, they reduce the synthesis of pro-inflammatory prostaglandins (PGs). [13] COX enzymes are an active component of inflammatory process. PGs cause vasodilatation and increase vascular permeability with the disruption of blood-ocular barrier with leucocyte migration and therefore edema formation. [14] Diclofenac sodium is an NSAID which blocks cyclooxygenase and lipoxygenase pathways. [15] There are several studies that reported the results of intravitreal diclofenac (IVD) in the literature. [16,17,18,20] Intravitreal diclofenac injection did not significant changes in electroretinography. [17] Diclofenac at a dose 500 µg was non toxic on the rabbit eye based on electroretinographic and histologic studies. [18] Also was found non toxic in human eyes. [17]

We aimed to report the results of patients who unresponsive to 3 intravitreal bevacizumab injections and received 500 µg/0.1mL IVD for diabetic macular edema.

A study reported that IVD can obtain significantly reduced CMT but not improvement in VA in uveitic cystoid macular edema. [16] An other study found that IVD has no significant effect on CMT and VA in patients with macular edema. [19] Significant effect of IVD on diabetic macular edema was reported in a study, [20] but our results was not similar with this study. Optic atrophy was observed in one eye after IVD. Changes in IOP was not significant in this case series. Endophthalmitis, intravitreal hemorrhage, and retina detachment were not observed.
CONCLUSION
Intravitreal diclofenac injection did not significant changes in BCVA, CMT and IOP in patients with DME that unresponsive to intravitreal bevacizumab injection. This study has some shortcomings such as small number of patients, lack of control group and electroretinography.

Conflicts of interest
The authors have disclosed no potential conflicts of interest, financial or otherwise.

REFERENCES


