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Original Article

Intravitreal diclofenac versus intravitreal bevacizumab in persistent diabetic macular edema: Anatomical and functional outcome

Amal ElBendary *; Amr H. Elkannishy

Abstract

Purpose: To compare the efficacy of diclofenac versus bevacizumab following single intravitreal injection in eyes with persistent diabetic macular edema.
Methods: Fifty eyes with persistent DME were randomly allocated to intravitreal injection of 500 μg/0.1 ml of diclofenac ($N = 20$) or 1.25 mg/0.05 mL of bevacizumab ($N = 20$) or to non-treatment (10 eyes). Preoperative and postoperative visual acuity, central, paracentral macular thickness and intraocular pressure (IOP) were recorded and compared between the three groups up to 4 weeks.
Results: Diclofenac and bevacizumab groups showed statistically significant reduction in central and paracentral macular thickness (diclofenac: $p = 0.006$, 0.02 and bevacizumab: $p = 0.02$, 0.01), without statistically significant difference between the two groups. The two groups showed no statistically significant difference in mean visual acuity or mean line improvement. Mean visual acuity improvement didn't reach statistical significance in either group. Diclofenac group showed statistically significant reduced IOP ($P = 0.02$). Control eyes did not show any change in mean visual acuity, macular thickness or IOP.
Conclusion: In persistent DME, diclofenac has a structural effect comparable to bevacizumab on central macular thickness. However, significant functional gain may not be accomplished by single injection. Unlike naïve DME, persistent cases may be confounded by systemic and local factors necessitating repeated injection of diclofenac.

Keywords: Bevacizumab, Diabetic macular edema, Diclofenac, Intravitreal injection

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Introduction

Inhibitors of angiogenesis have become the mainstay in the management of diabetic macular edema.[1] The Diabetic Retinopathy Clinical Research Network (DRCR.net) study found that intravitreal injection of anti-VEGF in patients with center involving DME plus deferred or prompt focal/grid laser photocoagulation is superior to focal/grid laser alone at 1-year.[2] Patients receiving intravitreal injection had significantly improved visual acuity compared to either sham, laser photocoagulation or observation as documented by different studies including RISE and RIDE, LUCIDATE and BLOT.[3–5]

The pathogenesis of diabetic retinopathy is multifactorial. The main mechanism is disruption of the blood-retinal barrier and increased vascular permeability. Other factors implicated

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Mansoura Ophthalmic Center, Mansoura University, Egypt

* Corresponding author at: Mansoura Ophthalmic Center, Gomhoria Street, Zip code: 35516, Mansoura, Egypt. Fax: +20 2256104.
e-mail address: amal_elbendary@mans.edu.eg (A. ElBendary).

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in the pathophysiology of the disease include inflammation and ischemia.[6]

Systemic factors including hyperlipidemia, higher systolic blood pressure, renal dysfunction, and higher HbA1c may further complicate the underlying pathology and exaggerate the clinical picture.[7,8]

Because prostaglandins are inflammatory mediators, they have become targets for potential therapy.[9] Non-steroidal anti-inflammatory drugs (NSAID) are potent inhibitors of prostaglandins (PGs) synthesis by suppression of the arachidonic acid transformation.[10]

The role of non-steroidal anti-inflammatory drugs in the management of different types of macular edema had been reported with both topical and intravitreal preparations[11–14] Diclofenac 0.1% (Novartis Ophthalmics, Duluth, GA), an aryl acetic acid derivative, is FDA approved for reducing inflammation after cataract surgery and decreasing pain after refractive surgery.[15] Bromfenac may be more potent as an inhibitor of COX-2 than diclofenac,[16] but this finding has not been consistently reported. In addition, the relative importance of COX-1 versus COX-2 inhibition in ocular disease remains unproven.[17]

To a lesser extent, the role of NSAID in diabetic macular edema has been evaluated in a limited number of clinical studies. Initial results using intravitreal diclofenac showed that it has a promising outcome.[18,19] But contradiction still exists about its effect on macular thickness, visual acuity and intraocular pressure level (IOP). In addition, studies on persistent cases of DME are scarce. The aim of this work is to compare the efficacy of diclofenac versus bevacizumab following single intravitreal injection in eyes with persistent diabetic macular edema.

Patients and methods

This prospective interventional controlled study included fifty eyes of 46 patients presented with persistent diabetic macular edema. The study was approved by the institutional review board of faculty of medicine, Mansoura University, code number: R/17.05.07.36. Eyes were randomized to receive either intravitreal diclofenac (the product is not labeled for use and is still investigational), intravitreal bevacizumab (FDA approved for colorectal carcinoma) or receive no treatment serving as a control group. Informed consent was obtained from all patients after explanation of the nature and possible consequences of the study following all the guidelines required by the institutional review board of ethical committee. The study followed the tents of the Declaration of Helsinki.

Inclusion criteria: All diabetic eyes with clinically significant macular edema associated with diffuse or focal thickening involving fovea were included in the study. Persistent macular edema was defined as one or more of the following: eyes receiving previous intravitreal injection and or laser photocoagulation with no favorable response, chronic macular edema of more than 6 month duration, coexistent systemic disease (hypertension, hyperlipidemia and or renal dysfunction), poorly controlled hyperglycaemia with HBA1C > 7 mg/dL, patients with history of non-compliance to systemic and or ocular therapeutic regimen.

Exclusion criteria: macular edema induced by tangential traction of epiretinal membrane, history of previous vitreoretinal surgery, elevated IOP, patients with vitreomacular traction, eyes with ischemic maculopathy on fluorescein angiography. All patients underwent a complete ophthalmic examination including best corrected visual acuity (BCVA), IOP, slit lamp biomicroscopy, fundus photography, and fluorescein angiography. Spectral domain optical coherence tomography (3D- OCT2000, Topcon Corp, Tokyo, Japan) was used to measure foveal (central macular thickness), parafoveal (paracentral macular thickness) and perifoveal regions. Scans were used to evaluate the condition of the posterior vitreous face and the degree of photoreceptor integrity (detected by OCT as continuity, interruption or destruction of inner segment/outer segment junction). On OCT, diffuse thickening was defined as thickening of the foveal (central) and 4 parafoveal (paracentral) regions; corresponding to OCT thickening within 1 mm and 3 mm circles diameter respectively, centered on the fovea. Focal thickening was defined as thickening of the foveal and <4 parafoveal regions. Thickened foveal and parafoveal zones exceeding the age, sex, and race-matched database are highlighted by the machine software in pink (corresponding to $\geq$280 μ and 300 μ respectively).

Ten eyes served as control, while forty eyes were randomly allocated to one of the following treatment modalities: intravitreal injection of 500 μg/0.1 ml of commercially available diclofenac preparation originally prescribed for systemic use (Voltaren, Novartis Pharma AG., Basle, Switzerland) (group 1: $N = 20$) or intravitreal injection of 1.25 mg/0.05 mL of bevacizumab [Avastin; Genentech, Inc., South San Francisco, CA, USA) (group 2: $N = 20$). Diclofenac is available in 75 mg/3 ml. After aspiration of 1 ml (containing 25 mg), 4 ml of distilled water was added. Therefore, each I ml contains 5 mg diclofenac. Then 0.1 cc containing 500 μg of diclofenac was injected intravitreally.

Technique of injection

All maneuvers were done under complete aseptic conditions in the operating room with an operating microscope. After application of topical anesthetic, 5% povidone-iodine was applied to the periocular area, eyelids, eyelashes and conjunctival sac.

Patients received either drug; 0.1 cc diclofenac (500 μg) or 0.05 bevacizumab (1.25 mg). Injection into the vitreous cavity was performed via pars plana approach, 4 mm posterior to the limbus in the inferotemporal quadrant using a 27- gauge needle. Immediate compression was applied at the site of injection using a sponge to avoid reflux. Following the injection, a topical antibiotic drops as well as an ointment were applied, and the eye was patched overnight. All patients were prescribed topical antibiotic eye drops for one week. Subjects were followed up at one day, one week, 4 weeks after intravitreal injection. After one day and one week, patients were examined for visual acuity, IOP, evidence of infection or uveitis and possible complications. At week 4, BCVA was measured and post-injection imaging with OCT was done. Any increase in BCVA $\geq$ 1 Snellen line was considered an improvement. Follow up was limited to 4 weeks considering the maximal therapeutic effect of bevacizumab.

Statistical analysis was done using (SPSS v16 Inc., Chicago, IL, USA). Wilcoxon Signed Rank test was used for within-group comparison. For comparison between groups,

one-way ANOVA test was used for numerical variables. A 95% confidence level was set for all tests.

The primary outcome measure was a reduction in central, paracentral macular thickness and improvement of visual acuity. Pretreatment characteristics, as well as post injection BCVA, central and paracentral macular thickness, were compared between the diclofenac, bevacizumab and control groups.

Results

Fifty eyes of 46 patients with persistent DME were included in the study. The mean age was 58.3 years (range: 23–68 years) Thirty-one were females and15 were males. Forty eyes received either diclofenac or bevacizumab, while 10 eyes served as control. All eyes were followed up for 4 weeks to detect any change in best corrected visual acuity, IOP and or macular thickness from baseline data. Baseline characteristics of study groups at the entry were summarized in Table 1. No significant difference was detected between groups with regard to age, sex, duration of diabetes, best-corrected visual acuity, IOP, mean central (foveal) and paracentral (parafoveal) macular thickness.

In patients receiving intravitreal diclofenac (Fig. 1), mean pre-injection foveal thickness decreased from 383.6 ± 88.7 μ to 327.0 ± 67.0 μ at 4th week postoperatively. The difference was statistically significant ($p = 0.006$). Mean pre-injection para-foveal thickness decreased from 371.5 ± 47.5 μ to 343.5 ± 38.6 μ at 4th week postoperatively. The difference was statistically significant ($p = 0.02$) (Table 2). In patients receiving bevacizumab (Fig. 2), mean pre-injection

Table 1. Base line data of the study groups.

	Diclofenac	Bevacizumab	Control	*P*
No of eyes	20	20	10	
Age	60.2	62.3	58	0.15
Duration of diabetes (years)	14.0 ± 1.7	13.0 ± 8.3	15.0 ± 2.3	0.26
Gender* (female:male)	12:8	11:9	8:2	0.9
†IOP (mmHg)	16.1 ± 2.3	16.8 ± 0.7	14.8	0. 7
Visual acuity in LOGMAR	0.8	0.5	0.7	0.07
Central macular thickness	383.6 ± 88.7 μ	333.3 ± 105.1 μ	367.5 + 1.1 μ	0.26
Paracentral macular thickness	371.5 ± 47.5 μ	353.1 ± 55.7 μ	362.4 ± 1.5 μ	0.49

Independent sample *t*-test.
* Chi-square with continuity correction.
† IOP: intraocular pressure.

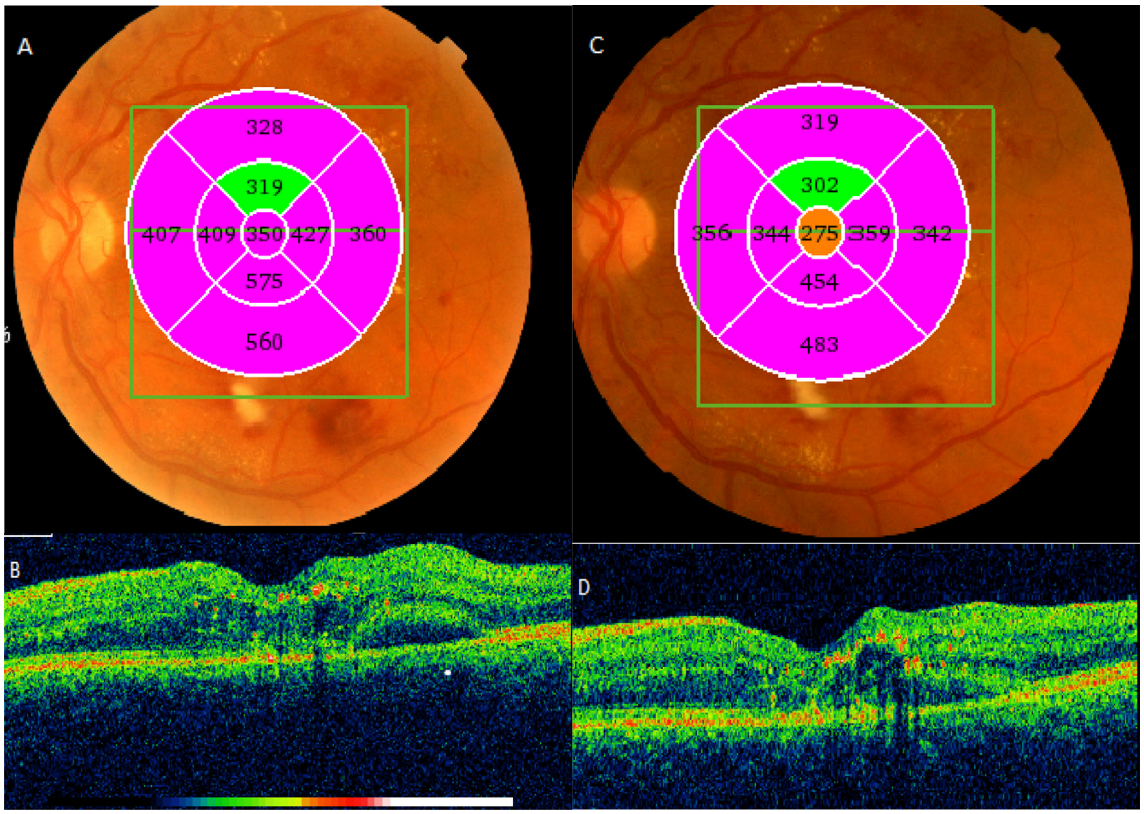

Fig. 1. Intravitreal diclofenac. (A) Preoperative thickness map showing foveal and parafoveal thickening in the nasal, temporal and inferior quadrants. (B) Preoperative b-scan showing diffuse macular edema and sensory retinal detachment. (C) Postoperative thickness map after one month showing a significant reduction of foveal and parafoveal thickness. (D) Postoperative b-scan reveals a corresponding reduction of macular edema.

Table 2. Central and paracentral macular thickness reduction following diclofenac and bevacizumab injection.

Group	Central ''foveal'' thickness (μ)			Paracentral ''parafoveal'' thickness (μ)		
	Pre-injection	Post-injection	*P	Pre-injection	Post-injection	*P
Diclofenac	383.6 + 88.7	327.0 + 67.0	0.006	371.5 + 47.5	343.5 + 38.6	0.02
Bevacizumab	333.3 + 105.0	307.9 + 78.6	0.02	353.1 + 55.7	330.0 + 24.1	0.01
Control	367.5 + 1.1 μ	363.1 + 1.4 μ	0.8	362.4 ± 1.5 μ	368.3 + 1.0 μ	0.6
†P	0.26	0.01		0.49	0.004	

* P = within group comparison (Wilcoxon Signed Rank test).
† P = Between group comparison (one-way ANOVA testing).

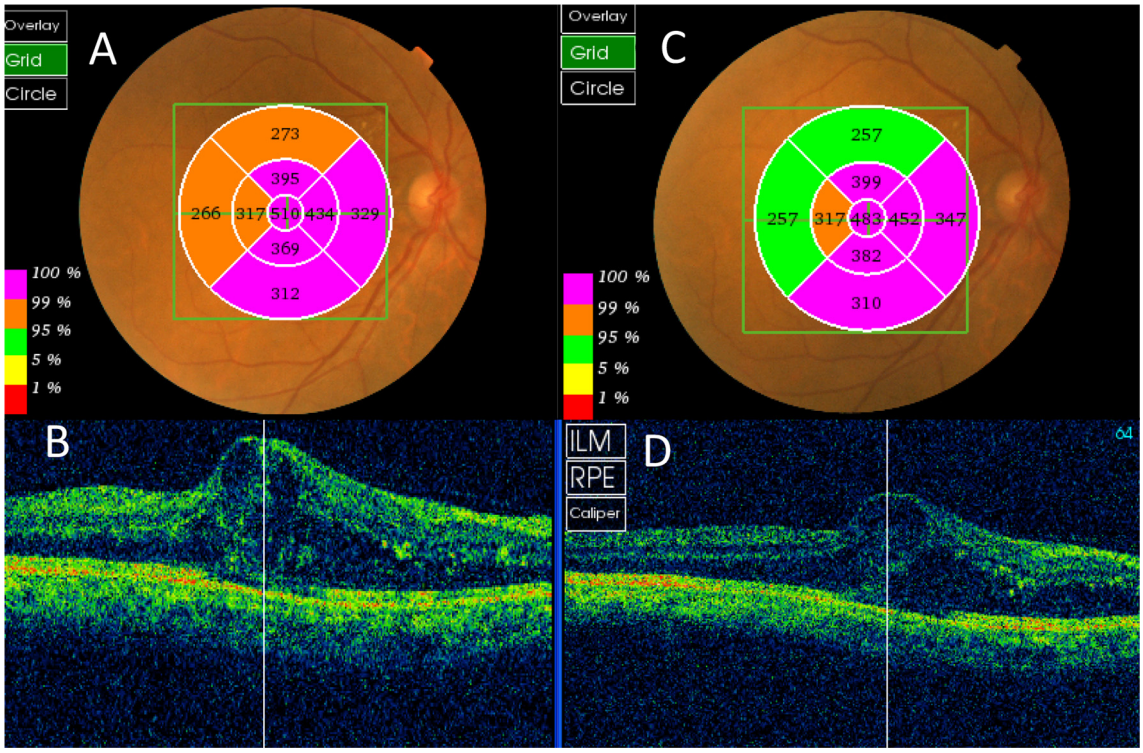

Fig. 2. Intravitreal bevacizumab. (A) Preoperative thickness map showing foveal and parafoveal thickening in all quadrants. (B) Preoperative b-scan showing diffuse macular edema with cystoids thickening of the fovea. (C) Postoperative thickness map after one month showing mild reduction of foveal thickness. (D) Postoperative b-scan reveals a corresponding reduction of foveal edema.

foveal thickness decreased from 333.3 ± 105.0 μ to 307.9 ± 78.6 μ at 4th week postoperatively. The difference was statistically significant ($p = 0.02$). Mean pre-injection para-foveal thickness decreased from 353.1 ± 55.7 μ to 330.0 ± 24.1 μ at 4th week postoperatively. The difference was statistically significant ($p = 0.01$) (Table 2).

None of the eyes in control group (Fig. 3) showed a clinically significant change in mean foveal (363.1 ± 1.4 μ, $p = 0.8$) or parafoveal thickness (368.3 ± 1.0 μ, $p = 0.6$) (Table 2) at the 4th week.

ANOVA testing for group comparison revealed a statistically significant difference in foveal thickness (0.01) and parafoveal thickness (0.004) between the three groups (Table 2). Post hoc analysis revealed no statistically significant difference in mean foveal ($p = 0.47$) or parafoveal thickness ($p = 0.24$) between diclofenac and bevacizumab groups. However, a statistically significant difference in mean foveal ($p = 0.01$) and parafoveal ($p = 0.03$) thickness was detected between diclofenac and control eyes (Table 3). Similarly, a statistically significant difference in mean foveal ($p = 0.03$) and parafoveal ($p = 0.001$) thickness was detected between bevacizumab and control eyes (Table 3).

Mean post-injection visual acuity in diclofenac treated eyes improved in 40% of eyes. Mean visual acuity increased from 0.17 to 0.22 but did not reach statistical significance ($p = 0.12$). Twenty percent of these eyes achieved one line improvement, 10% improved by 2 lines and 10% improved by > 2 lines. Mean line improvement was 1.7 (Table 4). Mean post-injection visual acuity in bevacizumab-treated eyes improved in 50% of eyes. Mean visual acuity increased from 0.32 to 0.37 but did not reach statistical significance ($p = 0.45$). About 18.7% of these eyes achieved one line improvement, 18.7% improved by 2 lines and 12.5% improved by >2 lines. Mean line improvement was 1.8 (Table 4). None of the eyes in the control group showed a clinically significant change in visual acuity ($p = 0.6$).

ANOVA testing for group comparison revealed no statistically significant difference in post-injection VA between the three groups ($p = 0.2$). No statistically significant difference in mean post-injection visual acuity ($p = 0.2$), mean line

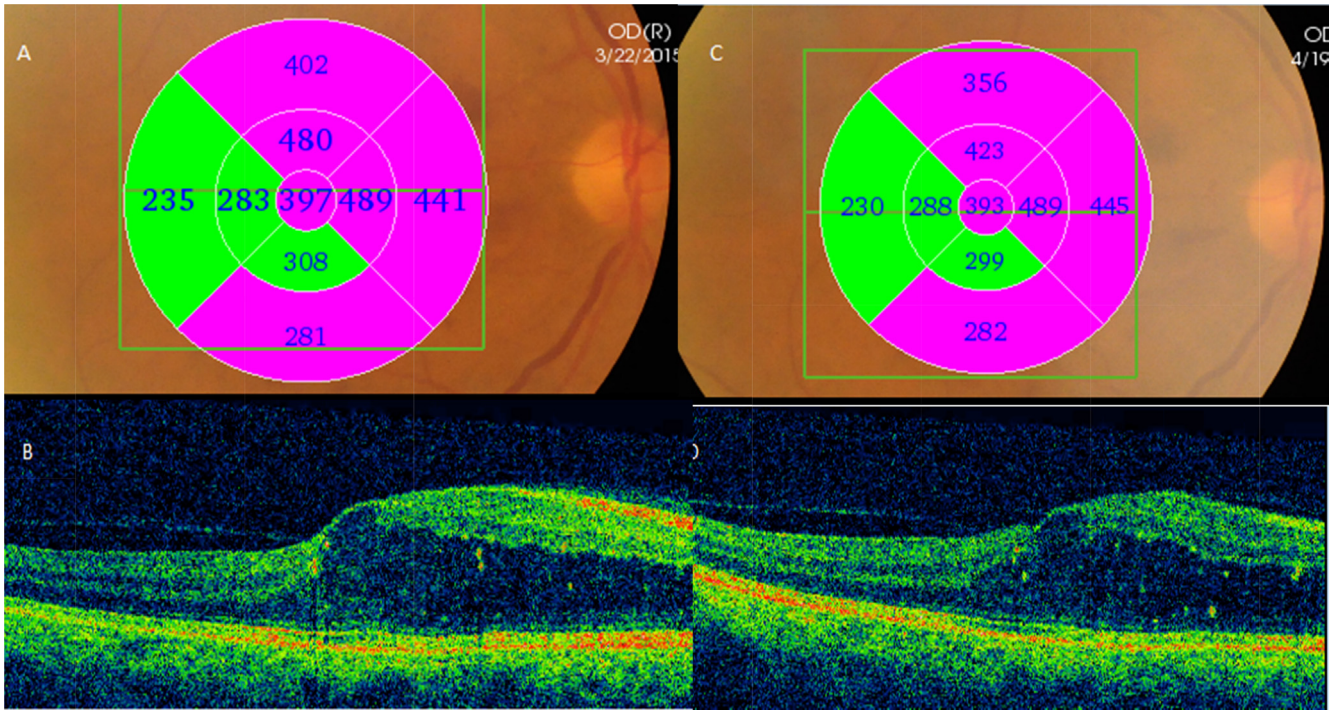

Fig. 3. Control group. (A) Thickness map showing foveal and parafoveal thickening in the nasal and superior quadrants. (B) b-scan showing diffuse macular edema in foveal and nasal parafoveal region. (C) Thickness map after one month showing persistent foveal and parafoveal thickening. (D) Postoperative b-scan after one month reveals persistence of macular edema.

Table 3. Post Hoc analysis of thickness difference between groups following intravitreal injection.

Dependent variable	Mean difference (μ)	Significance	95% confidence interval
Central thickness			
Control:			
Diclofenac	36.00	0.01	2.4–90.4
Bevacizumab	55.05	0.03	3.6–106.4
Paracentral thickness control:			
Diclofenac	24.5	0.03	1.3–47.6
Bevacizumab	37.9	0.001	16.6–59.2

improvement ($p = 0.8$) or percentage of improved eyes ($p = 0.6$) was detected between diclofenac and bevacizumab-treated eyes (Table 4).

Diclofenac group showed statistically significant reduced IOP from 18.2 to 16.3 mmHg ($P = 0.02$). In bevacizumab-treated eyes, no significant change in IOP followed injection. None of the eyes in the control group showed IOP changes over the period of study. None of the patients in either group developed injection-related complications.

Discussion

In the present study, both groups showed a statistically significant reduction in mean central macular thickness, while visual improvement was modest and did not reach statistical significance in either group.

Topical and systemic anti-inflammatory preparations have been recently tried for management of diabetic macular edema with considerable effect.[19–21] However, the use of topical agents in diabetic macular edema is still a matter of controversy. High-quality evidence through randomized clinical trials is still needed to decide whether to use topical NSAIDs in cases of diabetic macular edema.[22] The diabetic retinopathy clinical research (DRCR) network reported that

Table 4. Visual acuity outcome in diclofenac and bevacizumab groups.

	Diclofenac group	Bevacizumab group	Control group	†*P*
Mean pre-injection ‡VA	0.8	0.7	0.7	0.7
Mean post injection ‡VA	0.7	0.6	0.8	0.2
*P	0.12	0.45	0.6	
Mean line improvement	1.7 + 1.5	1.8 + 1.3	–	0.8
Eyes with improved	40%	50%	–	0.6
vision (%)	4 (20%)	3 (18.7%)		
One line	2 (10%)	3 (18.7%)		
2 lines	2 (10%)	2 (12.5%)		
>2 lines	12(60%)	12 (50%)		
Eyes with stable vision (%)			–	

* *P* = within group comparison (Wilcoxon Signed Rank test).
† *P* = between group comparison (ANOVA).
‡ VA: visual acuity in Log MAR.

topical nepafenac 0.1% in non-central DME, three times daily for one year likely does not have a meaningful effect on OCT-measured retinal thickness. However, they concluded that the lack of beneficial effect does not preclude the possibility of benefit from other delivery methods of non-steroidal anti-inflammatory drugs, such as intravitreal injection and that reduction in retinal volume from nepafenac was potentially possible.[23]

In the present study, the mean reduction of foveal (central) thickness in diclofenac group was 56 μ versus 28 μ reduction of parafoveal (non-central thickness). Whereas bevacizumab showed less effect on central (25 μ reduction) and paracentral regions (23 μ reduction). In phase II randomized clinical trial evaluating the short-term effect of intravitreal bevacizumab for DME, It was found that only half of bevacizumab group showed more than 11% reduction in central macular thickness.[24] Soheilian et al.[19] working on naïve diabetic macular edema recorded contradictory results where the difference of macular thickness between eyes treated with bevacizumab and diclofenac was in favor of bevacizumab, but not to a significant level.

Faghihi et al. (2017) reported a reduction in central macular thickness and macular volume from baseline in eyes with naïve DME receiving either intravitreal bevacizumab or diclofenac, but there was no significant difference in between.[25] In a previous small trial, intravitreal diclofenac achieved a comparable therapeutic effect to triamcinolone on retinal thickness in eyes with diffuse DME.[18] Most NSAI act through inhibition of prostaglandins synthesis by suppression of the arachidonic acid transformation, catalyzed by COX-1 and COX-2. However, diclofenac can also inhibit the lipoxygenase pathway. Therefore, diclofenac has a spectrum of activity similar to corticosteroids and this property may explain its pronounced anti-inflammatory effect.[10,26] On the other hand, coexisting systemic factors may play a role in the therapeutic effect of drugs. A decrease in macular edema with ranibizumab therapy has been reported to inversely correlate with serum HbA1c.[27]

Mean visual acuity improvement in diclofenac group was comparable to bevacizumab group (40% vs 50%). Both groups showed improved mean visual acuity compared to preoperative values. However, visual gain did not reach statistical significance in either group. Previous studies showed that nepafenac was more effective than fluorometholone in preventing angiographic CME following cataract surgery and was associated with rapid visual recovery.[28] The extent to which diclofenac can improve visual acuity may be related to the severity of diabetic macular edema. In a pilot non-controlled study conducted on five eyes, mild cases of diabetic macular edema showed statistically significant improved visual acuity following topical nepafenac for 6 months.[14] Sohelian et al.[19] recorded statistically significant improvement of visual acuity in diclofenac-treated eyes versus bevacizumab-treated eyes. Their study included diabetics with naïve DME. In addition, only eyes with good visual acuity were included (≥20/300).

Although several studies reported the extended effect of topical[11] and intravitreal diclofenac[12,18] up to 8–12 weeks, repeated injection may be required to reach statistically improved visual acuity. Faghihi et al.[25] reported that visual acuity of eyes with naïve DME was significantly improved in diclofenac and bevacizumab-treated eyes. Comparison of BCVA at 6 months of follow-up between the two groups - based on the number of injections-showed improved VA with an increased number of injections.

Therefore, the functional outcome of bevacizumab may be underestimated by a single intravitreal injection. Patients may achieve a satisfactory level after completing the loading dose. Similarly, diclofenac treated eyes may need reinjection. In either group, the outcome results of the present study may reflect poorer response associated with coexisting systemic factors.

In severe and persistent grades of macular edema, pre-treatment structural characteristic may also influence the visual outcome and underestimate the therapeutic effect of drugs. Photoreceptor loss was associated in most of our cases (detected by OCT as interruption or destruction of inner segment/outer segment junction). In addition, all grades of visual acuity were included in the study.

Naïve DME was previously evaluated for the effect of both bevacizumab and diclofenac.[19] However, it is preferred to target persistent types of DME that represent a local challenging clinical situation. Therefore, in those cases or countries where frequent anti-VEGF injection represents a socioeconomic burden, diclofenac may offer a suitable alternative. The role of inflammation may be more evident in persistent cases of DME where chronicity allows for more inflammatory mediators to act on the retina. In other words, persistent cases of DME may be more prone to anti-inflammatory agents.

The comparable effect of diclofenac to bevacizumab in eyes with persistent DME may offer an opportunity for a certain category of patients at high risk for AntiVEGF complications (ischemic heart, hypertension, previous cerebral stroke).

The potential IOP lowering effect of NSAI recorded in the present study adds a superior benefit to its use. The influence of diclofenac ophthalmic solution on the IOP lowering effect of topical 0.5% timolol and 0.005latanoprost in primary open-angle glaucoma patients had been reported by Costalgia et al.[29] Similarly, Ozyol et al.[30] founded that Nepafenac potentiates the IOP-lowering effects of three different prostaglandin analogs in primary open-angle glaucoma patients. In addition, several clinical trials had recorded the reduction of IOP following both topical and intravitreal diclofenac. In patients with diabetes, topical diclofenac was able to decrease IOP after cataract surgery.[31] Intravitreal diclofenac injection was associated with a reduction of IOP by 2–4 mm in patients with DME.[18,25] On the other hand, the incidence of sustained elevated IOP in patients receiving intravitreal anti-VEGF injections was found to be significant.[32]

Limitations of this study include a small sample size, short-term follow-up period. The outcome results may be underestimated by several factors including single, injection, confounding systemic and local variables, and structural characteristics of eyes with persistent macular edema.

In conclusion: In persistent DME, diclofenac has a structural effect comparable to bevacizumab on central macular thickness. However, a significant functional gain may not be accomplished by a single injection. Unlike naïve DME, persistent cases may be confounded by systemic and local factors necessitating repeated injection of diclofenac.

Conflict of interest

The authors declared that there is no conflict of interest.

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